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A Systematic Review Update

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Stroke Prevention in Patients With Atrial Fibrillation: A Systematic Review Update

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None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

This report may periodically be assessed for the currency of conclusions. If an assessment is done, the resulting surveillance report describing the methodology and findings will be found on the Effective Health Care Program Web site at: www.effectivehealthcare.ahrq.gov. Search on the title of the report.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States.

The Patient-Centered Outcomes Research Institute (PCORI) was established to fund research that can help patients and those who care for them make better informed decisions about the health care choices they face every day. PCORI partnered with AHRQ to help fulfill PCORI's authorizing mandate to engage in evidence synthesis and make information from comparative effectiveness research more available to patients and providers. PCORI identifies topics for review based on broad stakeholder interest. After identifying specific topics, multistakeholder virtual workshops are held by PCORI to inform the individual research protocols.

The reports and assessments provide organizations, patients, clinicians, and caregivers with comprehensive, evidence-based information on common medical conditions and new health care technologies and strategies. They also identify research gaps in the selected scientific area, identify methodological and scientific weaknesses, suggest research needs, and move the field forward through an unbiased, evidence-based assessment of the available literature. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review and public comment prior to their release as a final report.

AHRQ expects that the EPC evidence reports and technology assessments, when appropriate, will inform patients and caregivers, individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

If you have comments on this evidence report, they may be sent by mail to the Task Order Officer: Aysegul Gozu, M.D., M.P.H., Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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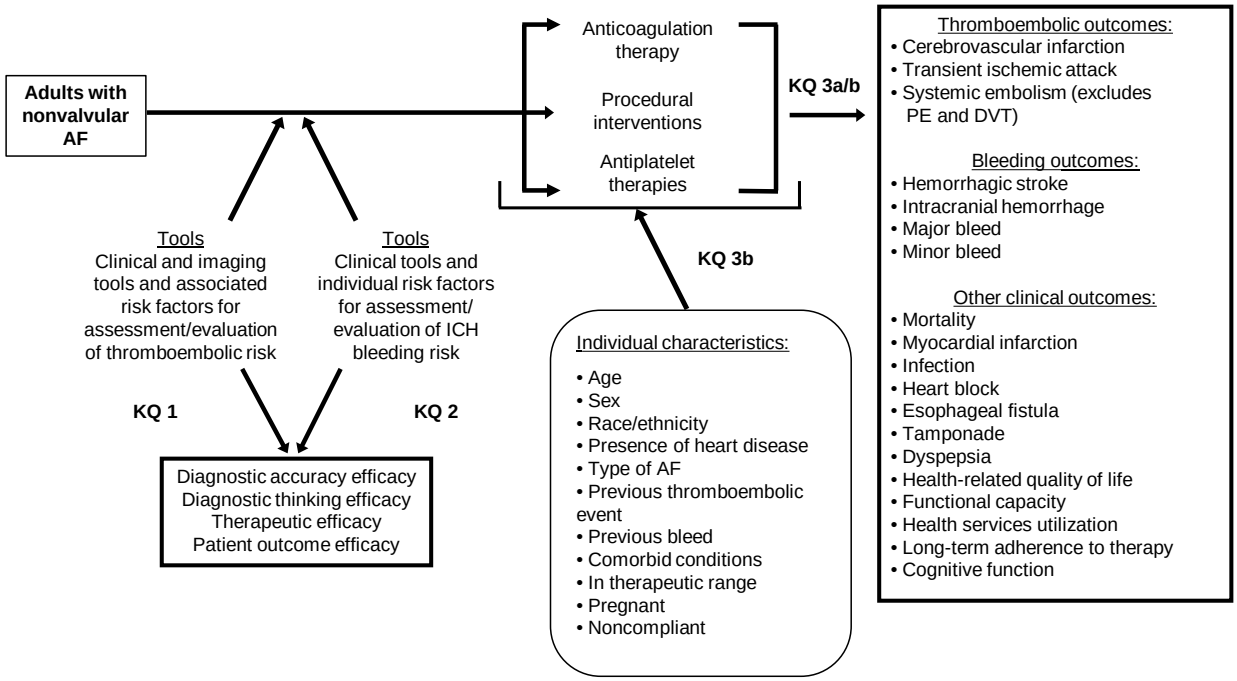
Evidence Summary

Introduction

This systematic review is an update of an earlier report published in 2013 which evaluated questions related to stroke prevention in patients with atrial fibrillation (AF) and atrial flutter. Given evidence that has emerged since the publication of the 2013 report, this review focuses on updating and expanding the earlier work in three key areas: (1) evaluating the accuracy and utility of clinical tools and imaging tools to predict thromboembolic event risk, (2) evaluating the accuracy and utility of clinical tools used to predict bleeding risk, and (3) exploring the comparative safety and effectiveness of various interventions to prevent thromboembolic events in patients with nonvalvular atrial fibrillation (Figure A). In addition, this review explores the strengths and weaknesses of shared decisionmaking tools available to aid patients and clinicians in selecting an intervention to prevent stroke.

Figure A. Analytic framework



Abbreviations: AF=atrial fibrillation; DVT=deep vein thrombosis; KQ=Key Question; ICH=intracranial hemorrhage; PE=pulmonary embolism

Results/Key Findings

Accuracy and Utility of Clinical and Imaging Tools To Predict Stroke Risk

- $CHADS_2$ score (continuous): Based on a meta-analysis of 14 studies (10 low risk of bias, 4 medium risk of bias, 761,128 patients), there is moderate strength of evidence (SOE) that the continuous $CHADS_2$ score provides limited prediction of stroke events (c-statistic of 0.69; 95% confidence interval [CI] 0.66 to 0.73).
- $CHADS_2$ score (categorical): Based on a meta-analysis of 16 studies (11 low risk of bias, 5 medium risk of bias, 548,464 patients), there is moderate SOE that the categorical $CHADS_2$ score provides limited prediction of stroke events (c-statistic of 0.66; 95% CI 0.63 to 0.69).
- CHA_2DS_2-VASc (continuous): Based on a meta-analysis of 17 studies (13 low risk of bias, 4 medium risk of bias; 511,481 patients), there is moderate SOE that the continuous CHA_2DS_2-VASc score provides limited prediction of stroke events (c-statistic of 0.67; 95% CI 0.64 to 0.70).
- CHA_2DS_2-VASc (categorical): Based on a meta-analysis of 13 studies (8 low risk of bias, 5 medium risk of bias; 496,683 patients), there is low SOE that the categorical CHA_2DS_2-VASc score provides limited prediction of stroke events (c-statistic of 0.64; 95% CI 0.58 to 0.70).
- Framingham score (categorical): Based on a meta-analysis of 6 studies (5 low risk of bias, 1 medium risk of bias; 282,572 patients), there is moderate SOE that the categorical Framingham score provides limited prediction of stroke events (c-statistic of 0.63; 95% CI 0.62 to 0.65).
- ABC score (categorical): Based on a meta-analysis of 4 studies (4 low risk of bias, 25,614 patients), there is moderate SOE that the categorical ABC score provides limited prediction of stroke events (c-statistic of 0.67; 95% CI 0.63 to 0.71).
- Echocardiography: There is insufficient evidence for the relationship between findings on echocardiography (transthoracic) and subsequent stroke based on 5 studies (3 low risk of bias, 2 medium risk of bias; 1,228 patients) that reported discrepant results.
- Comparative accuracy: $CHADS_2$ and CHA_2DS_2-VASc have the most evidence predicting stroke events accurately when directly compared with other scores. This finding was, however, statistically significant only for the comparison with the Framingham categorical score. Other comparisons were not possible given limited data.
- Limitations: Included studies used heterogeneous populations; some participants were on and some were off antiplatelets and anticoagulants at baseline. Also, few studies used clinical validation in their report of stroke rates, instead relying on administrative data, chart review, or other measures that did not use consistent definitions and were not similar across studies, complicating synthesis of their findings. Furthermore, although event rates were consistently reported, c-statistics and measures of calibration, strength of association, and diagnostic accuracy were inconsistently reported.
- The outcome of impact on clinical decisionmaking (diagnostic thinking, therapeutic efficacy, and patient outcome efficacy) was not assessed by any studies.

Accuracy and Utility of Clinical Tools To Predict Bleeding Risk

- AF patients on warfarin: 13 studies (10 low risk of bias, 2 medium risk of bias, 1 high risk of bias; 197,312 patients) compared different risk scores (Bleeding Risk Index [BRI], $HEMORR_2HAGES$, HAS-BLED, ATRIA, ABC) in predicting major bleeding events. These studies differed markedly in population, major bleeding rates, and statistics reported for evaluating risk prediction scores for major bleeding events. Evidence favors HAS-BLED based on two studies demonstrating that it has statistically significantly higher prediction (by c-statistic) for major bleeding events than other scores among patients on warfarin, but the majority of comparative studies which evaluated HAS-BLED showed no statistically significant differences in prediction abilities, reducing the strength of evidence (moderate SOE).
- Chronic kidney disease (CKD) and major bleeding: Eight studies (7 low risk of bias, 1 medium risk of bias; 322,010 patients) evaluated the risk of major bleeding in patients with CKD. All studies demonstrated increased risk of bleeding in patients with CKD (moderate SOE) although do not formally evaluate the use of a tool incorporating CKD.
- AF patients on warfarin: 1 study (low risk of bias; 48,599 patients) compared $HEMORR_2HAGES$ and HAS-BLED in predicting intracranial hemorrhage (ICH). This study showed no statistically significant difference in prediction abilities between the two scores (low SOE).
- AF patients on aspirin alone: Three studies (2 low risk of bias, 1 medium risk of bias; 177,538 patients) comparing different combinations of bleeding risk scores (BRI, $HEMORR_2HAGES$, and HAS-BLED) in predicting major bleeding events showed no statistically significant differences (low SOE).
- AF patients not on therapy: Six studies (4 low risk of bias, 2 medium risk of bias; 310,607 patients) comparing different combinations of bleeding risk scores (BRI, $HEMORR_2HAGES$, HAS-BLED, and ATRIA) in predicting major bleeding events showed no statistically significant differences (low SOE).
- Limitations: Although studies consistently reported event rates and c-statistics, measures of tool calibration, strength of association, and diagnostic accuracy were inconsistently reported.
- The outcome of impact on clinical decisionmaking (diagnostic thinking and therapeutic efficacy) was not assessed by any studies.

Comparative Safety and Effectiveness of Interventions To Prevent Thromboembolic Events

- Acetylsalicylic acid (ASA) versus vitamin K antagonist (VKA; warfarin): Based on 5 observational studies involving 251,578 patients, warfarin reduces the risk of nonfatal and fatal ischemic stroke compared with aspirin (moderate SOE); however, based on 3 studies involving 212,770 patients, warfarin is also associated with increased rates of major bleeding complications compared with aspirin (moderate SOE)
- ASA+clopidogrel versus ASA: In patients not eligible for warfarin, two good quality RCTs involving 8,147 patients showed lower rates of any stroke (HR 0.72, 95% CI 0.62 to 0.83) for combination therapy of aspirin and clopidogrel compared to ASA alone (moderate SOE). In the largest RCT (7,554 patients), the combination of aspirin and

clopidogrel was associated with higher rates of major bleeding than aspirin alone (HR 1.57, 95% CI 1.29 to 1.92) (moderate SOE).

- Warfarin versus clopidogrel: Based on 1 large observational, good quality study involving 54,636 patients, warfarin reduces the risk of nonfatal and fatal ischemic stroke compared with clopidogrel monotherapy, with no evidence of differences in major bleeding (moderate SOE).
- ASA+clopidogrel versus warfarin: Based on two large, good-quality RCTs involving 60,484 patients, warfarin is superior to aspirin plus clopidogrel for the prevention of stroke or systemic embolism (high SOE). In one good quality RCT of 6,706 patients, warfarin is superior to aspirin plus clopidogrel for the reduction in any minor bleeding (moderate SOE) however warfarin increased hemorrhagic stroke risk compared to ASA+ clopidogrel (moderate SOE). There was no evidence of a difference between therapies for MI, death from vascular causes or all-cause mortality (moderate SOE for both outcomes).
- Clopidogrel+warfarin versus warfarin: Clopidogrel+warfarin shows a trend toward a benefit on stroke prevention (low SOE) and is associated with increased risk of nonfatal and fatal bleeding compared with warfarin alone (moderate SOE). These findings are based on 1 good-quality observational study involving 52,349 patients.
- Warfarin+aspirin+clopidogrel versus warfarin: Triple therapy increases the risk of nonfatal and fatal bleeding (moderate SOE) and also shows a trend toward increased ischemic stroke (low SOE) compared with warfarin alone. These findings are based on 1 good-quality observational study involving 52,180 patients
- Thrombin inhibitors (dabigatran) versus warfarin: Based on 1 large good-quality RCT involving 18,113 patients and 35 observational studies involving 1,737,961 patients we found:
    - Dabigatran at a 150mg dose is superior to warfarin in reducing the incidence of the composite outcome of stroke (including hemorrhagic) or systemic embolism (RR 0.66, 95% CI 0.53 to 0.82), with no statistically significant difference in the occurrence of major bleeding (RR 0.93, 95% CI 0.81 to 1.07) (high SOE for both outcomes), all-cause mortality(RR 0.88, 95% CI 0.77 to 1.00) (low SOE), or myocardial infarction (MI) risk (low SOE).
    - Dabigatran at a 110mg dose is similar to warfarin for the composite outcome of stroke or systemic embolism (RR 0.91, 95% CI 0.74 to 1.11) (moderate SOE). It is associated with a reduction in the risk of major bleeding (RR 0.80, 95% CI 0.69 to 0.93) when compared with warfarin (high SOE), but there is no evidence of a difference in all-cause mortality or MI risk (low SOE for both outcomes). Note the 110mg dose is currently not approved for stroke prevention in patients with AF in the US.
    - Observational studies were inconsistent with RCT evidence for the outcomes of all-cause mortality (observational studies demonstrated a benefit for patients on dabigatran, while RCT studies suggested no evidence of a difference on either dose) and MI risk (observational studies did not show a difference, RCT studies suggested an increase with the 150mg dose of dabigatran).
- Xa inhibitor (apixaban) versus ASA: Apixaban is superior to aspirin in reducing the incidence of stroke or systemic embolism (HR 0.45, 95% CI 0.32 to 0.62) with similar major bleeding risk (HR 1.13, 95% CI 0.74 to 1.75), in patients who are not suitable for

warfarin (moderate SOE for both outcomes). These findings are based on 1 good quality RCT involving 5,599 patients.

- Xa inhibitor (apixaban) versus warfarin: Apixaban is superior in reducing the incidence of (1) stroke or systemic embolism (HR 0.79, 95% CI 0.66 to 0.95) (high SOE), (2) the risk of major bleeding (0.69, 95% CI 0.60 to 0.80) (high SOE), and (3) all-cause mortality (low SOE) when compared with warfarin. These findings are based on 1 large good-quality RCT involving 18,201 patients, and 29 observational studies with 1,251,855 patients.
- Xa inhibitor (rivaroxaban) versus warfarin: Rivaroxaban is similar to warfarin in preventing stroke or systemic embolism (HR 0.88, 95% CI 0.74 to 1.03) (moderate SOE), with similar rates of major bleeding (low SOE) and all-cause mortality (moderate SOE). These findings are based on 1 large, good-quality RCT involving 14,264 patients and 26 observational studies with 1,483,949 patients. Inconsistent with the RCT findings, observational studies supported a reduction in stroke or systemic embolism and a trend towards a reduction in ischemic or uncertain stroke, while also providing evidence of a small increase in the risk of major bleeding.
- Xa inhibitor (edoxaban) versus warfarin: Edoxaban (either 60mg or 30mg dose) is superior in reducing hemorrhagic stroke (low dose HR 0.33, 95% CI 0.22 to 0.50; high dose HR 0.54, 95% CI 0.38 to 0.77) (moderate SOE) and the risk of major bleeding (moderate SOE) though did not differ in overall stroke risk (moderate SOE), myocardial infarction (moderate SOE) or all-cause mortality (moderate SOE for high dose). There was low SOE that low dose edoxaban (30 mg) reduced all-cause mortality. These findings are based on 1 large, good-quality RCT involving 21,105 patients. Note that the 60 mg once-daily dose of edoxaban is approved by the FDA to treat only NVAF patients with creatinine clearance (CrCL) >50 to ≤ 95 mL/min, while 30 mg once-daily dose of edoxaban is approved to treat NVAF in patients with renal dysfunction (CrCL 15 to 50 mL/min).
- Percutaneous left atrial appendage (LAA) closure versus warfarin: LAA shows a trend toward a benefit over warfarin for all strokes (including ischemic or hemorrhagic) and all-cause mortality (low SOE for both outcomes). Although LAA with percutaneous closure results in less frequent major bleeding than warfarin (low SOE), it is also associated with a higher rate of adverse safety events such as pericardial effusion and device embolization (moderate SOE). These findings are based on 1 good-quality RCT involving 707 patients and 4 observational studies involved 1,430 patients.

Discussion

Additional details about this systematic review are described in Table A.

Observational Studies Versus RCT Evidence

- Within the included set of observational studies, use of direct oral anticoagulants and comparative effectiveness analyses of the different oral anticoagulants often have inconsistent findings. These inconsistencies likely resulted from confounding, selection bias, different endpoint definitions, rigor and completeness of followup, and variations in decisionmaking practice between trial populations and real world scenarios.

- When considered together, the findings from observational and RCT studies were inconsistent related to all-cause mortality and myocardial infarction for dabigatran versus warfarin.
    - The observational studies demonstrated a benefit in all-cause mortality for patients on dabigatran compared with warfarin. RCT evidence, however did not demonstrate evidence of a difference. In addition, observational studies did not show a difference in myocardial infarction while RCT studies suggested an increase with dabigatran.
- Xa inhibitors (all-cause mortality): The observational studies did not show a reduction in all-cause mortality across Xa inhibitors, whereas RCTs showed reduction in all-cause mortality across Xa inhibitors.
- Other RCT findings were supported by existing observational studies.

Shared Decisionmaking Tools

- While many publications have described decision support tools for anticoagulation for patients with nonvalvular AF, these tools are all early in development, haven't been validated, and the tools are not in clinical use.
- Future studies are required to evaluate how decision aids influence actual choices and clinical outcomes.

Key Limitations and Research

Gaps

- For risk prediction tools, further studies are needed that: (1) report complete data across the full continuous range of scores; (2) use validated clinical outcomes for stroke and bleeding; and (3) compare all available risk scores using consistent and appropriate statistical evaluations such as c-statistics.
- There is a need for a tool that could be used for decisionmaking about antithrombotic therapy in AF patients taking into account both thromboembolic and bleeding risks.
- Additional studies utilizing prospectively constructed databases (registries) with longer-term outcomes data that compare all available risk prediction tools would be of great use in better clarifying which risk score system is superior in predicting major bleeding or thromboembolic risk.
- It is important to have new studies with head-to-head comparisons of direct oral anticoagulants (DOACs). Given variability in patient populations, concomitant therapies, and underlying patient care, indirect comparisons across RCTs in this field is of limited use.
- There are also many novel invasive treatments for treating AF such as left atrial appendage (LAA) closure devices but the evidence remains sparse about these interventions in terms of stroke prevention. Studies need to be conducted in patients who receive these procedures to determine if and how anticoagulation strategies should be modified in patients receiving these procedures.
- An area worthy of further study is the use of the direct oral anticoagulants in specific populations of patients such as those with severe kidney disease (end-stage renal disease), older adults, patients with comorbid diseases, or frail patients.

Table A. Summary of review characteristics

Population Included in the Review
Key inclusion criteria: Adults ≥18 years of age with nonvalvular atrial fibrillation (paroxysmal, persistent, or permanent), including those with atrial flutter
Key exclusion criteria: Patients with known reversible causes of atrial fibrillation (e.g., postoperative atrial fibrillation or hyperthyroidism); those under 18 years of age
Key Topics and Interventions Covered by the Review
1. The accuracy and utility[a] of clinical and imaging tools used to predict stroke and clot risk Clinical tools including: - $CHADS_2$ score - CHA_2DS_2-VASc score - Framingham risk score - ABC stroke risk score Imaging tools including: - Transthoracic echo - Transesophageal echo - CT scans - Cardiac MRIs
2. The accuracy and utility[a] of clinical tools used to predict bleeding risk Clinical tools including: - HAS-BLED score - $HEMORR_2HAGES$ score - ATRIA score - Bleeding Risk Index - ABC bleeding risk score
3. The comparative safety (in terms of bleeding risk) and effectiveness (in terms of stroke prevention) of various pharmacologic and procedural interventions used to prevent stroke and blood clots in patients with nonvalvular atrial fibrillation Pharmacologic interventions including: - *Anticoagulants* - Warfarin - Direct oral anticoagulants (dabigatran, apixaban, rivaroxaban, edoxaban) - *Antiplatelets* - Clopidogrel - Aspirin - Dipyridamole - Combinations of antiplatelets (e.g., aspirin + dipyridamole) Procedural interventions including: - Surgical interventions (e.g. left atrial appendage occlusion, resection/removal) - Minimally invasive interventions (e.g., AtriClip, LARIAT) - Transcatheter (e.g., WATCHMAN, AMPLATZER, PLAATO)
Timing of the Review
Beginning search date: January 1, 2000
End search date: February 14, 2018
Important Studies Underway

Population Included in the Review
RCTs involving direct comparisons of newer oral anticoagulants: • Comparison of Efficacy and Safety Among Dabigatran, Rivaroxaban, and Apixaban in Non-Valvular Atrial Fibrillation (NCT02666157) – targeted enrollment of 3672, to be completed December 2018 The Danish Non-vitamin K Antagonist Oral Anticoagulation Study in Patients With Atrial Fibrillation (NCT03129490) – targeted enrollment of 11,000, to be completed September 2021

[a] Utility is defined as the impact on clinical and patient decisionmaking including diagnostic thinking, therapeutic efficacy, and patient outcome efficacy.

Abbreviations: ABC=age, biomarkers, clinical history; ATRIA=Age, female, diabetes, congestive heart failure, hypertension, proteinuria; $CHADS_2$=congestive heart failure, hypertension, age >75, diabetes, stroke/transient ischemic attack; CHA_2DS_2-VASc=Congestive heart failure/left ventricular ejection fraction ≤40%, hypertension, age ≥75, diabetes, stroke/transient ischemic attack/thromboembolism, vascular disease, age 65-74, sex; HAS-BLED=hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly (> 65), drugs/alcohol concomitantly; $HEMORR_2HAGES$=Hepatic or renal disease, ethanol (alcohol) abuse, malignancy, older (> 75), reduced platelet count or function, rebleeding risk, hypertension (uncontrolled), anemia, genetic factors, excessive fall risk, stroke history; MRI=magnetic resonance imaging

Introduction

Background

Atrial fibrillation (AF) is an irregular supraventricular tachyarrhythmia (any tachycardic rhythm originating above the ventricular tissue). It is characterized by uncoordinated atrial activation with consequent deterioration of mechanical function.[1] Atrial flutter is a common abnormal heart rhythm, similar to AF. Both conditions are types of supraventricular tachycardia in which the upper chambers of the heart beat too fast, which results in loss of effective atrial muscle contractions. Within this systematic review, we will use AF to include patients with either atrial fibrillation and atrial flutter.

AF is the most common cardiac arrhythmia seen in clinical practice, accounting for approximately one-third of hospitalizations for cardiac rhythm disturbances. The estimated prevalence of AF is 0.4 percent to 1 percent in the general population,[2,3] occurring in about 2.2 million people in the United States. The prevalence increases to about 6 percent in people 65 years of age or older, and to 10 percent in people 80 years of age or older.[4] It is estimated that by the year 2050 there will be 12.1 million Americans with AF, representing more than a two-fold increase since 2000. However, this estimate assumes no further increase in the age-adjusted incidence of AF beyond 2000. If the incidence of AF increases at the same pace, then the projected number of adults with AF would be 15.9 million, a three-fold increase from 2000.[5]

Management of AF involves three distinct areas, namely, rate control, rhythm control, and prevention of thromboembolic events. This review will focus on prevention of thromboembolic events.

Atrial Fibrillation and Stroke

Although generally not as immediately life-threatening as ventricular arrhythmias, AF is associated with significant morbidity and mortality. Patients with AF have increased risk of embolic stroke, heart failure, and cognitive impairment; reduced quality of life; and higher overall mortality.[6-8] Patients with AF have a five-fold increased risk of stroke, and it is estimated that up to 25 percent of all strokes in the elderly are a consequence of AF.[4] Further, AF-related strokes are more severe than other types of stroke, with AF patients being twice as likely to become bedridden than patients with stroke from other etiologies and more likely to die from the stroke.[9-11] Consistent with the nature of these events, AF-related stroke constitutes a significant economic burden, costing Medicare approximately $8 billion annually.[12]

The rate of ischemic stroke among patients with nonvalvular AF averages 5 percent per year, which is 2 to 7 times that of the general adult population.[9] The risk of stroke increases from 1.5 percent for patients with AF who are 50 to 59 years of age to 23 percent for those who are aged 80 to 89.[10] Congestive heart failure, hypertension, age greater than 75 years, diabetes mellitus, and prior stroke or transient ischemic attack (TIA) are considered independent risk factors for stroke as well as for AF. Aggressive primary prevention and intervention after these risk factors are present is essential to optimally manage the increased risk of developing AF or stroke independently or together.

Note: The reference list follows the appendixes.

Stroke Prevention Strategies in Atrial Fibrillation

A 2013 AHRQ Comparative Effectiveness Review (CER) evaluated questions related to stroke prevention in patients with AF and atrial flutter.[13] The original review found that $CHADS_2$ (congestive heart failure, hypertension, age >75, diabetes, stroke/transient ischemic attack) and CHA_2DS_2-VASc (congestive heart failure/left ventricular ejection fraction ≤40%, hypertension, age ≥75, diabetes, stroke/TIA/thromboembolism, vascular disease, age 65-74, sex) scores have the best prediction ability for stroke events in patients with AF, whereas HAS-BLED provides the best prediction ability of bleeding risk. The review found insufficient evidence on imaging tools such as transthoracic echo (TTE), transesophageal echo (TEE), computed tomography (CT) scans, or cardiac magnetic resonance imaging (MRI) in relation to risk stratification for thromboembolic events. Newer anticoagulants (direct oral anticoagulants [DOACs]) resulted in reduced stroke and bleeding events when compared with warfarin, and apixaban showed better efficacy and similar safety to aspirin in patients who are not candidates for warfarin. Given the uncertainties which remained within the limitations of the available evidence, and the new data which have emerged since that report, an update of the systematic review was commissioned.

Risk Stratification

Stroke prevention in AF is complex. Strategies for preventing thromboembolic events can be categorized into (1) optimal risk stratification of patients and (2) prophylactic treatment of patients identified as being at risk. Appropriate allocation of treatment to patients at the highest risk is critical to reduce morbidity after stroke in AF patients. However, as will be discussed, the prevention of stroke in AF comes at a cost, namely bleeding. As a result, risk stratification is paramount in patients with AF. For example, treatment with high-risk medications that can cause bleeding may unnecessarily expose patients with a low probability of thromboembolic events to the complications of monitoring and increased risk of bleeding. Likewise, not treating patients at high risk for thromboembolic events increases the likelihood of such an event. Risk stratification allows the appropriate matching of patients at risk with appropriate therapy, recognizing that there is a clinical balance that needs to be struck when treating a patient at high risk of stroke with a medication that increases the risk of major or life-threatening bleeds. The ultimate goal of risk stratification is achieving maximum treatment benefit with the lowest risk of complications for each patient based on his/her individual risk for each outcome. How best to balance the various outcomes of interest with their differing safety and effectiveness—and patient preferences for these outcomes—is challenging.

As mentioned previously, independent risk factors for stroke include congestive heart failure, hypertension, older age (≥75 years), diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, and female sex, and several of these factors are associated with AF. These risk factors are the elements that form the $CHADS_2$ and CHA_2DS_2-VASc scores.[14,15] The $CHADS_2$ score ranges from 0 to 6, with increasing scores corresponding to increasing stroke risk, and is easy to calculate and apply in clinical practice. The adjusted annual rates of stroke vary from 1.9 percent in patients with a $CHADS_2$ score of 0 to 18.2 percent in patients with a $CHADS_2$ score of 6.[14] Similarly, the CHA_2DS_2-VASc score ranges from 0 to 9, with increasing scores corresponding to increasing stroke risk, and is easy to calculate and apply in clinical practice.[1] The adjusted annual rates of stroke vary from 1.3 percent in patients with a CHA_2DS_2-VASc score of 1 to 15.2 percent in patients with a CHA_2DS_2-VASc score of 9.[16] A number of studies have examined the appropriate populations and therapies for adequate stroke prophylaxis in AF. The 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society

(AHA/ACC/HRS) Guideline for the Management of Patients with Atrial Fibrillation recommends the use the CHA_2DS_2-VASc score to estimate the stroke risk, and states oral anticoagulation is indicated for patients with a score ≥2 and should be considered for patients with a score of 1 (i.e., with one risk factor).[17]

Use of Anticoagulation Therapy

While anticoagulation for prevention of stroke can be beneficial, it is not without risks. Assessing the risk of bleeding in patients with AF who are being considered for anticoagulation is as important as assessing the risk of stroke. Unfortunately, in clinical practice it is challenging to estimate the tradeoff between stroke risk and risk of bleeding complications from long-term anticoagulation therapy because many risk factors for stroke are also associated with increased risk of bleeding. Prothrombin time is a blood test that measures the time (in seconds) that it takes for a clot to form in the blood. It indirectly measures the activity of five coagulant factors (I, II, V, VII and X) involved in the coagulation cascade. Some diseases and the use of some oral anticoagulation therapy (e.g., vitamin K antagonists [VKAs]) can prolong the prothrombin time. In order to standardize the results, the prothrombin time test can be converted to an international normalized ratio (INR) value, which provides the result of the actual prothrombin time over a normalized value. It has been demonstrated that an INR value of 2 to 3 provides the best tradeoff between preventing ischemic events and causing bleeding. Clinicians use the prothrombin time and INR as clinical tools to guide anticoagulation therapy.

Many factors are potentially related to bleeding risk in general (older age, known cerebrovascular disease, uncontrolled hypertension, history of myocardial infarction or ischemic heart disease, anemia, and concomitant use of antiplatelet therapy in anticoagulated patients). The HAS-BLED score was developed for estimating bleeding risk in patients with chronic AF treated with warfarin and is one of the most widely examined scores for bleeding risk in AF. Scores range from 0 to 9. A score ≥3 indicates a high risk of bleeding with oral anticoagulation and/or aspirin.[18] The HAS-BLED score may aid decisionmaking in clinical practice and is recommended by the 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation.[17]

Based on the original systematic review, however, the strength of evidence was low for the CHA_2DS_2-VASc score and moderate for the HAS-BLED score. After the initial review, several evidence gaps remain, including how best to predict the overall clinical risk of patients (combining both their risk of stroke and their risk of bleeding), how best to use imaging studies to assess thromboembolic risk, and how to increase the dissemination of point-of-care tools to improve risk assessment and guide treatment choices for clinicians.

Therapeutic Options for Stroke Prevention in Atrial Fibrillation

Much of the focus of AF management has been on treatment strategies for stroke prevention. Antithrombotic therapies are the mainstays used to prevent thromboembolic events in patients with AF. VKAs are highly effective for the prevention of stroke in patients with nonvalvular AF. VKAs such as warfarin have been in use for more than 50 years. These compounds create an anticoagulant effect by inhibiting the y-carboxylation of vitamin K-dependent factors (II, VII, IX, and X).[19] In a meta-analysis of 29 randomized controlled trials (RCTs) including 28,000 patients with nonvalvular AF, warfarin therapy led to a 64 percent reduction in stroke (95% CI 49% to 74%) compared with placebo. Even more importantly, warfarin therapy was associated with a 26 percent reduction in all-cause mortality (95% CI 3% to 34%).[20]

Unfortunately, two critical issues regarding stroke prevention in AF remain: (1) despite existing evidence, only a minority of patients who have AF and are at risk for stroke receive optimal treatment for thromboembolic prevention,[21,22] and (2) patients with AF on stroke prophylaxis with warfarin still have higher rates of stroke than non-AF patients,[17] suggesting that gaps still exist in our understanding of risk stratification and treatment. With the introduction of DOACs for stroke prevention, providers, and patients have wider choices available for treatment. Accordingly, identifying high-risk patients and choosing the optimal treatment have become even more complex.

In recent years (since 2009), four large trials comparing direct oral anticoagulants with VKAs have been completed, with a combined sample size of over 71,000 subjects:

- RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy), with approximately 18,000 subjects and evaluating the direct Factor IIa (thrombin) inhibitor dabigatran (2009)[23]
- ROCKET AF (Rivaroxaban Once-daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation), with approximately 14,000 subjects and evaluating the direct factor Xa inhibitor rivaroxaban (2011)[24]
- ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation), with approximately 18,000 subjects and evaluating the direct factor Xa inhibitor apixaban (2011)[25]
- ENGAGE-AF TIMI-48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48), with approximately 21,000 subjects and evaluating the direct Xa inhibitor edoxaban (2013)[26]

At the time of release of this report, all four of these agents (dabigatran, rivaroxaban, apixaban, and edoxaban) have been approved by the U.S. Food and Drug Administration (FDA). Additional anticoagulant therapies in the investigational stage (without FDA approval) include idraparinux. Only the 150mg dose of dabigatran has been approved for atrial fibrillation. Dabigatran 110mg is not approved for stroke prevention in atrial fibrillation in the US. In addition, studies evaluating procedural interventions of stroke prevention are also entering the evidence base.

Table 1 provides an overview of the therapeutic options currently considered for stroke prevention for patients with AF. Following recent recommendations from the European Society of Cardiology on the management of AF,[27] antiplatelet agents are no longer recommended for stroke prevention in AF. Because the ACC/AHA/HRS Guidelines have not yet been updated with a similar recommendation,[17] we include antiplatelet agents as a comparator of interest but do not include it in the table.

Table 1. Major therapeutic options for stroke prevention in atrial fibrillation

Treatment	Description
Vitamin K antagonists (VKA)	VKAs such as warfarin, have been the standard-of-care for stroke prevention in patients with atrial fibrillation (AF) for decades. However, it is often difficult to achieve and maintain the international normalized ratio (INR), a measure of anticoagulation, within a therapeutic range (2.0-3.0), and multiple food and drug interactions make the management of VKAs very difficult. In addition, the need to monitor the international normalized ratio (INR) on a regular basis can discourage some patients from taking VKAs. These important challenges associated with VKA treatment have ignited the interest in developing novel therapeutic options, with better efficacy and safety profiles.
Direct oral anticoagulants (DOACs)	Currently, there are four DOACs approved for stroke prevention in patients with nonvalvular AF: dabigatran (thrombin inhibitor), apixaban, rivaroxaban, and edoxaban (all factor Xa inhibitors). These agents have been studied in large randomized trials. With the availability of these drugs for clinical use, additional knowledge is needed to help inform decisionmaking related to whether these medications are safe and effective in patient populations not included or not well represented in clinical trials and to better understand the relative risks and benefits of these drugs based on individual patient characteristics.
Procedural interventions	Procedural interventions for stroke prophylaxis have emerged and are growing in their use. For example, left atrial appendage (LAA) occlusive devices are an alternative treatment strategy used to prevent blood clot formation in patients with AF. Although evidence is sparse, for patients with AF who are elderly (at high risk for falls), have a prior bleeding history, are pregnant, and/or noncompliant, LAA occlusion may be a better stroke prevention strategy.

Abbreviations: AF=atrial fibrillation; DOAC=direct oral anticoagulant; INR=international normalized ratio; LAA=left atrial appendage; VKA=vitamin K antagonist

Scope and Key Questions

Scope of the Review

There are several areas of insufficient evidence and uncertainty within the field of stroke prevention in patients with AF:

- The comparative diagnostic accuracy and impact on clinical decisionmaking of available clinical and imaging tools for predicting thromboembolic and bleeding risk in patients with AF are uncertain.
- There is a lack of information to guide decisions regarding the best specific anticoagulant (versus warfarin) for a given patient.
- The safety and effectiveness of DOACs are unclear in patients not included or not well-represented in randomized controlled trials (e.g., patients with moderate to severe chronic kidney disease (CKD) with estimated glomerular filtration rate [GFR]<60, valvular heart disease, extremes of body mass index [BMI], older age, women, multiple comorbidities, and a history of bleeding or frequent falls).
- The relative safety and effectiveness of DOACs as compared to left atrial appendage (LAA) occlusion devices are uncertain.

This systematic review was commissioned by the Patient-Centered Outcomes Research Institute (PCORI) to update the report published in 2013 that evaluated questions related to stroke prevention in patients with AF and atrial flutter.[13] Given the evidence that has emerged since the publication of the 2013 report, this review focuses on updating and expanding on that report in three key areas: evaluating the accuracy and utility of imaging tools used to prevent stroke and clot risk, evaluating the accuracy and utility of clinical tools used to predict bleeding risk, and exploring the comparative safety and effectiveness of various pharmacologic interventions used to prevent blood clots in patients with nonvalvular atrial fibrillation. In addition, this review explores the strengths and weaknesses of shared decisionmaking tools available to aid patients and clinicians in selecting an intervention to prevent stroke.

To increase applicability to the U.S. setting, we restricted our review to interventions available in the United States. For each Key Question (KQ), we further considered whether the comparative safety and effectiveness of the interventions evaluated differ among specific patient subgroups of interest, including patients with comorbid conditions, such as dementia, or renal or hepatic failure; patients with multiple coexisting conditions (e.g., combinations of hypertension, diabetes, congestive heart failure, coronary artery disease, and high cholesterol); patients with prior stroke (by type of event); patients with prior bleed (by type of bleed); patients in the therapeutic range (versus those not in range); type of AF (paroxysmal, persistent, and permanent); patients stratified by age; pregnant patients; patients stratified by race/ethnicity; and patients who are noncompliant with treatment.

Key Questions

The KQs for this systematic review update derive from the original review and have been updated based on stakeholder feedback obtained by PCORI. These questions were constructed using the general approach of specifying the Populations, Interventions, Comparators, Outcomes, Timings, and Settings of interest (PICOTS; see the section on "Inclusion and Exclusion Criteria" in the Methods chapter for details).

The KQs considered in this CER are:

- **KQ 1.** In patients with nonvalvular atrial fibrillation, what are the comparative diagnostic accuracy and impact on clinical decisionmaking (diagnostic thinking, therapeutic efficacy, and patient outcome efficacy) of available clinical and imaging tools and associated risk factors for predicting thromboembolic risk?
- **KQ 2.** In patients with nonvalvular atrial fibrillation, what are the comparative diagnostic accuracy and impact on clinical decisionmaking (diagnostic thinking, therapeutic efficacy, and patient outcome efficacy) of clinical tools and associated risk factors for predicting bleeding events?
- **KQ 3.** What are the comparative safety and effectiveness of specific anticoagulation therapies, antiplatelet therapies, and procedural interventions for preventing thromboembolic events:
    (a) In patients with nonvalvular atrial fibrillation?
    (b) In specific subpopulations of patients with nonvalvular atrial fibrillation?

Contextual Question (CQ)

Contextual Questions are not systematically reviewed but instead use a "best evidence" approach prioritizing evidence based on study design, reporting, and relevance. Information about the

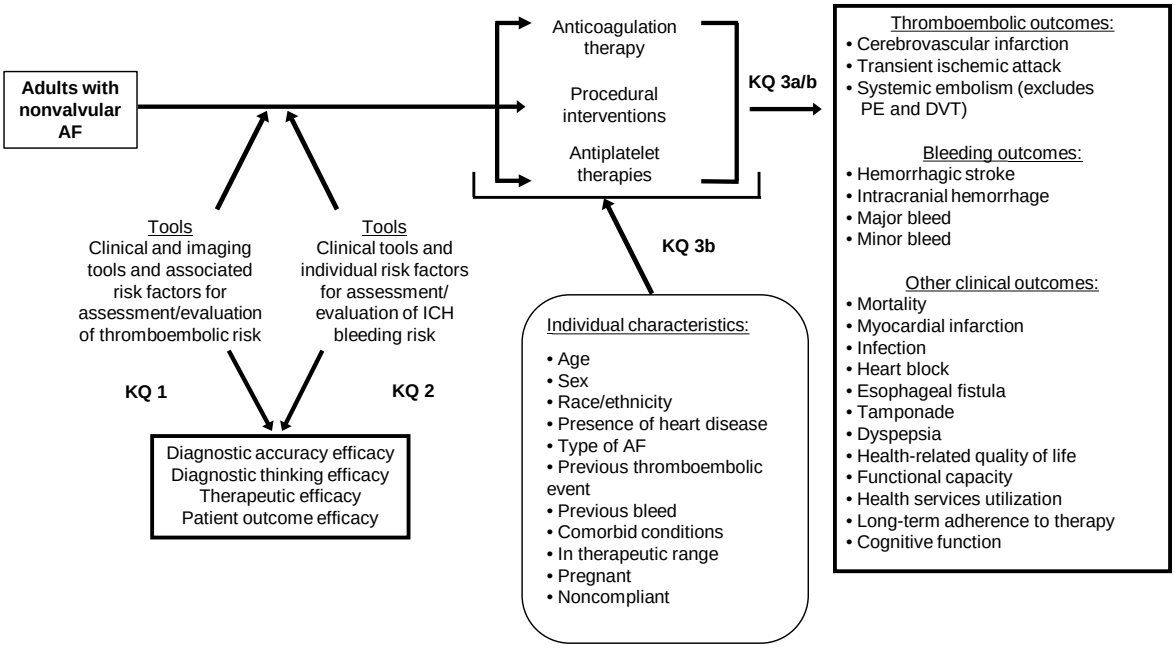
contextual question may be included as part of the introduction or discussion section and related as appropriate to the systematic review.

- **CQ:** What are currently available shared decisionmaking tools for patient and provider use for stroke prophylaxis in atrial fibrillation, and what are their relative strengths and weaknesses?

Analytic Framework

Figure 1 depicts the analytic framework for this project.

Figure 1. Analytic framework



Abbreviations: AF=atrial fibrillation; DVT=deep vein thrombosis; KQ=Key Question; ICH=intracranial hemorrhage; PE=pulmonary embolism

This figure depicts the KQs within the context of the PICOTS described elsewhere in this document. The patient population of interest is adults with nonvalvular AF. Interventions of interest are clinical and imaging tools for predicting thromboembolic risk (KQ 1); clinical tools and individual risk factors for predicting intracranial hemorrhage bleeding risk (KQ 2); and anticoagulation therapies, procedural interventions, and antiplatelet therapies in patients with nonvalvular AF (KQ 3a) and in specific subpopulations of patients with nonvalvular AF (e.g., age, presence of heart disease, type of AF, previous thromboembolic event, previous bleed, comorbid conditions, patients in therapeutic range, pregnant patients, and noncompliant patients) (KQ 3b). Outcomes of interest are thromboembolic events (cerebrovascular infarction; TIA; and systemic embolism, excluding pulmonary embolism and deep vein thrombosis); bleeding outcomes (hemorrhagic stroke, intracranial hemorrhage [intracerebral hemorrhage, subdural hematoma], major bleed, and minor bleed); other clinical outcomes (mortality, myocardial infarction, infection, heart block, esophageal fistula, tamponade, dyspepsia [upset stomach], health-related quality of life, healthcare utilization, and adherence to therapy); and efficacy of the

risk assessment tools (diagnostic accuracy, diagnostic thinking, therapeutic, and patient outcome efficacy).

Organization of This Report

The remainder of the report details our methodology and presents the results of our literature synthesis, with summary tables and strength of evidence grading for major comparisons and outcomes. In the discussion section, we offer our conclusions, summaries of findings, and other information that may be relevant to translating this work for clinical practice and future research.

Appendixes provide further details on our methods and the studies we assessed, as follows:

- Appendix A. Exact Search Strings
- Appendix B. Data Abstraction Elements
- Appendix C. List of Included Studies
- Appendix D. List of Excluded Studies
- Appendix E. Key to Included Primary and Companion Articles
- Appendix F. Characteristics of Included Studies
- Appendix G. Outcomes for Specific Subgroups of Interest: Detailed Study Findings
- Appendix H. PCORI Methodology Standards Checklist
- Appendix I. Expert Guidance and Review

Methods

The methods for this Comparative Effectiveness Review (CER) follow those suggested in the Agency for Healthcare Research and Quality (AHRQ) *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (hereafter referred to as the *Methods Guide*)[28] and *Methods Guide for Medical Test Reviews* (hereafter referred to as the *Medical Test Guide*).[29] Certain methods map to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.[30]

Review Protocol

This systematic review is an update of an earlier report published in 2013 which evaluated questions related to stroke prevention in patients with atrial fibrillation (AF) and atrial flutter.[13] Given the uncertainties which remained within the limitations of the available evidence, and the new data which have emerged since that report, an update of the systematic review was commissioned.

The Patient-Centered Outcomes Research Institute (PCORI) convened two multi-stakeholder virtual workshops in December 2016 and January 2017 to gather input from end users of research and clinical, content, and methodological experts on scoping for the updated review, prioritization of Key Questions, a discussion of changes in the evidence base since the prior review, and emerging issues in AF. The protocol for this update was developed based upon findings from the January 2017 workshop, and builds upon Key Questions (KQs) 1-3 from the original report. The finalized protocol for this systematic review update is posted on the Effective Healthcare (EHC) Web site (www.effectivehealthcare.ahrq.gov). The PROSPERO registration is CRD42017069999.

Literature Search Strategy

Search Strategy

To identify published literature relevant to the KQs, we searched PubMed®, Embase®, and the Cochrane Database of Systematic Reviews (CDSR), limiting the search to studies published from January 1, 2000 to February 14, 2018. Studies published prior to 2011 were incorporated from our original systematic review. The updated search then specifically targeted evidence from August 1, 2011, to February 14, 2018. The databases were selected based on the approaches utilized in the original systematic review. An experienced search librarian guided all searches. Exact search strings are provided in Appendix A. We supplemented the electronic searches with a manual search of citations from a set of key primary and systematic review articles.[31-85] The reference list for identified pivotal articles was hand-searched and cross-referenced against our database, and additional relevant manuscripts were retrieved. All citations were imported into an electronic bibliographical database (EndNote® Version X7; Thomson Reuters, Philadelphia, PA). While the draft report is under peer review, we will update the search. We will include any eligible studies identified either during that search or through peer or public reviewer recommendations in the final report.

Additionally, our findings from the literature identified in this update were combined with the findings for the KQs of interest from the original review (KQs 1-3). Modifications made to the PICOTS (Populations, Interventions, Comparators, Outcomes, Timings, and Settings of interest) criteria for the KQs considered in this update broadened aspects of both the

interventions and outcomes of interest. We therefore reviewed the citations which were excluded from the previous systematic review at the full-text level because they did not include either outcomes of interest or interventions of interest (N=190)[13] to determine which, if any, studies should now be included as part of the update. Identified eligible studies were incorporated into this report.

To identify relevant gray literature, the EPC Scientific Resource Center notified stakeholders that the EPC was interested in receiving information that the stakeholders would consider relevant to the KQs. Solicitations included a notice posted in the Federal Register and on the AHRQ Effective Health Care Web site. We also searched ClinicalTrials.gov for two purposes: (1) to identify relevant articles from completed studies that may not have appeared in our other search strategies and (2) as one mechanism to ascertain publication bias in recent studies. For the latter goal, we sought to identify completed but unpublished studies that could impact the findings of the review. Search terms used for ClinicalTrials.gov are provided in Appendix A. We also explored the possibility of publication bias specifically in our quantitative synthesis of the included literature through meta-analysis techniques such as a funnel plot when appropriate.

To identify key literature to address the Contextual Question (CQ), we designed a specific search string for PubMed (provided in Appendix A). We also considered studies that were identified as addressing the KQs, as well as reviews captured by our search that discuss currently available shared decisionmaking tools for stroke prophylaxis in atrial fibrillation. CQs are not systematically reviewed and use a "best evidence" approach. The CQ is discussed within the context of the Discussion of this report.

Inclusion and Exclusion Criteria

The PICOTS criteria used to screen articles for inclusion/exclusion at both the title-and-abstract and full-text screening stages are detailed in Table 2.

Table 2. Inclusion and exclusion criteria

PICOTS Element	Inclusion Criteria	Exclusion Criteria
Populations	• Adults (≥18 years of age) • Patients with nonvalvular AF (including atrial flutter): o Paroxysmal AF (recurrent episodes that self-terminate in less than 7 days) o Persistent AF (recurrent episodes that last more than 7 days until stopped) o Permanent AF (continuous) o Patients with AF who experience acute coronary syndrome • Subgroups of interest for KQ 3 include (but are not limited to): o Age o Sex o Race/ethnicity o Presence of heart disease o Type of AF o Comorbid conditions (such as moderate to severe chronic kidney disease (eGFR<60), dementia) o When in therapeutic range o When non-adherent to medication o Previous thromboembolic event o Previous bleed o Pregnant	• Patients who have known reversible causes of AF (including but not limited to postoperative, hyperthyroidism) • All subjects are <18 years of age, or some subjects are under <18 years of age but results are not broken down by age
Interventions	KQ 1: Clinical and imaging tools and associated risk factors for assessment/evaluation of thromboembolic risk: • Clinical tools include: o $CHADS_2$ score o CHA_2DS_2-VASc score o Framingham risk score o ABC stroke risk score • Individual risk factors include: o INR level o Duration and frequency of AF o Age o Prior stroke o Type of AF o Cognitive impairment o Falls risk o Presence of heart disease o Presence and severity of CKD o DM o Sex o Race/ethnicity o Cancer o HIV • Imaging tools include: o Transthoracic echo (TTE) o Transesophageal echo (TEE) o CT scans o Cardiac MRIs	None

PICOTS Element	Inclusion Criteria	Exclusion Criteria

	KQ 2: Clinical tools and individual risk factors for assessment/evaluation of intracranial hemorrhage bleeding risk:
	• Clinical tools include:
	  o HAS-BLED score
	  o $HEMORR_2HAGES$ score
	  o ATRIA score
	  o Bleeding Risk Index
	  o ABC Bleeding Risk score
	• Individual risk factors include:
	  o INR level
	  o Duration and frequency of AF
	  o Age
	  o Prior stroke
	  o Type of AF
	  o Cognitive impairment
	  o Falls risk
	  o Presence of heart disease
	  o Presence and severity of CKD
	  o DM
	  o Sex
	  o Race/ethnicity
	  o Cancer
	  o HIV
	
	KQ 3: Anticoagulation, antiplatelet, and procedural interventions:
	• Anticoagulation therapies:
	  o VKAs: Warfarin
	  o Newer anticoagulants (direct oral anticoagulants [DOACs])
	  ▪ Direct thrombin Inh-DTI: Dabigatran
	  ▪ Factor Xa inhibitors:
	  • Rivaroxaban
	  • Apixaban
	  • Edoxaban
	• Antiplatelet therapies:
	  o Clopidogrel
	  o Aspirin
	  o Dipyridamole
	  o Combinations of antiplatelets
	  ▪ Aspirin+dipyridamole
	• Procedures:
	  o Surgeries (e.g., left atrial appendage occlusion, resection/removal)
	  o Minimally invasive (e.g., Atriclip, LARIAT)
	  o Transcatheter (WATCHMAN™, AMPLATZER™, PLAATO)	

PICOTS Element	Inclusion Criteria	Exclusion Criteria
Comparators	• KQ 1: Other clinical or imaging tools listed for assessing thromboembolic risk • KQ 2: Other clinical tools listed for assessing bleeding risk • KQ 3: Other anticoagulation therapies, antiplatelet therapies, or procedural interventions for preventing thromboembolic events	For KQ 3, studies that did not include an active comparator
Outcomes	• Assessment of clinical and imaging tool efficacy for predicting thromboembolic risk and bleeding events (KQs 1 and 2): o Diagnostic accuracy efficacy o Diagnostic thinking efficacy (defined as how using diagnostic technologies help or confirm the diagnosis of the referring provider) o Therapeutic efficacy (defined as how the intended treatment plan compares with the actual treatment pursued before and after the diagnostic examination) o Patient outcome efficacy (defined as the change in patient outcomes as a result of the diagnostic examination) Patient-centered outcomes for KQ 3 (and for KQ 1 [thromboembolic outcomes] and KQ 2 [bleeding outcomes] under "Patient outcome efficacy"): • Thromboembolic outcomes: o Cerebrovascular infarction o TIA o Systemic embolism (excludes PE and DVT) • Bleeding outcomes: o Hemorrhagic stroke o Intracranial hemorrhage (intracerebral hemorrhage, subdural hematoma) o Major and minor bleed (stratified by type and location)[a] • Other clinical outcomes: o Mortality ▪ All-cause mortality ▪ Cardiovascular mortality o Myocardial infarction o Infection o Heart block o Esophageal fistula o Cardiac tamponade o Dyspepsia o Health-related quality of life o Functional capacity o Health services utilization (e.g., hospital admissions, outpatient office visits, ER visits, prescription drug use) o Long-term adherence to therapy	Study does not include any outcomes of interest

PICOTS Element	Inclusion Criteria	Exclusion Criteria
	o Cognitive function	
Timing	• Timing of followup not limited	None
Setting	• Inpatient and outpatient	Studies which were conducted exclusively in Asia, Africa, or the Middle East[b]
Study design	• Original peer-reviewed data • N ≥20 patients • RCTs, prospective and retrospective observational studies	• Not a clinical study (e.g., editorial, nonsystematic review, letter to the editor, case series, case reports) • Abstract-only or poster publications; articles that have been retracted or withdrawn • Because studies with fewer than 20 subjects are often pilot studies or studies of lower quality,[86,87] we excluded them from our review • Systematic reviews, meta-analyses, or methods articles (used for background and component references only) • Observational studies that are only relevant to KQ 3 (treatment), have fewer than 1000 patients, and only target pharmacological interventions[c]
Publications	• English-language publications • Published on or after January 1, 2000	• Non–English-language publications[d] • Relevant systematic reviews, meta-analyses, or methods articles (will be used for background only)

[a]Different classification systems are used for bleeding (e.g., International Society on Thrombosis and Haemostasis [ISTH], Global Utilization Of Streptokinase And Tpa For Occluded Arteries [GUSTO], and Thrombolysis In Myocardial Infarction [TIMI]). Systems of classification used across studies vary. We report data based on the studies' classification system(s) and incorporate this information into any quantitative synthesis of the data. We did not expect studies to provide enough granular data to classify the events ourselves.

[b]This criterion excludes areas of the world where clinical practice differs significantly from standards in the United States.

[c]Observational studies with fewer than 1000 patients targeting only pharmacological interventions were considered by the investigators to be insufficiently powered to modify decisionmaking relative to other evidence available to be searched. Note this exclusion does not restrict observational studies that target nonpharmacologic interventions where evidence is more sparse and smaller studies may have a larger impact on the review findings.

[d]Due to (1) the high volume of literature available in English language publications, (2) the focus of our review on applicability to populations in the United States, and (3) the scope of our KQs, it is the opinion of the investigators that the resources required to translate non-English articles was not justified by the low potential likelihood of identifying relevant data unavailable from English-language sources.

Abbreviations: ABC=age, biomarkers, clinical history; AF=atrial fibrillation; ATRIA=age, female, diabetes, congestive heart failure, hypertension, proteinuria, eGFR <45 or ESRD; $CHADS_2$=congestive heart failure, hypertension, age >75, diabetes, stroke/TIA; CHA_2DS_2-VASc=congestive heart failure/left ventricular ejection fraction ≤40%, hypertension, age ≥75, diabetes, stroke/TIA/thromboembolism, vascular disease, age 65-74, sex; CKD=chronic kidney disease; CT=computed tomography;

DM=diabetes mellitus; DTI=direct thrombin inhibitor; DVT=deep vein thrombosis; eGFR=estimated glomerular filtration rate; ER=emergency room; ESRD=end-stage renal disease; HAS-BLED=hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly (>65), drugs/alcohol concomitantly; HEMORR$_2$HAGES=hepatic or renal disease, ethanol (alcohol) abuse, malignancy, older (>75), reduced platelet count or function, rebleeding risk, hypertension (uncontrolled), anemia, genetic factors, excessive fall risk, stroke history; HIV=human immunodeficiency virus; INR=international normalized ratio; KQ=Key Question; MRI=magnetic resonance imaging; PE=pulmonary embolism; PICOTS=Populations, Interventions, Comparators, Outcomes, Timing, Settings; PLAATO=Percutaneous Left Atrial Appendage Transcatheter Occlusion; RCT=randomized controlled trial; TIA=transient ischemic attack; VKA=Vitamin K antagonists

Study Selection

Using the prespecified inclusion and exclusion criteria described in Table 2, two investigators independently reviewed titles and abstracts for potential relevance to the KQs. Articles included by either reviewer underwent full-text screening. At the full-text review stage, paired researchers independently reviewed the articles and indicated a decision to "include" or "exclude" the article for data abstraction. When the two reviewers arrived at different decisions about whether to include or exclude an article, they reconciled the difference through review and discussion, or through a third-party arbitrator. Articles meeting eligibility criteria were included for data abstraction. At random intervals during screening, quality checks by senior team members were made to ensure that screening and abstraction were consistent with inclusion/exclusion criteria and abstraction guidelines. All screening decisions were made and tracked in a Distiller SR software program (Evidence Partners Inc, Manotick, ON, Canada).

Appendix C provides a list of all articles included for data abstraction. Appendix D provides a list of articles excluded at the full-text screening stage, with reasons for exclusion.

To inform the CQ, we searched the studies included to address the KQs as well as reviews captured by our search that discuss currently available shared decisionmaking tools for stroke prophylaxis in atrial fibrillation. The CQ is discussed within the context of the Discussion of the report.

Data Extraction

The research team created data abstraction forms and evidence table templates for abstracting data for each KQ. Based on clinical and methodological expertise, a pair of investigators was assigned to abstract data from each eligible article. One investigator abstracted the data, and the second reviewed the completed abstraction form alongside the original article to check for accuracy and completeness. Disagreements were resolved by consensus, or by obtaining a third reviewer's opinion if consensus could not be reached. Articles which represented evidence from the same overall study were linked to avoid duplication of patient cohorts.

We designed the data abstraction forms to collect the data required to evaluate the specified eligibility criteria for inclusion in this review, as well as demographic and other data needed for determining outcomes (intermediate, final, and adverse events outcomes). We paid particular attention to describing the details of diagnostic tools (e.g., instrument version, administration mode), details of the treatment (e.g., dosing, co-interventions, methods of procedural therapies), patient characteristics (e.g., etiology of AF, history of prior bleed or stroke) and study design (e.g., RCT versus observational) that may be related to outcomes. In addition, we described comparators carefully, as treatment standards may have changed during the period covered by this review. The safety outcomes were framed to help identify adverse events, including those from drug therapies and those resulting from procedural complications. Data necessary for assessing quality and applicability, as described in the *Methods Guide*,[28] were abstracted. Before the data abstraction form templates were used, they were pilot-tested with a sample of included

articles to ensure that all relevant data elements were captured and that there was consistency/reproducibility between abstractors. Forms were revised as necessary before full abstraction of all included articles. Some outcomes were reported only in figures. In these instances, we used the web-based software, EnGauge Digitizer (http://digitizer.sourceforge.net/) to convert graphical displays to numerical data. Appendix B provides a detailed listing of the elements included in the data abstraction forms. Final abstracted data will be uploaded to the Systematic Review Data Repository (SRDR) per EPC requirements.

Quality (Risk of Bias) Assessment of Individual Studies

We assessed methodological quality, or risk of bias, for each individual study using tools specific to the study's characteristics. For all studies, we used the following strategy: (1) classify the study design, (2) apply predefined criteria for appraisal of quality, and (2) arrive at a summary judgement of the study's quality. For studies assessing diagnostic accuracy, we used the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool, following guidance for use of that tool to arrive at an overall judgement as defined in Table 3.[88]

Table 3. Definitions of overall quality assessment ratings for diagnostic studies

Rating	Description
Low risk of bias	No major features that risk biased results. Randomized controlled trials are considered a high-quality study design, but studies that include consecutive patients representative of the intended sample for whom diagnostic uncertainty exists may also meet this standard. A "low risk" study avoids the multiple biases to which medical test studies are subject (e.g., use of an inadequate reference standard, verification bias), and key study features are clearly described, including the comparison groups, outcomes measurements, and characteristics of patients who failed to have actual state (diagnosis or prognosis) verified.
Medium risk of bias	Susceptible to some bias, but flaws not sufficient to invalidate the results. The study does not meet all the criteria required for a rating of low risk, but no flaw is likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems.
High risk of bias	Significant flaws imply biases of various types that may invalidate the results. The study has significant biases determined a priori to be major or "fatal" (i.e., likely to make the results either uninterpretable or invalid).

For nondiagnostic studies, we used the Cochrane Risk of Bias tool for randomized studies[89,90] and the Risk Of Bias In Nonrandomised Studies of Interventions (ROBINS-I) tool for observational studies.[91,92] We rated each study as being of good, fair, or poor quality based on its adherence to well-accepted standard methodologies. For each study, one investigator made an assessment of methodological quality which was then reviewed by a second investigator; disagreements were resolved by consensus or by a third investigator if agreement was not reached.

Quality assessment was outcome-specific, such that a given study that analyzed its primary outcome well but did an incomplete analysis of a secondary outcome could be assigned a different quality grade for each of the two outcomes. We applied this outcome-specific quality assessment to groups of outcomes that have lower risk of detection bias (e.g., mortality) and those at higher risk of detection bias (e.g., quality of life outcomes). Studies of different designs were evaluated within the context of their respective designs.

To indicate the summary judgment of the quality of individual nondiagnostic studies, we used the summary ratings of good, fair, or poor based on the classification scheme presented in Table 4.

Table 4. Definitions of overall quality assessment ratings for nondiagnostic studies

Quality Rating	Description
Good (low risk of bias)	These studies had the least bias, and the results were considered valid. These studies adhered to the commonly held concepts of high quality, including the following: a clear description of the population, setting, approaches, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytical methods and reporting; no reporting errors; a low dropout rate; and clear reporting of dropouts.
Fair (medium risk of bias)	These studies were susceptible to some bias, but not enough to invalidate the results. They did not meet all the criteria required for a rating of good quality because they had some deficiencies, but no flaw was likely to cause major bias. The study may have been missing information, making it difficult to assess limitations and potential problems.
Poor (high risk of bias)	These studies had significant flaws that might have invalidated the results. They had serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.

We did not formally re-evaluate quality ratings for articles considered in this report that were included within the original systematic review. The quality assessments performed in the original review were based on QUADAS-2 for KQs 1 and 2, and for KQ 3, on an approach described in the *Methods Guide*[28] that used a similar strategy of (1) classifying the study design, (2) applying predefined criteria for quality and critical appraisal, and (3) arriving at a summary judgment of the study's quality. Criteria considered for each study type were derived from core elements described in the *Methods Guide* (details available in the prior report).[13] When we identified additional publications describing results from a study that was included within the prior review, we reviewed the new article(s) in the context of the prior quality rating to determine if any adjustment to the prior quality rating was warranted. Quality ratings for individual studies are presented in Appendix F.

Data Synthesis

We began by summarizing key features of the included studies for each KQ. To the degree that data were available, we abstracted information on study design; patient characteristics; clinical settings; diagnostic tools; and intermediate, final, and adverse event outcomes. We ordered our findings by treatment or diagnostic comparison, and then within these comparisons by outcome, with long-term final outcomes emphasized.

We reviewed and highlighted studies using a hierarchy-of-evidence approach. The best evidence available (normally RCTs) was the focus of our synthesis for each KQ. If high quality evidence was not available, we described any lower quality evidence we were able to identify, but we underscored the elements that influenced our assessment of lower quality and the uncertainties in our findings. We assessed whether the inclusion of lower quality studies would change any of our conclusions and performed sensitivity analyses excluding such evidence where appropriate.

We determined the feasibility of completing a quantitative synthesis (i.e., meta-analysis) based on the volume of relevant literature, conceptual homogeneity of the studies in terms of study population and outcomes, and completeness of the reporting of results. We grouped interventions by prediction tool (KQs 1 and 2) and drug class or procedure (KQ 3), when

appropriate. We required three appropriate studies to consider meta-analysis of intervention studies and three to consider meta-analysis of observational diagnostic test studies. Given concerns about quality, we did not include observational studies in quantitative synthesis that did not use propensity matching for controls or similar methods.

When at least three comparable studies reported the same outcome, we used the R statistical package (version 3.1.2) (The R Foundation), with the "metafor" meta-analysis library (version 1.9-7) to synthesize the available evidence quantitatively. We used the random-effects DerSimonian and Laird estimator[93] to generate summary values. In addition, we used the Knapp–Hartung approach to adjust the standard errors of the estimated coefficients. We explored heterogeneity using graphical displays and test statistics (Q and I^2 statistics), while recognizing that the ability of statistical methods to detect heterogeneity may be limited. We perform quantitative and qualitative syntheses separately by study type and discuss their consistency qualitatively. When we were able to calculate hazard ratios (HRs), we assumed that a HR between 0.8 and 1.2 with a narrow confidence interval that also crossed 1.0 suggested no clinically significant difference between treatment strategies; in such cases, we describe the treatment strategies being compared as having "comparable efficacy." For some outcomes, study quality or other factors affected comparability; these exceptions are explained on a case-by-case basis.

For KQ 1 and KQ 2, we synthesized available c-statistics which quantify the prediction/discrimination ability of the studied tools. Since these tools are not binary, summary receiver operating characteristic (ROC) curves were not considered as would have been possible for binary diagnostic tests. The c-statistics were pooled by considering their estimated values (point estimates) and confidence intervals, and the "Generic point estimates" effect specification option in the Comprehensive Meta-Analysis software. For a clinical prediction rule, we assumed that a c-statistic <0.6 had no clinical value, 0.6–0.7 had limited value, 0.7–0.8 had modest value, and >0.8 has prediction adequate for genuine clinical utility.[94] Of note, a risk score may have a statistically significant association with a clinical outcome, but the relationship may not be discriminated enough to allow clinicians to accurately and reproducibly separate patients who will and will not have the outcome. In addition, the c-statistic value is almost always higher when assessing prediction accuracy in the patient data set used to develop the model than in independent sets of patients; we therefore indicate when studies being discussed were actually used to develop the models they describe.

For KQ 3 we focus on the statistical significance of our findings for the individual outcomes but do not make recommendations on whether specific differences are clinically relevant.

We hypothesized that the methodological quality of individual studies, study type, the characteristics of the comparator, and patients' underlying clinical presentation would be associated with the intervention effects, causing heterogeneity in the outcomes. Where there were sufficient studies, we performed subgroup analyses and/or meta-regression analyses to examine these hypotheses.

Strength of the Body of Evidence

We identified a set of comparisons and outcomes for strength of evidence grading with the goal of selecting outcomes of greatest importance for decisionmaking. We rated strength of evidence using the approach described in the *Methods Guide*.[28,95] and *Medical Test Guide.*[29] We graded the strength of evidence for each outcome individually; thus, the strength of evidence for

two separate outcomes in a given study may be graded differently. These grades are presented in the strength of evidence tables in the Discussion section of the report.

Briefly, the approach requires assessment of five domains: study limitations (previously named risk of bias), consistency, directness, precision, and reporting bias, which includes publication bias, outcome reporting, and analysis reporting bias. Note that reporting bias was not possible to assess for the diagnostic studies. The five domains were considered qualitatively, and a summary rating of "high," "moderate," or "low" strength of evidence was assigned after discussion by two reviewers. In some cases, high, moderate, or low ratings were impossible or imprudent to make—for example, when no evidence was available or when evidence on the outcome was too weak, sparse, or inconsistent to permit any conclusion to be drawn. In these situations, a grade of "insufficient" was assigned. The four-level rating scale is described in Table 5. Outcomes based on evidence from RCTs or observational studies started with a "high" or "low" strength of evidence rating, respectively, and were downgraded for inconsistency, indirectness, or imprecision. Studies of risk prediction outcomes started with moderate strength of evidence.[96] We assumed that outcomes based on only 1 study should not be downgraded for lack of consistency if the study included more than 1,000 patients. Intention-to-treat (ITT) findings were evaluated when available and form the basis of our strength of evidence ratings. When ITT findings were not available and only on-treatment findings were reported, our confidence in the stability and precision of our findings was reduced, and therefore the related strength-of-evidence rating was lowered. Finally, when outcomes were assessed by RCTs and observational studies, we focused our strength of evidence rating on the findings from the RCTs and then increased or decreased the strength of evidence rating depending on whether findings from the observational studies were consistent or inconsistent with those from the RCTs. We provided greatest weight to findings from large RCTs.

Table 5. Definition of strength of evidence grades

Rating	Definition
High	We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable, i.e., another study would not change the conclusions.
Moderate	We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
Low	We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
Insufficient	We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

Applicability

We assessed applicability across the KQs using the method described in the *Methods Guide*.[28,97] In brief, we used the PICOTS format to organize information relevant to applicability. The most important applicability concern is whether the outcomes observed for any individual study, with its specific patient population and methods of implementing interventions, can be confidently extrapolated to a broader context. Differences in intervention methods or study population characteristics (e.g., age, comorbidities) can affect the rates of events observed in both control and intervention groups, and may limit the generalizability of the findings. Specific

criteria considered in applicability assessments are listed in Appendix B. We used these data to evaluate applicability to clinical practice, paying special attention to study eligibility criteria, demographic features of the enrolled population in comparison to the target population, characteristics of the intervention used in comparison with care models currently in use, and clinical relevance and timing of the outcome measures. We summarized issues of applicability qualitatively.

Peer Review and Public Commentary

Experts in the fields of internal medicine, cardiovascular medicine, electrophysiology, hematology, geriatric medicine, clinical trial and systematic review methodology, health services research, and patient advocates were invited to provide external peer review of the draft report. AHRQ, PCORI, and an associate editor also provided comments. In addition, the draft report was posted on the AHRQ EHC Web site from February 5, 2018, to March 22, 2018, to elicit public comment. We have addressed all reviewer comments and have documented our responses in a disposition of comments report that will be made available 3 months after the Agency posts the final systematic review on the EHC Web site. A list of peer reviewers submitting comments on the draft report is provided in the front matter of this report.

Results

Introduction

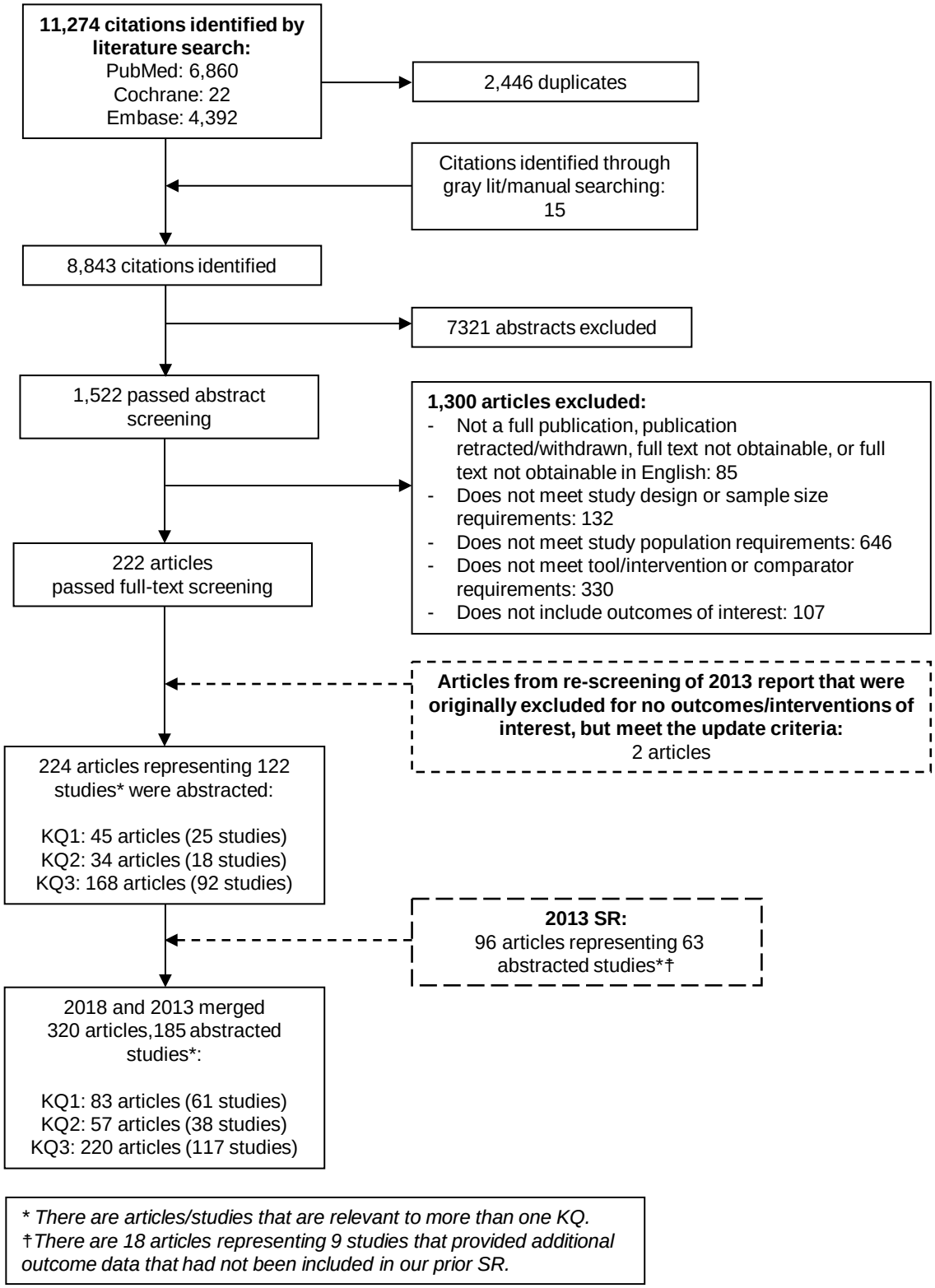
In what follows, we begin by describing the results of our literature searches. We then provide a brief description of the included studies. The remainder of the chapter is organized by Key Question (KQ). Under each of the three KQs, we begin by listing the key points of the findings, followed by a brief description of included studies and a detailed synthesis of the evidence. The detailed syntheses are organized first by risk stratification strategy or treatment comparison and then by outcome. We conducted quantitative syntheses where possible, as described in the Methods chapter.

Results of Literature Searches

Figure 2 depicts the flow of the 2018 search update through the literature search and screening process. In this 2018 search of PubMed®, Embase®, and CDSR, we retrieved 11,274 additional unique citations. Manual searching of gray literature databases, bibliographies of key articles, and information received through requests for scientific information packets identified 15 additional citations, for a total of 8,843 citations. After applying inclusion/exclusion criteria at the title-and-abstract level, 1,522 full-text articles were retrieved and screened. Of these, 1,300 were excluded at the full-text screening stage, leaving 222 articles for data abstraction. In addition to these new articles, we reviewed articles that were previously excluded in the 2013 Agency for Healthcare Research and Quality report for outcomes of interest. Out of the 190 articles excluded for outcomes or interventions from the 2013 report, we identified 2 studies which now met our expanded inclusion criteria and therefore that could be added to this update bringing the total to 224 articles for abstraction. These 224 articles described 122 unique studies. The relationship of the studies identified as part of our 2018 search to the review questions is as follows: 25 studies relevant to KQ 1, 18 studies relevant to KQ 2, and 92 studies relevant to KQ 3. When we merge these results with the includes from the 2013 report and consider duplicate references and companion articles it totals to 320 articles representing 185 studies and is broken down as follows: 61 studies relevant to KQ 1, 38 studies relevant to KQ 2, and 117 studies relevant to KQ 3 (some studies were relevant to more than one KQ).

Appendix C provides a detailed listing of included articles. Appendix D provides a complete list of articles excluded at the full-text screening stage, with reasons for exclusion. Appendix E provides a "study key" table listing the primary and companion publications for the many study groupings throughout this report.

Figure 2. Literature flow diagram



Abbreviation: KQ=Key Question; SR=systematic review

Description of Included Studies

Overall, we included 185 studies represented by 320 publications: 61 studies were relevant to KQ 1, 38 studies to KQ 2, and 117 studies to KQ 3. In the 2018 update, we focused on studies conducted in areas of the world where clinical practice are similar to practices in the United States. Therefore, we excluded studies that were conducted exclusively in Asia, Africa, South America, or the Middle East. Out of the 185 studies, there were 13 trials that conducted research in multiple countries around the globe (7%). The rest of the studies were conducted in continental Europe or United Kingdom (47%), the United States or Canada (45%), and unspecified or other locations (1%). Further details on the studies included for each KQ are provided in the relevant results sections, below, and in Appendix F.

We searched the ClinicalTrials.gov registry of clinical studies to identify completed but unpublished studies as a mechanism for ascertaining publication bias. We acknowledge that this is not an exhaustive strategy, as several other registries also exist with differing geographical focus and varying degrees of overlap in their trial listings; however, in the opinion of the investigators, the widely used, U.S.-based ClinicalTrials.gov registry provided the most relevant information to the populations and interventions of interest in this review. In the original report (searching back to 2000) this search found 14 trial records for which we did not identify publications. These were all considered potentially relevant to KQ 3. The 2018 updated search (searching back to July 2012) yielded 146 additional trial records. A single reviewer identified 26 of these records as potentially relevant to this current review. Of those 26 records, 16 had expected completion dates of 1 year or more prior to our search. From that group of 16 trials, we identified publications for 6. The remaining 10 trial records for which we did not identify publications were all considered potentially relevant to KQ 3. All but one of these studies are observational. Given the large body of evidence already available for KQ3 (117 studies including 22 RCTs) this lessens the potential that there is significant publication bias in the evidence base that would impact our overall conclusions for any of the Key Questions.

Key Question 1. Predicting Thromboembolic Risk

KQ 1. In patients with nonvalvular atrial fibrillation, what are the comparative diagnostic accuracy and impact on clinical decisionmaking (diagnostic thinking, therapeutic efficacy, and patient outcome efficacy) of available clinical and imaging tools and associated risk factors for predicting thromboembolic risk?

Key Points

- $CHADS_2$ score (continuous): Based on a meta-analysis of 14 studies (10 low risk of bias, 4 medium risk of bias, 761,128 patients), there is moderate SOE that the continuous $CHADS_2$ score provides limited prediction of stroke events (c-statistic of 0.69; 95% CI 0.66 to 0.73).
- $CHADS_2$ score (categorical): Based on a meta-analysis of 16 studies (11 low risk of bias, 5 medium risk of bias, 548,464 patients), there is moderate SOE that the categorical $CHADS_2$ score provides limited prediction of stroke events (c-statistic of 0.66; 95% CI 0.63 to 0.69).
- CHA_2DS_2-VASc (continuous): Based on a meta-analysis of 17 studies (13 low risk of bias, 4 medium risk of bias; 511,481 patients), there is moderate SOE that the continuous CHA_2DS_2-VASc score provides limited prediction of stroke events (c-statistic of 0.67; 95% CI 0.64 to 0.70).
- CHA_2DS_2-VASc (categorical): Based on a meta-analysis of 13 studies (8 low risk of bias, 5 medium risk of bias; 496,683 patients), there is low SOE that the categorical CHA_2DS_2-VASc score provides limited prediction of stroke events (c-statistic of 0.64; 95% CI 0.58 to 0.70).
- Framingham score (categorical): Based on a meta-analysis of 6 studies (5 low risk of bias, 1 medium risk of bias; 282,572 patients), there is moderate SOE that the categorical Framingham score provides limited prediction of stroke events (c-statistic of 0.63; 95% CI 0.62 to 0.65).
- ABC score (categorical): Based on a meta-analysis of 4 studies (4 low risk of bias, 25,614 patients), there is moderate SOE that the categorical ABC score provides limited prediction of stroke events (c-statistic of 0.67; 95% CI 0.63 to 0.71).
- Echocardiography: There is insufficient evidence for the relationship between findings on echocardiography (transthoracic) and subsequent stroke based on 5 studies (3 low risk of bias, 2 medium risk of bias; 1,228 patients) that reported discrepant results.
- Comparative accuracy: $CHADS_2$ and CHA_2DS_2-VASc have the most evidence predicting stroke events accurately when directly compared with other scores. This finding was, however, statistically significant only for the comparison with the Framingham categorical score. Other comparisons were not possible given limited data.
- Limitations: Included studies used heterogeneous populations; some participants were on and some were off antiplatelets and anticoagulants at baseline. Also, few studies used clinical validation in their report of stroke rates, instead relying on administrative data, chart review, or other measures that did not use consistent definitions and were not

similar across studies, complicating synthesis of their findings. Furthermore, although event rates were consistently reported, c-statistics and measures of calibration, strength of association, and diagnostic accuracy were inconsistently reported.

- The outcome of impact on clinical decisionmaking (diagnostic thinking, therapeutic efficacy, and patient outcome efficacy) was not assessed by any studies.

Description of Included Studies

In order to inform clinical decisionmaking regarding the net clinical benefit of anticoagulation, we have focused this review on studies evaluating the risk scores most typically utilized for prospective estimation of stroke risk in clinical settings.

Overall, 61 studies described in 83 publications investigated our included tools for determining stroke risk in patients with nonvalvular AF and met the other inclusion criteria for KQ 1.[14,16,23,25,26,98-174] The included studies explored tools in studies of diverse quality, design, funding, and geographical location. Additional study characteristics can be reviewed in Appendix Table F-1.

Forty-three included studies were of good quality or rated as low risk of bias,[14,16,23,25,26,98-100,102,104,107,110,112,113,115,117,120-122,125-129,136,138,142,143,148-150,153,154,156,158,160-163,165-167,173] 11 of fair quality or rated as medium risk of bias,[101,111,119,132,139,144,146,147,151,157,174] and 7 were of poor quality or rated as high risk of bias.[109,116,130,137,141,159,164] Studies with increased risk of bias had potential limitations related to handling of missing data, length of follow up between groups, blinding of outcomes assessors, whether confounders were assessed with reliable measures, and whether potential outcomes were prespecified.

The studies covered broad geographical locations with 32 studies conducted in UK or continental Europe,[16,99,101,110-112,119,121,122,129,130,132,137,139,141-144,147-151,154,156-159,162,164,167,173] 18 exclusively in the United States,[14,98,100,102,104,107,109,116,117,127,138,146,160,161,163,165,166,174] 3 studies exclusively conducted in Canada,[128,136,153] and 7 multinational trials.[16,23,25,113,115,125,126] There was one study that did not report geographic location of enrollment.[115]

Ten studies were supported solely by industry,[23,25,26,102,107,113,115,125,137,154] 8 studies received solely government support,[14,111,127-129,146,151,160] 6 studies were supported by non-government, non-industry organizations,[109,116,139,156,157,163] 15 studies received funding from multiple sources including government, industry, non-government and non-industry,[16,101,104,110,117,120-122,126,136,153,165,167,173,174] and 22 studies did not report funding or it was unclear.[98-100,112,119,130,132,138,141-144,147-150,158,159,161,162,164,166]

We identified 52 studies using observational study design (prospective and retrospective cohorts)[14,16,98-102,104,109-112,116,117,119,121,122,125,127-130,132,136-139,141-144,146-151,153,154,156-162,164,166,167,174] while 9 studies were identified as randomized controlled trials (RCTs).[23,25,26,107,113,115,120,126,163]

Included studies often presented data for the categorical versions of stroke risk scores (i.e., risk score categorized in groupings of scores), though some also presented data for continuous versions of the scores. When available, we present data for both categorical and continuous scores. Included studies consistently presented results using stroke event rates (either stroke events per 100 patient-years or percent of individuals experiencing a stroke event within the followup period) and reported model discrimination/prediction using c-statistics. Measures of calibration, strength of association, and measures of diagnostic accuracy were inconsistently reported. The c-statistic, or area under the receiver operating characteristic curve, may not be optimal in assessing models that predict future risk or stratify individuals into risk categories,[175] but it is a commonly reported statistic for characterizing a predictive model's predictive abilities.

Because studies included in this section generally used the c-statistic to characterize risk scores, we have used it as a basis for comparing these scores within a given study population, while also keeping in mind its limitations. A few studies presented other means for comparing bleeding risk scores, such as net reclassification improvement (NRI), and we provide this information when available. As a reminder, for a clinical prediction rule, we assumed that a c-statistic <0.6 had no clinical value, 0.6–0.7 had limited value, 0.7–0.8 had modest value, and >0.8 has prediction adequate for genuine clinical utility.[94]

Detailed Synthesis

$CHADS_2$ Risk Tool

The $CHADS_2$ risk tool is calculated based on existence of the following clinical factors: Congestive heart failure, Hypertension, Age ≥75, Diabetes mellitus, prior Stroke/transient ischemic attack [2 points].[14] The $CHADS_2$ score ranges from 0 to 6, with increasing scores corresponding to increasing stroke risk, and is easy to calculate and apply in clinical practice. It can be applied either as a continuous score (in full detail across the range) or by grouping categorically in to different risk categories.

Twenty-nine studies directly compared $CHADS_2$ risk score and its predictive ability for thromboembolic events (stroke or peripheral arterial, but excluding venous thrombus or pulmonary embolism; Tables 6-8).[14,16,23,98,100,107,116-118,122,129,133,137,141-145,148-151,154,156-158,160,164,167] Twenty-two of the studies included patients on oral anticoagulant therapy.[23,98,100,107,116-118,133,137,141,144,145,148-151,154,156-159,164] One study examined $CHADS_2$ risk and stroke outcomes among patients undergoing coronary revascularization with PCI,[158] one study in patients after surgical Maze procedure,[100] one in elderly patients (mean age 74 years),[150] and one in Mediterranean patients.[156]

The use of $CHADS_2$ to predict stroke risk varied among the studies. Eight studies reported $CHADS_2$ score and stroke outcomes by individual $CHADS_2$ score.[14,98,118,129,142,154,160,167] Eight studies investigated the classical $CHADS_2$ risk as categorical variables: low ($CHADS_2$=0), moderate ($CHADS_2$=1–2), and high ($CHADS_2$=3–6).[16,23,107,117,148-150,164] Three studies examined the revised $CHADS_2$ score classification as continuous variables,[122,141,150] and five studies did not report results by categorical or continuous $CHADS_2$ score.[100,117,137,144,151] The remaining studies used varying categorical classifications.

Table 6. Thromboembolic event rate results (%) by $CHADS_2$ score with patients on antiplatelet/anticoagulant therapy

Study Design Categorical/ Continuous	No. of Patients	Outcome	0	1	2	3	4	5	6	Followup Period (Years)	Risk of Bias
Abraham, 2013[98] Observational Continuous	5,981	Annual % for stroke or TIA (excludes hemorrhagic stroke)	0.36	0.72	1.27	1.45	2.43	2.43	2.43	11.8	Low
Baruch, 2007[107] RCT Categorical	7,329	Annual % stroke	0	0	1	2.3	2.3	2.3	2.3	1.5	Low
Connolly, 2009[23] RCT Categorical	18,113	Annual % stroke	0.93	0.93	1.22	2.44	2.44	2.44	2.44	2	Low
Fang, 2008[117] Observational Categorical	10,932	Annual % stroke	0.39	2.0	2.0	2.42	2.42	2.42	2.42	6	Low
Fanola, 2017[118] Observational Continuous	2,898	Annual % event (composite of disabling stroke, life-threatening bleed, and all-cause mortality)	4.3	4.3	4.3	6.7	8.4	9.7	26.1	2.7	Low
Gupta, 2016[124] Observational Categorical	971	Annual % stroke	–	–	2.05	1.14	2.35	5.11	5.11	2.5	Low

Study Design Categorical/ Continuous	No. of Patients	Outcome	0	1	2	3	4	5	6	Followup Period (Years)	Risk of Bias
Lip, 2013[133] Observational Categorical	Aspirin: 2,791 Apixaban: 2,808	Annual % stroke	1.41	1.41	3.05	5.0	5.0	5.0	5.0	1.1	Low
Lip, 2010[16] Observational Categorical	1,084	Annual % stroke	1.4	2.4	2.4	3.2	3.2	3.2	3.2	1	Low
Morgan, 2009[137] Observational Categorical	5,513	Annual % stroke	0.46	0.46	1.165	1.165	1.165	1.165	1.165	2.8	High
Olesen, 2012[143] Observational Categorical	47,576	Annual % stroke	1.28	3.61	–	--	--	--	--	12	Low
Olesen, 2012[144] Observational Categorical	87,202	Annual % stroke	1.28	–	--	--	--	--	--	12	Low

Abbreviations: $CHADS_2$=Congestive heart failure, Hypertension, Age ≥75, Diabetes mellitus, prior Stroke/transient ischemic attack (2 points); No.=number; TIA=transient ischemic attack

Table 7. Thromboembolic event rate results (%) by $CHADS_2$ score with patients off therapy

Study Design Categorical/ Continuous	No. of Patients	Outcome	0	1	2	3	4	5	6	Followup Period (Years)	Risk of Bias
Friberg, 2012[122] Observational Continuous	182,678	Annual % stroke	0.9	4.9	6.8	11.1	16.8	18.9	19.4	1.5	Low
Gage, 2001[14] Observational Continuous	1,733	Annual % stroke	1.9	2.8	4.0	5.9	8.5	12.5	18.5	1.2	Low
Larsen, 2012[129] Observational Continous	1,603	Annual % stroke	1.2	2.2	4.1	4.0	19.5	11.5	0.0	5.4	Low
Olesen, 2011[142] Observational Continuous	73,538	Annual % Event (Hospital admission or death due to thromboembolism)	1.24	3.56	5.4	9.89	13.7	12.57	17.17	10	Low
Singer, 2013[160] Observational Continuous	10,927	Annual % stroke	0.36	1.20	2.59	3.72	6.19	4.23	10.84	2.4	Low
van den Ham, 2015[167] Observational Continuous	60,594	Annual % stroke	0.78	2.33	3.52	5.34	8.98	7.90	11.50	0.74	Low

Abbreviations: $CHADS_2$=Congestive heart failure, Hypertension, Age ≥75, Diabetes mellitus, prior Stroke/transient ischemic attack (2 points); No.=number

Table 8. Thromboembolic event rate results (%) by $CHADS_2$ score with patients on mixed or unclear anticoagulant/antiplatelet therapy

Study Design Categorical/ Continuous	No. of Patients	Outcome	0	1	2	3	4	5	6	Followup Period (Years)	Risk of Bias
Olesen, 2011[141] Observational Categorical	132,372	Annual % stroke	1.4	2.8	6.0	--	--	--	--	12	High
Olesen, 2012[145] Observational Categorical	6,438	Annual % stroke	0.23 (Age < 65) 2.05 (Age 65-74) 3.99 (Age ≥75	–	–	–	–	–	–	11	High
Ruiz Ortiz, 2010[157] Observational Categorical	796	Annual % stroke	1.0	0.6	0.5	2.4	2.9	–	–	2.4	Low

Abbreviations: $CHADS_2$=Congestive heart failure, Hypertension, Age ≥75, Diabetes mellitus, prior Stroke/transient ischemic attack (2 points); No.=number

CHA_2DS_2-VASc Risk Tool

The CHA_2DS_2-VASc risk score is calculated based on the following clinical characteristics: Congestive heart failure/left ventricular ejection fraction ≤ 40%, Hypertension, Age ≥75 [2 points], Diabetes mellitus, prior Stroke/transient ischemic attack/thromboembolism [2 points], Vascular disease, Age 65–74, Sex category female. The CHA_2DS_2-VASc score ranges from 0 to 9, with increasing scores corresponding to increasing stroke risk, and is easy to calculate and apply in clinical practice.[1] It can be reported as a continuous scale or by grouping different risk scores in to categories.

Twenty-four studies directly examined CHA_2DS_2-VASc risk score and its predictive ability for thromboembolic events (Tables 9-11).[16,98,101,103,110,118,119,121,122,125,129,133,141-144,150,151,155,159,160,164,167,173] One study examined the predictive value in elderly patients (mean age 74 years).[150] Eight studies had identical categorical classification of stroke risk by CHA_2DS_2-VASc score: low (score=0), moderate (score=1), and high (score=2–9).[16,110,141,142,147,150,164,173] Ten studies reported stroke outcomes by individual CHA_2DS_2-VASc score,[16,101,129,139,142,144,151,159,160,167] while one reported stroke outcomes by CHA_2DS_2-VASc score from 0 to 4 points.[143] Twelve studies examined stroke risk among patients not treated with oral anticoagulant therapy.[16,101,121,122,129,139,141-144,147,160]

Table 9. Thromboembolic event rate results (%) by CHA_2DS_2-VASc score with patients on antiplatelet/anticoagulant therapy

Study Design Categorical/ Continuous	No. of Patients	Outcome	0	1	2	3	4	5	6	7	8	9	Follow up Period (Years)	Risk of Bias

Study Design Categorical/ Continuous	No. of Patients	Outcome	0	1	2	3	4	5	6	7	8	9	Follow up Period (Years)	Risk of Bias

Study Design Categorical/ Continuous	No. of Patients	Outcome	0	1	2	3	4	5	6	7	8	9	Follow up Period (Years)	Risk of Bias
Olesen, 2012[144] Observational Categorical	87,202	Annual % stroke	1.28	_	_	_	_	_	_	_	_	_	12	Low
Philippart, 2016[147] Observational Categorical	8,053	Annual % stroke	0.67	2.06	3.73	3.73	3.73	3.73	3.73	3.73	3.73	3.73	2.4	Medium
Poli, 2011[150] Observational Categorical	662	Annual % stroke	0	2.8	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	3.6	Low
Potpara, 2012[151] Observational Categorical	345	Annual % stroke	0	_	_	_	_	_	_	_	_	_	12.1	Medium
Primary paper: Rivera-Caravaca, 2017[173] Relevant companion: Rivera-Caravaca, 2017[172]	1,125	Annual % stroke	0	0.31	1.64	1.64	1.64	1.64	1.64	1.64	1.64	1.64	6.5	Low

Study Design Categorical/ Continuous	No. of Patients	Outcome	0	1	2	3	4	5	6	7	8	9	Follow up Period (Years)	Risk of Bias

Abbreviation: CHA_2DS_2-VASc=Congestive heart failure/left ventricular ejection fraction ≤ 40%, Hypertension, Age ≥75 (2 points), Diabetes mellitus, prior Stroke/transient ischemic attack/thromboembolism (2 points), Vascular disease, Age 65–74, Sex category female; No.=number; NR=not reported

Table 10. Thromboembolic event rate results (%) by CHA_2DS_2-VASc score with patients off therapy

Study Design Categorical/ Continuous	No. of Patients	Outcome	0	1	2	3	4	5	6	7	8	9	Followup Period (Years)	Risk of Bias
Allan, 2017[101] Observational Continuous	14,990	Annual % stroke	0.2	0.7	1.4	2.6	4.0	6.2	12.1	14.5	17.6	24.3	2.2	Medium

Study Design Categorical/ Continuous	No. of Patients	Outcome	0	1	2	3	4	5	6	7	8	9	Followup Period (Years)	Risk of Bias
Forslund, 2014[121] Observational Continuous	9,959	Annual % stroke	0.24	0.39	1.68	2.89	3.95	5.34	6.74	8.13	6.88	6.88	1	Low
Friberg, 2012[122] Observational Continuous	182,678	Annual % stroke	0.3	1.0	3.3	5.3	7.8	11.7	15.9	18.4	17.9	20.3	1.5	Low
Larsen, 2012[129] Observational Continuous	1,603	Annual % stroke	0.9	1.1	2.4	3.4	4.2	3.8	23.1	11.3	0	0	5.4	Low
Nielsen, 2016[139] Observational Continuous	198,697	Annual % stroke	0.6	1.0	1.9	2.9	4.0	5.5	7.3	8.1	7.8	7.6	2.9	Medium
Olesen, 2011[142] Observational Continuous/ Categorical	73,538	Annual % event (hospital admission or death due to thromboembolism)	0.66	1.45	2.92	4.28	6.46	9.97	12.52	13.96	14.10	15.89	10	Low
Philippart, 2016[147] Observational Categorical	8,053	Annual % stroke	0.69	1.71	5.07	5.07	5.07	5.07	5.07	5.07	5.07	5.07	2.4	Medium

Study Design Categorical/ Continuous	No. of Patients	Outcome	0	1	2	3	4	5	6	7	8	9	Followup Period (Years)	Risk of Bias
Singer, 2013[160] Observational Continuous	10,927	Annual % stroke	0.04	0.55	0.83	1.66	2.80	4.31	4.77	4.82	7.82	16.62	2.4	Low
van den Ham, 2015[167] Observational Continuous	60,594	Annual % stroke	0.38	0.78	1.92	2.84	3.70	5.08	7.09	8.98	9.01	15.49	0.74	Low

Abbreviation: CHA_2DS_2-VASc=Congestive heart failure/left ventricular ejection fraction ≤ 40%, Hypertension, Age ≥75 (2 points), Diabetes mellitus, prior Stroke/transient ischemic attack/thromboembolism (2 points), Vascular disease, Age 65–74, Sex category female; No.=number

Table 11. Thromboembolic events by CHA_2DS_2-VASc score with patients on mixed or unclear anticoagulant/antiplatelet therapy

Study Design Categorical/ Continuous	No. of Patients	Outcome	0	1	2	3	4	5	6	7	8	9	Followup Period (Years)	Risk of Bias

Abbreviation: CHA_2DS_2-VASc=Congestive heart failure/left ventricular ejection fraction ≤ 40%, Hypertension, Age ≥75 (2 points), Diabetes mellitus, prior Stroke/transient ischemic attack/thromboembolism (2 points), Vascular disease, Age 65–74, Sex category female; No.=number; VKA=vitamin K antagonist

Framingham Risk Tool

This Framingham risk score calculator estimates the 5-year stroke risk of any person based on the following risk predictors: advancing age, female sex, increasing systolic blood pressure, prior stroke or transient ischemic attack, and diabetes.

Six studies reported the association of Framingham risk and stroke events among patients with AF (Tables 12-14).[16,107,117,122,164,165] All studies reported the individual risk factors associated with Framingham risk. Three studies reported stroke outcomes in patients without oral anticoagulant therapy,[16,122,165] and one study where all patients were on oral anticoagulant therapy.[107]

Table 12. Thromboembolic event rate results (%) by Framingham risk score with patients on antiplatelet/anticoagulant therapy

Study Design Categorical/ Continuous	No. of Patients	Outcome	Low	Moderate	High	Followup Period (Years)	Risk of Bias
Baruch, 2007[107] RCT Categorical	7,329	Annual % stroke	0.7	1.4	2.7	1.5	Low
Fang, 2008[117] Observational Categorical	10,932	Annual % stroke	0.81	–	3.9	6.0	Low
Van Staa, 2011[164] Observational Categorical	79,844	Annual % stroke	1.8	4.3	9.5	4	High

Abbreviation: No.=number; RCT=randomized controlled trial

Table 13. Thromboembolic event rate results (%) by Framingham risk score with patients on mixed or unclear underlying anticoagulant/antiplatelet therapy

Study Design Categorical/ Continuous	No. of Patients	Outcome	Low	Moderate	High	Followup Period (Years)	Risk of Bias
Friberg, 2012[122] Observational Categorical	182,678	Annual % stroke	1.8	5.9	11.8	1.5	Low
Lip, 2010[16] Observational Categorical	1,084	Annual % stroke	1.0	1.2	3.5	1	Low

Abbreviations: No.=number

Table 14. Thromboembolic event rate results (%) by Framingham risk score with patients on concomitant stroke prevention therapy (antiplatelet/anticoagulant) use[a]

Study Design Categorical/ Continuous	No. of Patients	Outcome	Low	Moderate	High	Followup Period (Years)	Risk of Bias
Wang, 2003[165] Observational NR	705	Annual % stroke	_	_	NR	4.3	Low

[a] Use of therapy uncertain; i.e., no vitamin K antagonist but antiplatelet use not reported.

ABC Risk Tool

ABC-stroke score is based on inclusion of Age, Biomarkers (cTnI-hs and NT-proBNP), and Clinical history (prior stroke/TIA). For each predictor, points are assigned on a 0–10 scale these points are summed across predictors. This total point score is then mapped to the corresponding predictions of 1- and 3-year risk of stroke or systemic embolism.

A study developing and validating the ABC risk tool reported stroke event rates for the various risk scores (Table 15).[126] Three other recent studies reported the association of the ABC-stroke risk score with the rates of thromboembolic events.[25,140,173] All studies included patients on oral anticoagulants and had categorical classification of stroke risk (<1%, 1%-2%, and >2%).[25,126,140,173]

Table 15. Thromboembolic event rate results (%) by ABC-stroke score with patients on antiplatelet/anticoagulant therapy

Study Design Categorical/ Continuous	No. of Patients	Outcome	<1%	1%	>2%	Follow-up Period (Years)	Risk of Bias
Hijazi, 2016[126] Observational Categorical	1400	Annual % stroke	0.56	1.29	3.22	3.4	Low
Primary paper: Granger, 2011[25] Relevant companion: Hijazi, 2017[170]	4,976	Annual % stroke	0.29	1.3	4.4	1	Low
Oldgren, 2016[140] Observational Categorical	18,113	Annual % stroke	TnT: 0.76 TnI: 0.74	TnT: 1.48 TnI: 1.41	TnT: 2.60 TnI: 2.61	1.9	Low

Study Design Categorical/ Continuous	No. of Patients	Outcome	<1%	1%	>2%	Follow-up Period (Years)	Risk of Bias
Primary paper: Rivera-Caravaca, 2017[173] Relevant companion: Rivera-Caravaca, 2017[172]	1,125	Annual % stroke	0.30	1.10	2.06	6.5	Low

Abbreviations: ABC=Age, biomarkers, clinical history; No.=number; TnI=troponin I; TnT=troponin T

Imaging Risk Tool

Seven studies examined specific anatomical findings on imaging studies and the association with stroke risk in patients with AF (Table 16).[109,124,138,161-163,166] One study used magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) quantification of left atrial appendage (LAA) dimensions.[109] Five studies utilized transesophageal echocardiography to examine imaging parameters associated with stroke risk in patients with AF,[138,161,166], one utilized transthoracic echocardiograph[124] and three used both transesophageal echocardiography and transthoracic echocardiography.[162,163]

In the study examining MRI/MRA characteristics, 144 patients with nonvalvular AF not on warfarin underwent MRI/MRA prior to catheter ablation for AF.[109] LAA volume, LAA depth, short and long axes of LAA neck, and numbers of lobes and their association with stroke risk were examined. In univariate analysis, LAA volume, LAA depth, and short and long axes of LAA neck were significantly associated with stroke risk. In multivariate analysis, the only MRI/MRA characteristic significant in the stroke prediction model was product of the short and long axes of the LAA neck (odds ratio [OR] 3.59; 95% CI 1.93 to 6.69; p<0.001).

In two of the studies examining echocardiography, the echo (imaging) parameters were added to existing AF stroke risk score or to clinical factors. In one study of randomly assigned patients to TEE, utilizing data from TTE and TEE with clinical factors (age, AF duration, AF etiology, previous embolism, diabetes, hypertension, congestive heart failure) produced the best risk prediction with a c-statistic of 0.72 (p<0.0001), which was better than the model with only TTE and TEE data (c-statistic 0.720, p<0.0001), clinical factors with TEE data only (c-statistic 0.67 p <0.0001) or clinical factors with TTE data only (c-statistic 0.59, p<0.0007).[163] In another study, which examined the use of TTE parameters only, it was found that in models adjusted for $CHADS_2$ score, aspirin use, and randomized treatment (edoxaban), 2 factors were independently associated with increased risks for death (but not TE events): (1) larger left ventricular (LV) end-diastolic volume index (HR [per 12.9 mL/m2]1.49; 95% CI 1.16 to 1.91) and (2) higher LV filling pressures measured by E/e' ratio (HR [per 4.6] 1.32; 95% CI 1.08 to 1.61). When these parameters were added to the clinical factors of HF, HTN, Age, DM, stroke, vascular disease, sex, creatinine clearance (CrCl), randomization, and aspirin treatment, the model that best predicted mortality included E/e'>13 (AUC 0.71, 95% CI 0.64 to 0.77).[124]In the final study which correlated TEE findings with $CHADS_2$ scores, it found that TEE markers of thrombogenic milieu were highly correlated with increasing $CHADS_2$ scores.[166]

Table 16. Thromboembolic events by echocardiographic criteria with patients on antiplatelet/anticoagulant therapy

Study Design	No. of Patients	Features Examined	Prediction of Thromboembolic Events	Risk of Bias
Beinart, 2011[109] Observational	144	LAA volume LAA depth LAA neck (short and long axes) Number of LAA lobes	LAA neck dimension (short x long axis), prediction of thromboembolic events: OR 3.59 per cm2 (95% CI 1.93 to 6.69, p<0.001)	Low
Gupta, 2016[124] Observational	971	LVEF (%) LVEDVI LV mass LVMI Abnormal LV Geometry LA diameter LAVI LA emptying fraction DTI e' average E/e' average Moderate or greater MR RVSP Clinical factors: HF, hypertension, Age, diabetes mellitus, stroke, vascular disease, sex, CrCl, randomization (edoxaban), aspirin	In multivariate-adjusted models, no features of cardiac structure and function were associated with thromboembolic risk independent of $CHADS_2$ score	Low
Nair, 2009[138] Observational	226	Presence or absence of LA thrombus on TEE	No evidence of a difference in stroke rates in patients with LA thrombus vs. those without LA thrombus (7% vs. 4%, p=NS)	Low
Stoddard, 2003[161] Observational	272	LA diameter LVEF LVEF<40% LA SEC Aortic plaque ≥5 mm Mobile PFO ≥grade 2 MV/AV strands Atrial septal aneurysm Mitral stenosis	Presence of LA thrombus (OR 7.7, 95% CI 2.7 to 21.6)	Low
Stollberger, 2004[162] Observational	409	<u>TTE:</u> LV fractional shortening Reduced LV systolic function LA diameter Valvular abnormalities <u>TEE:</u> LAA thrombus Spontaneous echo contrast LAA size LAA length LAA width LAA area, mean	None of the features examined were independent predictors of stroke or embolism	Low

Study Design	No. of Patients	Features Examined	Prediction of Thromboembolic Events	Risk of Bias
Thambidorai, 2005[163] Observational	571	TTE data: valvular disease, ejection fraction, atrial size, mitral stenosis) TEE data: spontaneous echocardiographic contrast, atheroma, and appendage velocities and diameter, patent foramen ovale Clinical data: age, AF duration, AF etiology, previous embolism, diabetes, hypertension, congestive heart failure	Clinical+TTE+ TEE: c-statistic 0.724 (p <0.0001) TEE+TTE only: c-statistic 0.720 (p <0.0001) Clinical+TEE: c-statistic 0.696 (p <0.0001) Clinical+ TTE: c-statistic 0.589 (p <0.0007)	Low
Yarmohammadi, 2013[166] Observational	2369	TEE data: screening LA or LAA thrombogenic milieu (SEC, sludge, and thrombus) Clinical data: $CHADS_2$ score	The prevalence of LA or LAA sludge or thrombus increased with increasing $CHADS_2$ scores (2.3%,7%, 8.5%, 9.9%, 12.3%, and 14.1% for scores of 0, 1, 2, 3, 4, and 5 or 6, respectively, p = 0.01). In a multivariate model, an ejection fraction ≤20% was the best predictor of LA or LAA sludge or thrombus (odds ratio 2.99, p < 0.001).	Low

Abbreviations: AV=aortic valve; CI=confidence interval; HR=hazard ratio; LA=left atrial; LAA=left atrial appendage; LV=left ventricular; LVEF=left ventricular ejection fraction; MR=mitral regurgitation; MV=mitral valve; NS=not statistically significant; OR=odds ratio; PFO=patent foramen ovale; SEC=spontaneous echocardiographic contrast; TEE=transesophageal echocardiography; TTE=transthoracic echocardiography; TTE-LAWV=transthoracic echocardiographic LAA wall velocity

International Normalized Ratio (INR) Tool

Six studies evaluated the predictor role of INR and its association with stroke risk in patients with AF.[127,130,137] One study considered the INR value on hospital admission,[127] three considered the time in therapeutic range (TTR) of INR,[102,125,137] and one study considered both TTR and the standard deviation of transformed INR.[130] One study of 13,559 patients on warfarin showed that an INR of <2.0 compared with an INR ≥2.0 independently increased the odds of a severe stroke (that resulted in death in the hospital or total dependence after discharge) in a multivariate model (OR 1.9; 95% CI 1.1 to 3.4).[127] The third study examined 19,180 patients on warfarin to determine if INR variability (standard deviation of transformed INR [SDT_{INR}]) has better predictive value for stroke events than TTR.[130] The HR for stroke events was higher for the SDT_{INR} than for the TTR (1.30; 95% CI 1.22 to 1.39 vs. 1.06; 95% CI 1.00 to 1.13). The thromboembolism rates (per patient-year) for patients with INR ≤1.49, 1.50–1.99, 2.00–2.49, 2.50–2.99, and ≥3.00 were 12.6, 2.7, 2.8, 0.9, and 2.9 percent, respectively.

In the studies examining TTR, one study of 6,108 patients, investigators examined the rate of stroke events on patients treated with warfarin after a mean followup of 1,025.1 days.[137] The study reported that only patients with $CHADS_2$ ≥2 and a TTR for warfarin (INR 2.0–3.0) of 71-100 percent during the study had a signification reduction in stroke risk (HR 0.20; 95% CI 0.05 to 0.82; p=0.025). Another study compared rates at 1-year between <65%TTR and ≥65% TTR

and found HR 2.55 (95% CI 1.61 to 4.03) in the group with the lower TTR.[125] In the third study, they examined TTR and whether the frequency of visits with a pharmacist in a year reduced thromboembolic events (frequent management >16 pharmacist interventions per year). Compared to less frequent management (<16 pharmacist visits per year) and TTR ≥65%, TTR <65% and frequent management (HR 1.94 95% CI 1.66 to 2.27), TTR <65% and less frequent management (HR 1.91; 95% CI 1.63 to 2.23), TTR ≥65%, and TTR ≥65% and frequent management (HR 1.10; 95% CI 0.89 to 1.36) all had higher incidence of stroke. This suggests that regardless of frequency of pharmacist intervention, patients with low TTR experienced more strokes or systemic embolisms.[102]

Pattern of Atrial Fibrillation and Stroke Risk

Three studies examined the pattern of AF (paroxysmal, persistent, and permanent) and stroke risk from large clinical trials.[25,131,133] In the subgroup reporting for the ARISTOTLE trial, there was no evidence of a difference in stroke rates among the 3 types of AF.[25] In a secondary analysis of the AVERROES trial, patients with paroxysmal AF suffered fewer thromboembolic events and deaths compared with those with persistent and permanent AF (Table 17).[133] The third study was a secondary analysis from the ENGAGE AF-TIMI 48 study and showed that patients with paroxysmal AF suffered fewer thromboembolic events than those with persistent or permanent AF.[131]

Table 17. Pattern of atrial fibrillation and stroke risk

Study (the original trial) Design	No. of Patients	Comparison Groups	Results Stroke Risk	Risk of Bias
Granger, 2011[25] (ARISTOTLE) RCT	18, 201	Warfarin (Permanent or persistent) vs. paroxysmal Apixaban (Permanent or persistent) vs. paroxysmal	Warfarin 1.7% vs. 1.1%-NS difference Apixaban 1.4% vs. 0.8%-NS difference p = 0.71 for interaction	Low
Link, 2017[131] (ENGAGE AF-TIMI 48) RCT	21,105	Paroxysmal vs. persistent Paroxysmal vs. permanent Persistent vs. permanent	HR 0.79 (0.66–0.96) p=0.015 HR 0.79 (0.67–0.93) p=0.004 HR 0.99 (0.85–1.16) p=0.95	Low
Lip, 2013[133] (AVERROES) RCT	5599	Aspirin Persistent vs. paroxysmal Permanent vs. paroxysmal Apixaban Persistent vs. paroxysmal Permanent vs. paroxysmal	Aspirin HR 2.15 (1.11–4.32) HR 1.99 (1.13–3.74) p=0.03 (for non paroxysmal vs paroxysmal AF) Apixaban HR 1.00 (0.38–2.48) HR 0.73 (0.34–1.63) p=0.65 (for non paroxysmal vs paroxysmal AF)	Low

Abbreviation: AF=atrial fibrillation; HR=hazard ratio; RCT=randomized controlled trial

Renal Impairment and Stroke Risk Studies

Numerous studies have examined the association of renal disease with stroke risk in patients with AF. There is limited consistency in how renal function is defined in these studies and some examine univariate associations and risk while others examined the addition of renal impairment with existing stroke risk prediction scores. There is also not consistency in separating the associations based on prophylactic treatment for stroke.

Seven studies matched inclusion criteria into the current systematic review.[25,105,115,123,128,133] Three studies showed renal function and stroke outcomes as part of subgroup analyses.[25,115,133] Each of these studies reported the association of renal impairment and stroke and systemic embolic risk differently. In subgroup analysis of the ARISTOTLE trial, no association was made between the level of renal impairment (creatinine clearance: severe/moderate [≤30 ml/min/ >30 to 50 ml/min], mild >50 to 80 ml/min, or none [>80 ml/min]) and stroke risk (p value for interaction 0.72).[25] Similar lack of association in subgroup reporting was found in the AVERROES trial when using estimated glomerular filtration rate (eGFR) across three categories of renal impairment (<50 ml/min, 50 to <80 mL/min, and ≥80 mL/min).[115] The third study was a secondary analysis of the AVERROES trial examined multivariate baseline risk factors for stroke risk in patients treated with either aspirin or apixaban with eGFR ≥ 60 mL/min compared to <60mL/min. For aspirin, the study found less stroke risk in treated patients with eGFR ≥60mL/min (HR 0.62; 95% CI 0.40 to 0.95; p=0.03), but no statistically significant risk in patients treated with apixaban (HR 1.47; 95% CI 0.70 to 3.26; p=0.32).[133]

Two studies examined the addition of renal impairment to $CHADS_2$ or CHA_2DS_2-VASc scores.[105,123] In the first study, in patients with NVAF adding renal impairment to $CHADS_2$ or CHA_2DS_2-VASc scores did not independently add to the predictive value of these scores at 1-year followup, whether it was defined by serum creatinine level (renal impairment: serum creatinine >1.5 mg/dl in men and >1.3 mg/dl in women) or the eGFR (≥ 60 ml/min/1.73 m^2, 30-59 ml/min/1.73 m^2, < 30 ml/min/1.73 m^2). Adjusting for $CHADS_2$, adding renal impairment 1-year HR 1.03 (95% CI 0.73 to 1.43) while adding eGFR as a categorical variable showed 1-year (HR 1.07 (95% CI 0.82 to 1.40).[105]

Two observational studies examined stroke and thromboembolic risk among patients untreated with OAC and treated with warfarin.[111,128] The results are shown in Table 18 for 1-year outcomes for both studies. Overall, both studies showed that across all strata of renal function that stroke risk was reduced with the use of warfarin with the exception of eGFR <15 mL/min/1.73 m^2 in Bonde et al.[111]

Table 18. Renal function and stroke risk

Study Design	No. of Patients	Renal Function (mL/min/1.73 m2)	Received Warfarin Stroke Rates	No Warfarin Stroke Rates	Risk of Bias
Bonde, 2016[111] Observational	17,349	eGFR≥90 eGFR 60–89 eGFR 30–59 eGFR 15–29 eGFR<15	2.52 (1.55 to 3.48) 2.75 (2.25 to 3.25) 4.06 (3.34 to 4.79) 9.77 (5.38 to 14.16) 14.14 (0 to 33.74) Event rates (95% CI)	2.71 (2.06 to 3.36) 4.09 (3.61 to 4.57) 8.54 (7.73 to 9.36) 13.57 (10.08 to 17.07) 14.51 (2.90 to 26.12) Event rates (95% CI)	Medium

Study Design	No. of Patients	Renal Function (mL/min/1.73 m2)	Received Warfarin Stroke Rates	No Warfarin Stroke Rates	Risk of Bias
Jun, 2017[128] Observational	14,892	eGFR≥90 eGFR 60–89 eGFR 45–59 eGFR 30-44 eGFR<30	1.2 2.5 2.4 3.1 4.5 Event rate per 100 person-years	3.6 4.0 4.5 6.1 8.7 Event rate per 100 person-years	Low

Abbreviation: eGFR=estimated glomerular filtration rate

Other Risk Factors Examined for Stroke Risk in AF

We found four additional studies included in the current review that examined unique risk factors and their association with stroke risk in AF.[104,120,135,155] One study examined HbA1c control and the duration of the diagnosis of Type 2 diabetes mellitus on stroke risk. In this study, it was found that neither poor glycemic control (HbA1c >9.0%, adj HR 1.04; 95% CI 0.57 to 1.92) nor moderately increased HbA1c (7.0% to 8.9%, adj HR 1.21; 95% CI 0.77 to 1.91) were significantly associated with an increased rate of ischemic stroke compared with patients who had HbA1c <7.0%. However, a duration of diabetes greater than three years was associated with an increased rate of ischemic stroke compared with duration less than three years (adj HR 1.74; 95% CI 1.10 to 2.76).[104]

Another study examined the presence of left ventricular systolic dysfunction (LVSD) defined as a left ejection fraction (LVEF ≤40%), HF symptoms with preserved ejection fraction (HFpEF) or no LVSD and no HF symptoms and their association with stroke risk. The interaction with treatment with apixaban versus warfarin was also reported. Overall, patients with LVSD (with or without HF symptoms) did not have different stroke risk compared to patients with HFpEF. Both groups had greater risk than patients without either HF or LVSD. Apixaban reduced this risk of stroke and thromboembolic events across all three groups (Table 19). Additionally, no association of LVSD and stroke risk was found (HR for each 10% decrease in LVEF was 1.02, 95% CI 0.94 to 1.11; p=0.65).[135]

Table 19. Left ventricular systolic dysfunction, heart failure, and stroke risk

Study Dsign	No. of Patients	Comparison Groups	Stroke Risk	Risk of Bias
McMurray, 2013[135] Observational	14,671	Overall: LVSD (EF <=40) HF symptoms (HFpEF) No LVSD/No HF <u>Apixaban vs. Warfarin:</u> LVSD (EF <=40) HF symptoms (HFpEF) No LVSD/No HF	Overall: HR 0.55 (95% CI 0.34 to 0.91) HR 1.15 (95% CI 0.89 to 1.48) HR NR Interaction p=0.52 (difference between three groups) <u>Apixaban vs. Warfarin:</u> HR 0.55 (95% CI 0.34 to 0.91) HR 0.98 (95% CI 0.65 to 1.49) HR 0.74 (95% CI 0.57 to 0.96) Interaction p=0.21 (difference between three groups)	Low

Abbreviations: EF = ejection fraction; HFpEF = HF symptoms with preserved ejection fraction; HR=hazard ratio NR= not reported;, LVSD=left ventricular systolic dysfunction; HF=heart failure

A third study examined the diagnosis of dementia using the Mini-Mental Status Examination (MMSE) at the time of enrollment into ACTIVE-W and examined its relationship to TTR and subsequent stroke and systemic embolic events (Table 20). The study showed that MMSE was an independent predictor of TTR, however, after controlling for TTR, MMSE (where MMSE score <26 suggests cognitive decline) no longer conferred increased risk of stroke or systemic embolic events (regardless of treatment with warfarin or clopidogrel with aspirin) suggesting that cognitive dysfunction is related to less effective anticoagulation and hence increased stroke risk.[120]

Table 20. Mini-Mental Status Examination and stroke risk

Study Design	No. of Patients	Comparison Groups	Results	Risk of Bias
Flaker, 2010[120] Observational	3371	<u>MMSE <26 vs. MMSE ≥26</u> Warfarin (adjusted for TTR) Clopidogrel with aspirin	 HR 1.21 (95% CI 0.47 to 3.12) p = 0.69 RR 0.61(95% CI 0.35 to 1.10) P = 0.10174	Low

Abbreviations: HR=hazard ratio RR=relative risk; MMSE=Mini-Mental Status Examination

Finally, a fourth study reported that the addition of cardiac troponin I, N-terminal pro-B-type natriuretic peptide, and D-dimer levels to CHA_2DS_2-VASc score improved stroke, systemic embolism and death prediction by improving the c-statistic from 0.586 (95% CI 0.565 to 0.607) to 0.708 (95% CI 0.688 to 0.728) (p< .001) and reclassification with a net reclassification improvement of 59.4% (p< .001).[155]

Summary: Comparison of Stroke Risk Scores and Meta-Analysis Results

Comparison of risk scores between study populations was complicated by some studies assessing risk of events with patients on therapy, others with patients not on any therapy, and finally others with patients who could be on or off antiplatelet or anticoagulation therapies. Second, the vast majority of studies did not clinically validate thromboembolic events, instead relying on administrative claims data, chart review, or other electronic methods for capturing data retrospectively. Identification of these events and comparison across studies was further complicated by the lack of standard definitions for defining thromboembolic events, which could have affected the estimates of the performance of these risk scores. Finally, not all studies reported c-statistics to help with determining the prediction ability of the risk prediction tools in the selected population making cross study comparisons difficult.

A total of 30 studies assessed c-statistics for a risk score of interest with 21 of studies directly investigating at least 2 risk scores of interest in the same population. Three studies used the same population to examine the performance of the $CHADS_2$, Framingham, and CHA_2DS_2-VASc scores.[107,122,164] These studies showed similar performance of all three scores in the same population, with similar c-statistics ranging from 0.56-0.67. Twelve studies used the same population to assess the risk prediction of $CHADS_2$ and CHA_2DS_2-VASc,[98,105,106,118,123,129,136,142,143,150,160,167] with c-statistics ranging from 0.58 to 0.89 overall, but with similar performance of the two scores in the same population. Three studies used the same population of patients to examine the $CHADS_2$ and Framingham risk scores, with similar performance of the two risk scores in the same populations.[16,117,165] Only one study compared CHA_2DS_2-VASc and Framingham risk scores in the same population with a c-statistic of 0.67 for the former (continuous variables) versus 0.64 for the latter.[122] Three studies examined the performance of the ABC-stroke score compared to CHA_2DS_2-VASc, with c-statistics ranging from 0.58 to 0.62 for CHA_2DS_2-VASc and 0.65 to 0.66 for the ABC risk score with the prediction abilities not being different from each other in two studies and the ABC-stroke score having slightly better predictive value in a shorter (3.5 years) time horizon, but no statistical difference in predictive value at a longer time horizon (6.5 years).[126,140,173]

Table 21 provides a summary of available c-statistics for predictive accuracy of the risk scores of interest. This table demonstrates both a range of scoring systems evaluated (continuous vs. categorical) as well as a range of c-statistics across studies, with the $CHADS_2$ score c-statistic estimates ranging from 0.52 to 0.82, the Framingham scores ranging from 0.62 to 0.69, ABC-stroke ranging from 0.65-0.68, and the CHA_2DS_2-VASc ranging from 0.52 to 0.89.

Table 21. C-statistics from studies comparing stroke risk scores of interest

Study	$CHADS_2$	Framingham	CHA_2DS_2-VASc	ABC-Stroke
Abraham, 2013[98]	Continuous: 0.65 (95% CI 0.62 to 0.67) Categorical: 0.65 (95% CI 0.62 to 0.67)	–	Continuous: 0.67 (95% CI 0.65 to 0.69) Categorical: 0.67 (95% CI 0.65 to 0.69)	–

Study	$CHADS_2$	Framingham	CHA_2DS_2-VASc	ABC-Stroke
Abumuaileq, 2015[99]	–	–	Continuous: Non-anticoagulated cohort: 0.69 (95 % CI 0.53 to 0.85) Anticoagulated cohort: 0.72 (95% CI 0.63 to 0.82)	–
Banerjee, 2013[105]	Categorical: 0.64 (95% CI 0.61 to 0.67)	–	Categorical: 0.64 (95% CI 0.62 to 0.67)	–
Banerjee, 2014[106]	Continuous: 0.641 (95% CI 0.607 to 0.676)	–	Continuous: 0.621 (95% CI 0.616 to 0.683)	–
Baruch, 2007[107]	Categorical (Classic): 0.64 (95% CI 0.61 to 0.67) Categorical (Revised): 0.64 (95% CI 0.61 to 0.67)	Categorical: 0.62 (95% CI 0.59 to 0.66)	Categorical: 0.65 (95% CI 0.61 to 0.68)	–
Fang, 2008[117]	Continuous: All patients: 0.60 Categorical: All patients: 0.58 Off therapy: 0.67	Continuous: All patients: 0.64 Categorical: All patients: 0.62 Off therapy: 0.69	–	–
Friberg, 2012[122]	Continuous: 0.66 (95% CI 0.65 to 0.66) Categorical (Revised): 0.61 (95% CI 0.61 to 0.62) Categorical (Classic): 0.64 (95% CI 0.64 to 0.65)	Continuous: 0.67 (95% CI 0.66 to 0.67) Categorical: 0.64 (95% CI 0.64 to 0.65)	Continuous: 0.67 (95% CI 0.67 to 0.68) Categorical: 0.56 (95% CI 0.56 to 0.57)	–
Friberg, 2015[123]	Continuous: 0.72 (95% CI 0.72 to 0.73)	–	Continuous: 0.71 (95% CI 0.71 to 0.72)	–
Gage, 2001[14]	Continuous: 0.82 (95% CI 0.80 to 0.84)	–		–

Study	$CHADS_2$	Framingham	CHA_2DS_2-VASc	ABC-Stroke
Hijazi, 2016[126]	–	–	Continuous: Derivation cohort: 0.62 (95% CI 0.60 to 0.65) Validation cohort: 0.58 (95% CI 0.49 to 0.67)	Categorical: Derivation cohort, TnI: 0.68 (95% CI 0.65 to 0.71) Derivation cohort, TnT: 0.67 (95% CI 0.65 to 0.70) Validation cohort, TnT: 0.66 (95% CI 0.58 to 0.74)
Primary paper: Granger, 2011[25] Relevant companion: Hijazi, 2017[170]	–	–	–	Categorical: Baseline data: TnI: 0.71 (95% CI 0.66 to 0.76) TnT: 0.70 (95% CI 0.65 to 0.75) 2 months: TnI: 0.72 (95% CI 0.66 to 0.77) TnT: 0.70 (95% CI 0.65 to 0.76)
Primary paper: O'Brien, 2015[176] Relevant companion: Inohara, 2017[168]	–	–	Continuous: 0.679 (95% CI 0.651 to 0.707)	–
Larsen, 2012[129]	Continuous: 0.68 (95% CI 0.59 to 0.76)	–	Continuous: 0.69 (95% CI 0.60 to 0.77)	–
Lip, 2010[16]	Continuous: 0.60 (95% CI 0.49 to 0.72) Categorical (Classic): 0.56 (95% CI 0.44 to 0.66) Categorical (Revised): 0.59 (95% CI 0.48 to 0.70)	Continuous: 0.69 (95% CI 0.60 to 0.78) Categorical: 0.64 (95% CI 0.53 to 0.74)	–	–
McAlister, 2017[136]	Categorical: 0.663 (95% CI 0.652 to 0.675)	–	Categorical: 0.661 (95% CI 0.649 to 0.672)	–

Study	$CHADS_2$	Framingham	CHA_2DS_2-VASc	ABC-Stroke
Oldgren, 2016[140]		–	Continuous: 0.60 (95% CI 0.57 to 0.64)	Categorical: 0.65 (95% CI 0.61to 0.69)
Olesen, 2011[142]	*Covariates analyzed as categorical variables:* Continuous: 0.78 (95% CI 0.76 to 0.80) Categorical: 0.81 (95% CI 0.80 to 0.83) *Covariates analyzed as continuous variables:* Continuous: 0.80 (95% CI 0.79 to 0.82) Categorical: 0.81 (95% CI 0.80 to 0.83)	–	*Covariates analyzed as categorical variables:* Continuous: 0.78 (95% CI 0.76 to 0.79) Categorical: 0.89 (95% CI 0.88 to 0.90) *Covariates analyzed as continuous variables:* Continuous: 0.79 (95% CI 0.78 to 0.81) Categorical: 0.89 (95% CI 0.88 to 0.90)	–
Olesen, 2012[143]	Categorical: 0.63 (95% CI 0.62 to 0.65)	–	Continuous: 0.66 (95% CI 0.65 to 0.68)	–
Philippart 2016[147]		–	Categorical: 0.588 (95% CI 0.577 to 0.599) Continuous: 0.641 (95% CI 0.631 to 0.652)	–
Poli, 2009[148]	Categorical: All patients: 0.68 On therapy: 0.52	–		–
Poli, 2011[150]	Continuous (Revised): 0.72 (95% CI 0.64 to 0.80) Categorical (Classic): 0.68 (95% CI 0.61 to 0.76) Categorical (Revised): 0.60 (95% CI 0.51 to 0.67)	–	Continuous: 0.72 (95% CI 0.65 to 0.80) Categorical: 0.52 (95% CI 0.44 to 0.61)	–
Potpara, 2012[151]	Categorical: 0.58 (95% CI 0.38 to 0.79)	–	Categorical: 0.72 (95% CI 0.61 to 0.84)	–

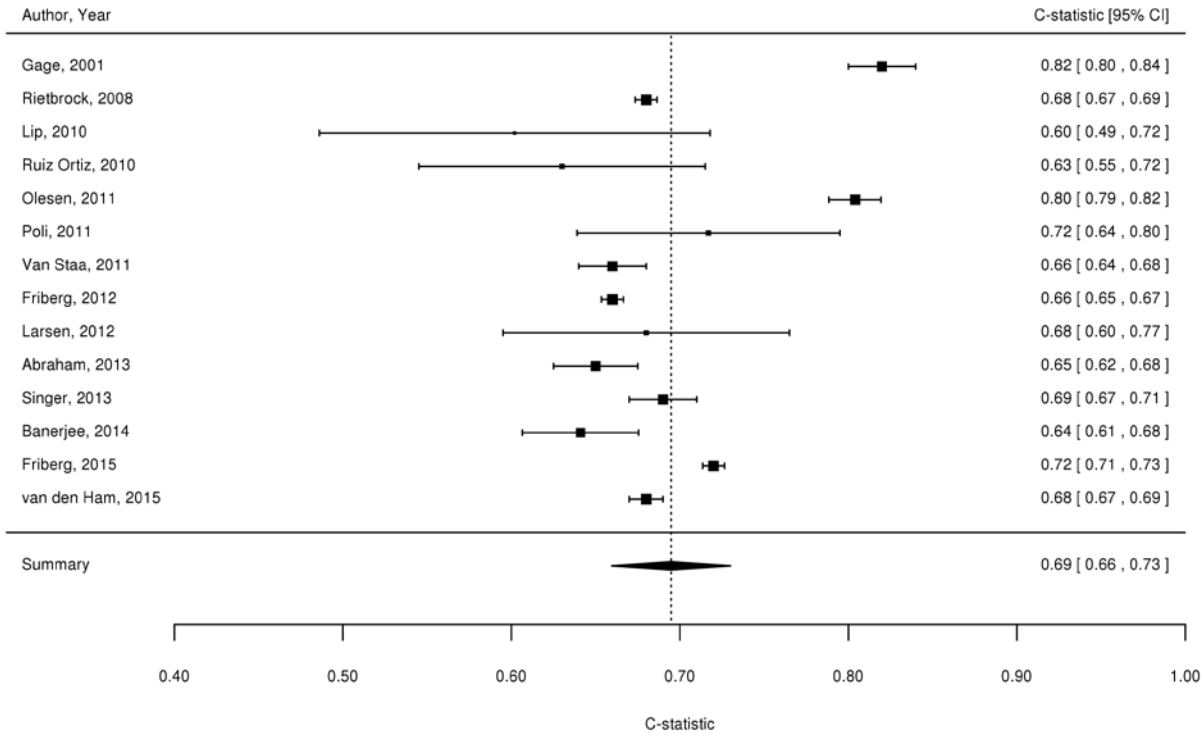
Study	$CHADS_2$	Framingham	CHA_2DS_2-VASc	ABC-Stroke
Rietbrock, 2008[154]	Continuous (Classic): 0.68 (95% CI 0.68 to 0.69) Continuous (Revised): 0.72 (95% CI 0.72 to 0.73)	–	–	–
Primary paper: Rivera-Caravaca, 2017[173] Relevant companion: Rivera-Caravaca, 2017[172]	–	–	Categorical (3.5 years): 0.600 (95% CI 0.567 to 0.625) Categorical (6.5 years): 0.620 (95% CI 0.590 to 0.648)	Categorical (3.5 years): 0.663 (95% CI 0.634 to 0.690) Categorical (6.5 years): 0.662 (95% CI 0.633 to 0.690)
Ruff, 2016[155]	–	–	Continuous: 0.586 (95% CI 0.565 to 0.607)	–
Ruiz Ortiz, 2010[157]	Continuous: 0.63 (95% CI 0.55 to 0.72)	–		–
Singer, 2013[160]	Continuous: 0.69 (95% CI 0.67 to 0.71) Categorical: 0.66 (95% CI 0.64 to 0.68)	–	Continuous: 0.70 (95% CI 0.68 to 0.72) Categorical: 0.58 (95% CI 0.57 to 0.59)	–
van den Ham, 2015[167]	Continuous: 0.68 (95% CI 0.67 to 0.69) Categorical (published low/moderate/high) 0.65 (95% CI 0.64 to 0.66) Categorical (optimized) 0.65 (95% CI 0.64 to 0.66)	–	Continuous: 0.68 (95% CI 0.67 to 0.69) Categorical (published low/moderate/high) 0.59 (95% CI 0.59 to 0.60) Categorical (optimized) 0.63 (95% CI 0.62 to 0.64)	–
Van Staa, 2011[164]	Continuous: 0.66 (95% CI 0.64 to 0.68) Categorical: 0.65 (95% CI 0.63 to 0.67)	Continuous: 0.65 (95% CI 0.63 to 0.68) Categorical: 0.62 (95% CI 0.60 to 0.64)	Continuous: 0.67 (95% CI 0.65 to 0.69) Categorical: 0.60 (95% CI 0.59 to 0.61)	–

Study	$CHADS_2$	Framingham	CHA_2DS_2-VASc	ABC-Stroke
Wang, 2003[165]	Categorical: 0.62	Categorical: 0.66 (SD 0.03)	–	–

Abbreviations: $CHADS_2$=Congestive heart failure, Hypertension, Age ≥75, Diabetes mellitus, prior Stroke/transient ischemic attack (2 points); CHA_2DS_2-VASc=Congestive heart failure/left ventricular ejection fraction ≤ 40%, Hypertension, Age ≥75 (2 points), Diabetes mellitus, prior Stroke/transient ischemic attack/thromboembolism (2 points), Vascular disease, Age 65–74, Sex category female; CI=confidence interval; SD=standard deviation

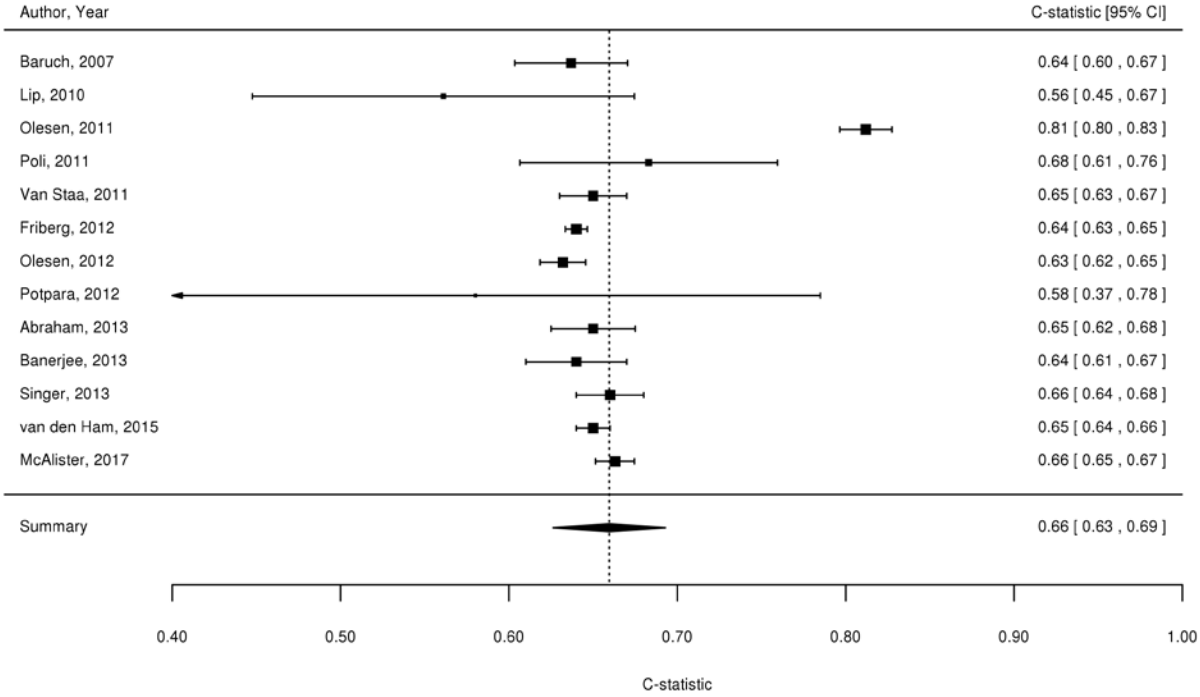
Sufficient data existed to permit meta-analysis of studies evaluating c-statistics for the $CHADS_2$ score using a continuous score (Figure 3, c-statistic = 0.69, 95% CI 0.66 to 0.73, I^2 = 97.7%, Q = 574.6, p<0.001) and categorical score (Figure 4, c-statistic = 0.66, 95% CI 0.63 to 0.69, I^2 = 97.2%, Q = 433.7, p<0.001), the Framingham categorical score (Figure 5), the CHA_2DS_2-VASc continuous score (Figure 6, c-statistic = 0.67, 95% CI 0.64 to 0.70, I^2 = 96.5%, Q = 459.4, p<0.001) and categorical score (Figure 7, c-statistic = 0.64, 95% CI 0.58 to 0.70, I^2 = 99.5%, Q = 2265.2, p<0.001), and the ABC stroke risk score (Figure 8, c-statistic = 0.67, 95% CI 0.63 to 0.71, I^2 = 37.9%, Q = 4.8, p=0.18).

Figure 3. Summary estimate of c-statistics for prediction ability of $CHADS_2$ continuous stroke risk score



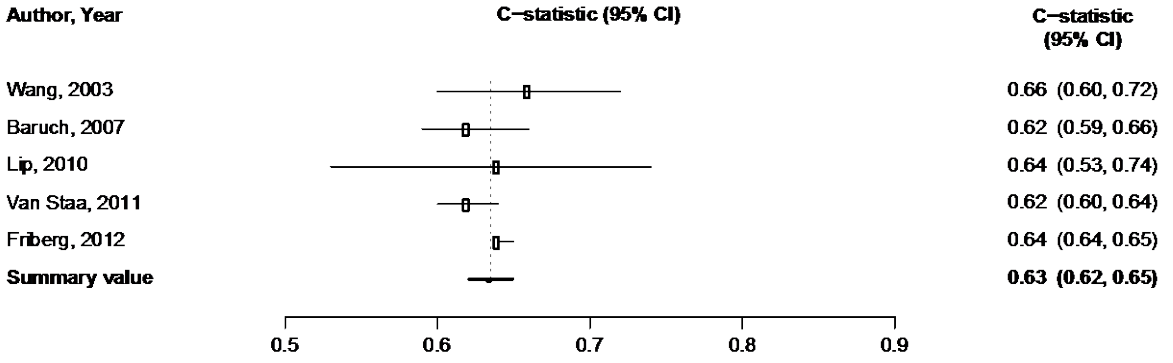
Abbreviations: $CHADS_2$=Congestive heart failure, Hypertension, Age ≥75, Diabetes mellitus, prior Stroke/transient ischemic attack (2 points); CI=confidence interval

Figure 4. Summary estimate of c-statistics for prediction ability of $CHADS_2$ categorical stroke risk score



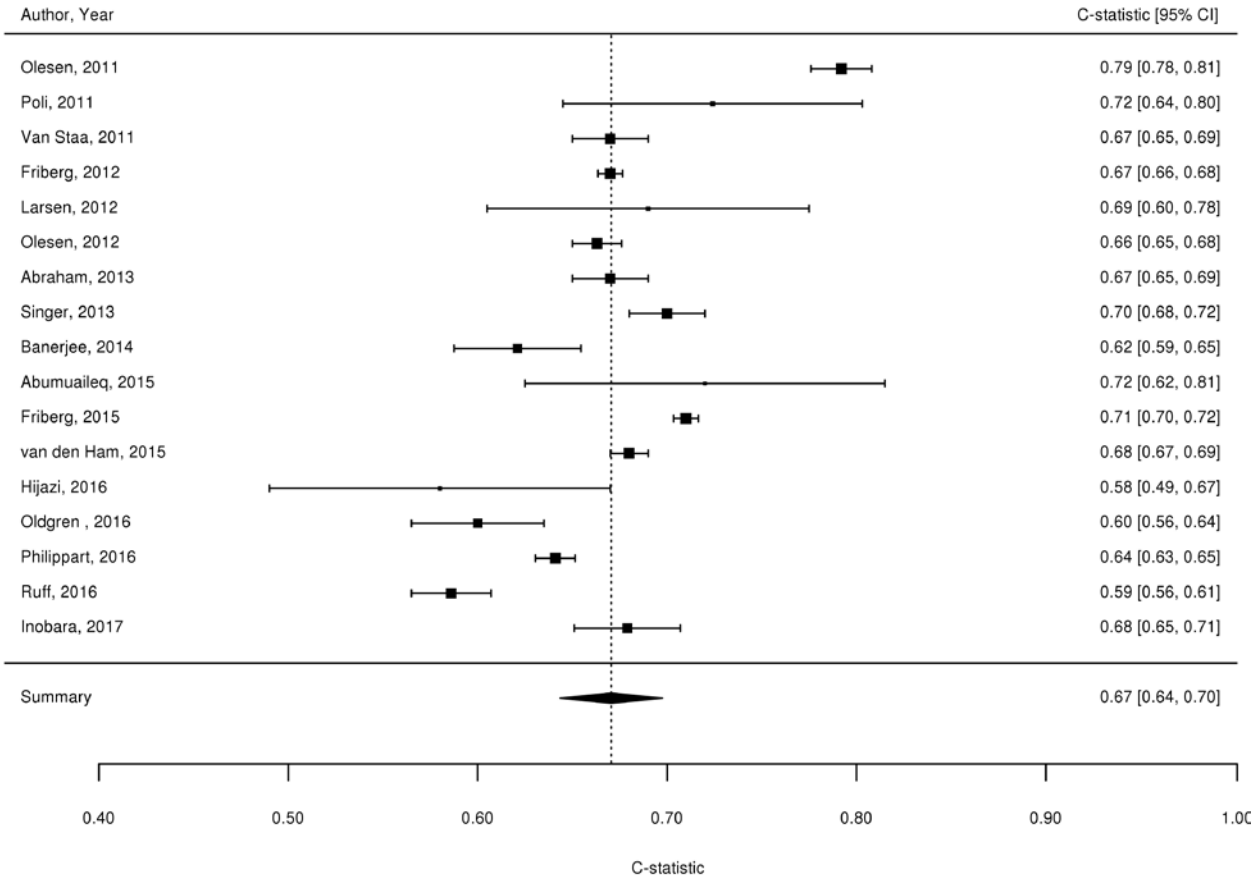
Abbreviations: $CHADS_2$=Congestive heart failure, Hypertension, Age ≥75, Diabetes mellitus, prior Stroke/transient ischemic attack (2 points); CI=confidence interval

Figure 5. Summary estimate of c-statistics for prediction ability of Framingham categorical stroke risk score



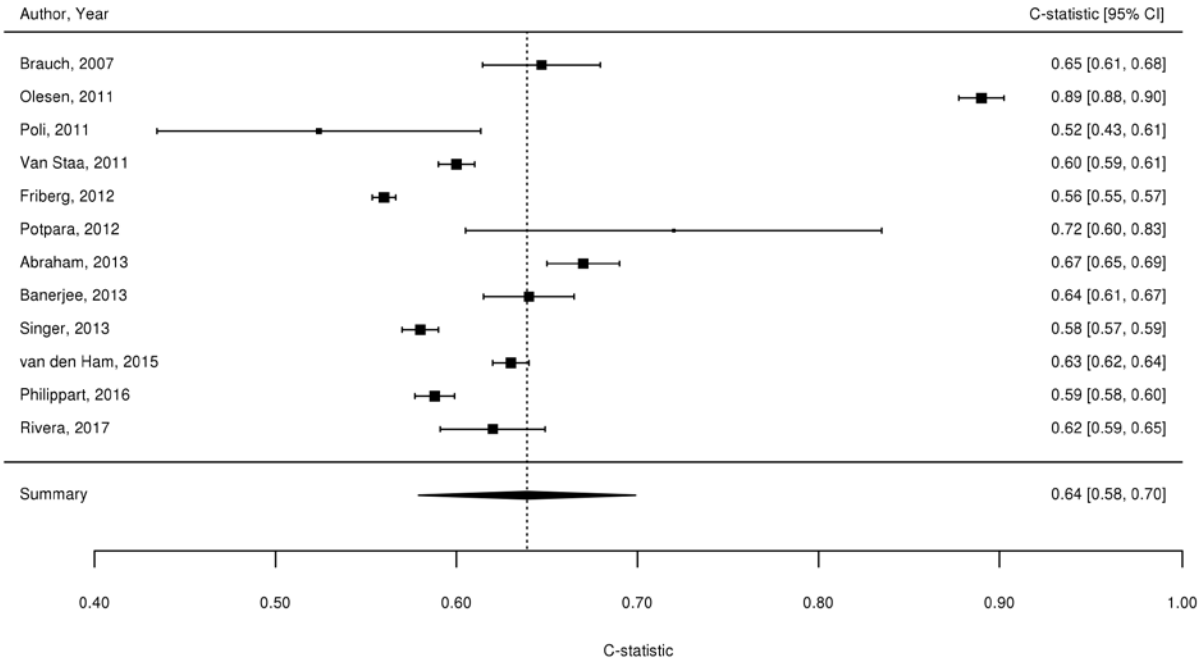
Abbreviation: CI=confidence interval

Figure 6. Summary estimate of c-statistics for prediction ability of CHA_2DS_2-VASc continuous stroke risk score



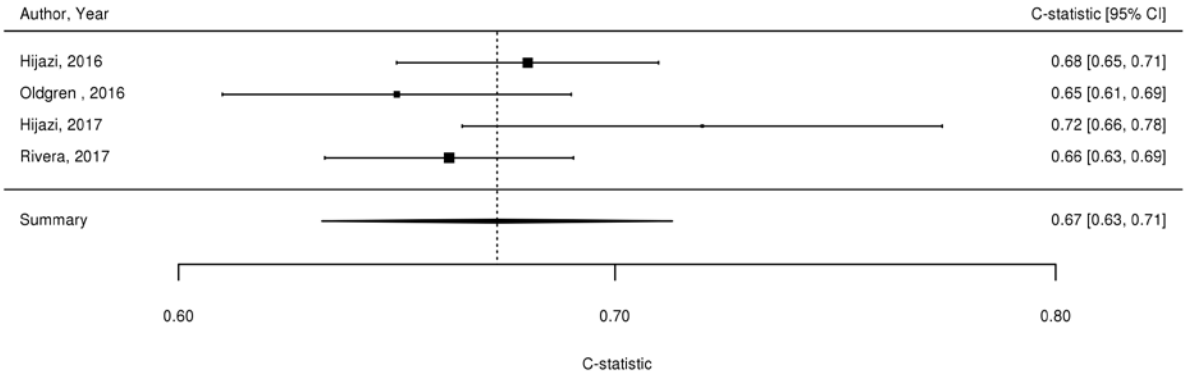
Abbreviations: CHA_2DS_2-VASc=Congestive heart failure/left ventricular ejection fraction ≤40%, Hypertension, Age ≥75 (2 points), Diabetes mellitus, prior Stroke/transient ischemic attack/thromboembolism (2 points), Vascular disease, Age 65–74, Sex category female; CI=confidence interval

Figure 7. Summary estimate of c-statistics for prediction ability of CHA_2DS_2-VASc categorical stroke risk score



Abbreviations: CHA_2DS_2-VASc=Congestive heart failure/left ventricular ejection fraction ≤ 40%, Hypertension, Age ≥75 (2 points), Diabetes mellitus, prior Stroke/transient ischemic attack/thromboembolism (2 points), Vascular disease, Age 65–74, Sex category female; CI=confidence interval

Figure 8. Summary estimate of c-statistics for prediction ability of ABC categorical stroke risk score



Abbreviations: ABC=age, biomarkers, clinical history; CI=confidence interval

These analyses demonstrated that the $CHADS_2$, the CHA_2DS_2-VASc, and the ABC stroke risk score all have comparable prediction abilities for stroke risk (all limited risk prediction with moderate SOE other than the CHA_2DS_2-VASc which had low SOE given imprecision). The $CHADS_2$ continuous scores does appear to be better predictor of risk than the Framingham categorical score (0.63 [95% CI 0.62 to 0.65]) given our included studies. Although several studies in Table 21 provide direct comparison evidence, our meta-analysis allows us to combine findings across studies and to synthesize findings between scores. Note that only the

Framingham categorical score has limited heterogeneity, while all other scores have substantial heterogeneity, reducing the strength of evidence.

Strength of Evidence

Table 22 summarizes the strength of evidence (SOE) for the thromboembolic risk prediction abilities of the included tools. This summary table represents only those studies that evaluated the risk prediction abilities of the tools using a c-statistic. Note we did not reduce the SOE for evaluating prediction of diagnostic tools through observational studies. We did allow for increased heterogeneity in findings when a greater number of studies were performed (e.g. $CHADS_2$ and CHA_2DS_2-VASc scores) and reduced our SOE if there were limited numbers of included studies (e.g., Framingham).

Table 22. Strength of evidence domains for prediction of thromboembolic risk

Outcome	Number of Studies (Subjects)	Risk of Bias	Consistency	Directness	Precision	SOE and Effect (95% CI)
$CHADS_2$ (Categorical)	16[16,98,107,117,122,132,136,142,143,148,150,151,160,164,165,167] (548,464)	Observational/ Moderate	Inconsistent	Direct	Precise	**SOE=Moderate** Limited risk prediction ability (c-statistics 0.66, 95% CI 0.63 to 0.69)
$CHADS_2$ (Continuous)	14[14,16,98,117,122,129,132,142,150,154,157,160,164,167] (489,335)	Observational/ Moderate	Inconsistent	Direct	Precise	**SOE=Moderate** Limited risk prediction ability (c-statistic=0.69; 95% CI 0.66 to 0.73)
CHA_2DS_2-VASc (Categorical)	13[98,107,122,132,136,142,147,150,151,160,164,167,173] (496,683)	Observational/ Moderate	Inconsistent	Direct	Imprecise	**SOE=Low** Limited risk prediction ability (c-statistic=0.64; 95% CI 0.58 to 0.70)
CHA_2DS_2-VASc (Continuous)	16[98,99,122,126,129,132,140,142,143,147,150,155,160,164,167,176] (511,481)	Observational/ Moderate	Inconsistent	Direct	Precise	**SOE=Moderate** Limited risk prediction ability (c-statistic=0.66; 95% CI 0.63 to 0.69)
Framingham (Categorical)	6[16,107,117,122,164,165,177] (282,572)	Observational/ Moderate	Consistent	Direct	Precise	**SOE=Moderate** Limited risk prediction ability (c-statistic=0.63; 95% CI 0.62 to 0.65)
Framingham (Continuous)	4[16,117,122,164] (274,538)	Observational/ Moderate	Consistent	Direct	Imprecise	**SOE=Low** Limited risk prediction ability (c-statistic ranges between 0.64 and 0.69 across studies)

Outcome	Number of Studies (Subjects)	Risk of Bias	Consistency	Directness	Precision	SOE and Effect (95% CI)
ABC (Categorical)	4[25,126,140,172] (25,614)	Observational/ Moderate	Consistent	Direct	Imprecise	**SOE=Moderate** Limited risk prediction ability (c-statistic=0.67; 95% CI 0.63 to 0.71)
Imaging Risk Tools	7[109,124,138,161-163,166] (4,962)	Observational/ Moderate	Inconsistent	Direct	Imprecise	**SOE=Insufficient**

Abbreviations: $CHADS_2$=Congestive heart failure, Hypertension, Age ≥75, Diabetes mellitus, prior Stroke/transient ischemic attack (2 points); CHA_2DS_2-VASc=Congestive heart failure/left ventricular ejection fraction ≤ 40%, Hypertension, Age ≥75 (2 points), Diabetes mellitus, prior Stroke/transient ischemic attack/thromboembolism (2 points), Vascular disease, Age 65–74, Sex category female; CI=confidence interval; INR=international normalized ratio; NA=not applicable; SOE=strength of evidence

Key Question 2. Predicting Bleeding Events

KQ 2. In patients with nonvalvular atrial fibrillation, what are the comparative diagnostic accuracy and impact on clinical decisionmaking (diagnostic thinking, therapeutic efficacy, and patient outcome efficacy) of clinical tools and associated risk factors for predicting bleeding events?

Key Points

- AF patients on warfarin: 13 studies (10 low risk of bias, 2 medium risk of bias, 1 high risk of bias; 197,312 patients) compared different risk scores (Bleeding Risk Index [BRI], $HEMORR_2HAGES$, HAS-BLED, ATRIA, ABC) in predicting major bleeding events. These studies differed markedly in population, major bleeding rates, and statistics reported for evaluating risk prediction scores for major bleeding events. Evidence favors HAS-BLED based on two studies demonstrating that it has statistically significantly higher prediction (by c-statistic) for major bleeding events than other scores among patients on warfarin, but the majority of comparative studies which evaluated HAS-BLED showed no statistically significant differences in prediction abilities, reducing the strength of evidence (moderate SOE).
- Chronic kidney disease (CKD) and major bleeding: Eight studies (7 low risk of bias, 1 medium risk of bias; 322,010 patients) evaluated the risk of major bleeding in patients with CKD. All studies demonstrated increased risk of bleeding in patients with CKD (moderate SOE) although do not formally evaluate the use of a tool incorporating CKD.
- AF patients on warfarin: 1 study (low risk of bias; 48,599 patients) compared $HEMORR_2HAGES$ and HAS-BLED in predicting intracranial hemorrhage (ICH). This study showed no statistically significant difference in prediction abilities between the two scores (low SOE).
- AF patients on aspirin alone: 3 studies (2 low risk of bias, 1 medium risk of bias; 177,538 patients) comparing different combinations of bleeding risk scores (BRI, $HEMORR_2HAGES$, and HAS-BLED) in predicting major bleeding events showed no statistically significant differences (low SOE).

- AF patients not on therapy: 6 studies (4 low risk of bias, 2 medium risk of bias; 310,607 patients) comparing different combinations of bleeding risk scores (BRI, HEMORR$_2$HAGES, HAS-BLED, and ATRIA) in predicting major bleeding events showed no statistically significant differences (low SOE).
- Limitations: Although studies consistently reported event rates and c-statistics, measures of tool calibration, strength of association, and diagnostic accuracy were inconsistently reported.
- The outcome of impact on clinical decisionmaking (diagnostic thinking and therapeutic efficacy) was not assessed by any studies.

Description of Included Studies

In 2012, an expert panel recently recommended that, following stroke risk assessment, bleeding risk for all patients with AF be assessed using an available scoring tool.[178] The factors comprising the bleeding risk scores of interest (Table 23), as well as other risk factors not included in these scores (e.g., small vessel disease, cerebral amyloid angiopathy, and particular ApoE genotypes), are all individually associated with bleeding risk in patients with AF based on available data. In order to inform clinical decisionmaking regarding the net clinical benefit of anticoagulation, we have focused this review on studies evaluating the risk scores most typically utilized for prospective estimation of bleeding risk in clinical settings. Multiple studies evaluated $CHADS_2$ and CHA_2DS_2-VASc, which are risk scores validated for thromboembolic risk prediction, as predictors of bleeding events; however, because these scores are not used clinically for estimation of bleeding risk, we did not include them in our analysis.

Thirty-eight studies described in 57 papers met our inclusion criteria.[18,24-26,102,103,106-108,111,113,114,118,122,123,125,127,128,130,132,135,136,141,146,149,153,159,168,171,173,174,176,179-204]

Thirty-two studies were observational studies[18,102,107,111,122,125,127,128,130,132,136,141,146,149,153,159,173,174,176,179,181-186,190,192,193,195,198,200,203] while 6 studies were RCTs.[24,25,107,113,118,189] The included studies explored interventions in studies of diverse quality, funding, and geographical location. Additional study characteristics can be reviewed in Appendix Table F-2.

Sixteen studies were conducted in UK/Europe,[18,111,112,122,130,132,141,149,159,173,183,186,190,192,195,200] 12 studies conducted in the United States,[102,107,127,146,174,176,181,182,184,185,198,203] and 3 studies conducted in Canada,[128,136,153] Additionally, there were seven studies that were multinational trials.[23-26,113,125,189]

Of the 38 studies, 11 did not report a funding source or it was unclear[112,130,132,141,149,159,181,190,192,195,203] 12 used exclusively industry funding;[18,23-26,102,107,113,125,174,182,189] 8 used exclusively government funding;[111,127,128,146,173,186,198,200] and 7 used funding from multiple sources.[122,136,153,176,183-185]

Twenty nine studies were rated as having a low risk of bias,[18,23-26,102,107,112,113,122,125,127,128,136,149,153,173,176,181-185,189,190,192,198,200,203] 5 were rated as having a medium risk of bias,[111,132,146,174,186] and 4 were rated as having a high risk of bias.[130,141,159,195] Studies with increased risk of bias had potential limitations related fidelity to the intervention protocol, whether data was handled appropriately, whether the length of follow up differed between groups, whether outcomes assessors were blinded, and whether confounders were assessed with valie and reliable measures.

Included studies most often presented data for the categorical versions of bleeding risk scores (i.e., risk score categorized as "low," "medium," or "high"), though some also presented data for continuous versions of the scores. When available, we present data for both categorical and continuous scores. Included studies consistently presented results using bleeding event rates (either bleeding events per 100 patient-years or percent of individuals experiencing a bleeding event within the followup period) and reported model discrimination/prediction using c-statistics. Measures of calibration, strength of association, and measures of diagnostic accuracy were inconsistently reported. The c-statistic, or area under the receiver operating characteristic curve, may not be optimal in assessing models that predict future risk or stratify individuals into risk categories,[175] but it is a commonly reported statistic for characterizing a predictive model's predictive abilities. Because studies included in this section generally used the c-statistic to characterize risk scores, we have used it as a basis for comparing these scores within a given study population, while also keeping in mind its limitations. We do not directly compare data from different studies, as this would not be appropriate given inter-study differences in patient population, followup times, and definitions of outcomes. A few studies presented other means for comparing bleeding risk scores, such as net reclassification improvement (NRI), and we provide this information when available. As a reminder, for a clinical prediction rule, we assumed that a c-statistic <0.6 had no clinical value, 0.6–0.7 had limited value, 0.7–0.8 had modest value, and >0.8 has prediction adequate for genuine clinical utility.[94]

Table 23. Description and interpretation of included bleeding risk scores

Bleeding Risk Score	Reference	Risk Factors Included	Interpretation
ABC	Hijazi, 2016[189]	Age, biomarkers [GDF-15, cTnT-hs, and haemoglobin], and clinical history [previous bleeding]	Low <1%, medium 1-2%, high >2%
ATRIA	Fang, 2011[184]	Anemia, renal disease (CrCl <30) (3 points each); age ≥75 (2 points); any prior bleeding, hypertension (1 point each)	Low (0-3), moderate (4), high (5-10)
BRI	Beyth, 1998[205]	Age ≥65, GI bleed in past 2 weeks, previous stroke, comorbidities (recent MI, hematocrit <30%,diabetes, creatinine >1.5), with 1 point for presence of each condition and 0 if absent	Low (0), moderate (1-2), high (3-4)
HAS-BLED	Pisters, 2010[18]	Hypertension, abnormal renal (CrCl <50) or liver function (1 point each); stroke, bleeding history or predisposition, labile INR (TTR <60%), age >65, drugs of interest/alcohol (1 point each)	Low (0), moderate (1-2), high (≥3)
HEMORR$_2$HAGES	Gage, 2006[185]	Liver/renal disease, ethanol abuse, malignancy, age >75, low platelet count or function, rebleeding risk, uncontrolled hypertension, anemia, genetic factors (CYP2C9), risk of fall or stroke (1 point for each risk factor present with 2 points for previous bleed)	Low (0-1), moderate (2-3), high (≥4)

Abbreviations: ABC=age, biomarkers, clinical history; ATRIA=Anticoagulation and Risk Factors in Atrial Fibrillation; BRI=Bleeding Risk Index; cTnT-hs=high-sensitivity cardiac troponin T; CrCl=creatinine clearance; GDF=growth differentiation factor-15; GI=gastrointestinal; HAS-BLED=Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (> 65 years), Drugs/alcohol concomitantly; HEMORR$_2$HAGES=Hepatic or renal disease, Ethanol abuse, Malignancy, Older (age >75 years), Reduced platelet count or

function, Rebleeding risk (2 points), Hypertension (uncontrolled), Anemia, Genetic factors, Excessive fall risk, Stroke; INR=international normalized ratio; MI=myocardial infarction; TTR=time in therapeutic range

Detailed Synthesis

Major Bleeding

Overview

A total of 26 studies evaluated various risk scores for estimating major bleeding risk in patients with AF, including patients on warfarin, novel oral anticoagulants, aspirin, and no antithrombotic therapy.[18,122,132,141,149,159,168,173,176,179-186,189-192,194-196,198,200,201,203] In general, major bleeding constituted clinically significant bleeding episodes; however, differences existed in the definitions of major bleeding used in different studies. Large database and registry studies used standard sets of International Classification of Diseases, 9th Revision (ICD-9) codes, while other studies cited the 2005 International Society on Thrombosis and Haemostasis (ISTH) criteria for major bleeding.[206] This heterogeneity in the definitions of major bleeding used by the included studies is a limiting factor in comparing data across study populations for this KQ.

Studies most commonly evaluated tools among AF patients on warfarin, though some also provided data on other populations. Different studies compared scores for predicting major bleeding and utilized different statistics to describe their findings; studies most commonly presented major bleeding event rates and c-statistics. Results are presented below by risk score. The final subsection below presents a table summarizing available c-statistics for the risk scores among patients on different antithrombotic therapies. Due to the limited number of studies available, the variability in the application the scores, the differences in the definitions of bleeding outcomes, and the heterogeneity in the populations or subgroups of interest studied quantitative meta-analysis was not possible for the studied risk scores.

Bleeding Risk Index

The Bleeding Risk Index (BRI), also known as the Outpatient Bleeding Risk Index, is calculated based on existence of the following clinical factors: Age ≥65, GI bleed in past 2 weeks, previous stroke, comorbidities (recent MI, hematocrit <30%, diabetes, creatinine >1.5), with 1 point for presence of each condition and 0 if absent.[205] The BRI total score ranges from 0 to 4, with increasing scores corresponding to increasing bleeding risk, and is easy to calculate and apply in clinical practice. It is interpreted as low (0), moderate (1-2), high (3-4) risk of bleeding.

The BRI score was evaluated in seven included studies among AF patients with and without anticoagulation.[132,149,181,184,185,191,198] Five of these studies compared BRI with other risk scores of interest, while two did not provide comparisons with other risk scores of interest. Multiple studies presented major bleeding event rate data for BRI stratified by risk level among patients on warfarin (Table 24). Although different study populations had variable incidence of bleeding events, bleeding event rate generally increased with increased BRI in all studies for patients taking warfarin.

Among patients on warfarin, c-statistics for the categorical BRI ranged from 0.56–0.65, demonstrating moderate SOE for limited risk prediction ability (Table 25).[132,184,185,191,198] Three studies presented c-statistics for the categorical BRI in other populations; for patients on aspirin

alone, one study reported a c-statistic of 0.69,[185] while for patients not on antithrombotic therapy, c-statistics ranged from 0.50 to 0.65.[132,185,191]

Table 24. Summary of results for studies evaluating BRI (%) among patients on warfarin

Study Design	No. of Patients	Outcome	Low	Moderate	High	Followup Period (Years)	C-statistic[a]	Risk of Bias
Aspinall, 2005[181] Observational	543	Bleeding	0	2.3	11.1	1.02	NR	Low
Fang, 2011[184] Observational	3,063	Bleeding	0.39	1.31	3.96	3.5	Categorical: 0.59 (95% CI 0.58 to 0.61) Continuous: 0.68 (95% CI 0.65 to 0.70)	Low
Gage, 2006[185] Observational	1,604	Bleeding	1.1	4.9	8.8	0.82	0.65 (SE 0.03)	Low
Lip, 2011[191] Observational	3,665	Bleeding	2.1	3.9	4.0	1.36	0.56 (95% CI 0.51 to 0.60)	Low
Lip, 2012[132] Observational	3,607	Bleeding	NR	NR	NR	NR	Categorical: 0.56 (95% CI 0.53 to 0.59) Continuous: 0.60 (95% CI 0.56 to 0.63)	Medium
Poli, 2011[149] Observational	3,302	Bleeding	0.95	1.26	1.7	2.3	NR	Low
Shireman, 2006[198] Observational	26,345	Bleeding	0	1	2.5	0.25	0.61	Low

[a] C-statistics given are for categorical risk scores unless otherwise noted.

Abbreviations: BRI=Bleeding Risk Index; CI=confidence interval; No=number; NR=not reported; SE=standard error

HEMORR$_2$HAGES

The HEMORR$_2$HAGES tool is calculated based on existence of the following clinical factors: Liver/renal disease, ethanol abuse, malignancy, age >75, low platelet count or function, rebleeding risk, uncontrolled hypertension, anemia, genetic factors (CYP2C9), risk of fall or stroke (1 point for each risk factor present with 2 points for previous bleed).[185] The HEMORR$_2$HAGES total score ranges from 0 to 12 based upon eleven parameters, with

increasing scores corresponding to increasing bleeding risk, and is easy to calculate and apply in clinical practice. It is interpreted as low (0-1), moderate (2-3), high (≥4) risk of bleeding.

HEMORR$_2$HAGES was evaluated in thirteen included studies among patients with AF with and without anticoagulation.[18,122,132,173,179,182,184,185,190-192,194,201] Each of these eleven studies compared HEMORR$_2$HAGES with at least one other risk score of interest. Of note, one issue with the included studies is that different studies used different approaches to calculating patients' HEMORR$_2$HAGES score. Due to unavailability of information on genetic factors, multiple database studies left out the "genetic factors" component of the score[122,132,179,182,184,185] and so were, in effect, evaluating a modified HEMORR$_2$HAGES. Not all studies described in detail whether certain factors were omitted from their HEMORR$_2$HAGES calculation. Inter-study differences in approach to calculating HEMORR$_2$HAGES limited our ability to compare data across populations.

Multiple studies presented major bleeding event rate data for HEMORR$_2$HAGES among patients on warfarin, either continuous or stratified by risk level (Table 25). Although different study populations had variable incidence of bleeding events, bleeding event rate generally increased with increased HEMORR$_2$HAGES in all studies for patients taking warfarin.

Among patients on warfarin, c-statistics for the categorical HEMORR$_2$HAGES ranged from 0.51 to 0.78, demonstrating moderate SOE for limited risk prediction ability (Table 25).[18,122,132,173,179,182,184,185,190-192,194] Seven studies presented c-statistics for HEMORR$_2$HAGES in other populations; for patients on aspirin alone, c-statistics ranged from 0.60 to 0.83,[18,122,185] while for patients not on antithrombotic therapy, c-statistics ranged from 0.50 to 0.81.[18,122,132,185,191,192]

Table 25. Summary of results for studies evaluating HEMORR$_2$HAGES among patients on warfarin

Study Design	No. of Patients	Outcome	Low	Moderate	High	Event Rates for HEMORR$_2$HAGES Score (Continuous), %	Followup Period (Years)	C-statistic[a]	Risk of Bias
Apostolakis, 2012[179] Observational	4,576	Bleeding	1.4	2.5	7.7	0=1.0 1=1.8 2=2.1 3=4.7 ≥4=7.6	1.17	0.60 (95% CI 0.51 to 0.69)	Low
Barnes, 2014[182] Observational	2,600	Bleeding	1.7	3.6	8.5	–	1	0.66 (95% CI 0.61-0.74)	Low
Fang, 2011[184] Observational	3,063	Bleeding	0.72	2.49	3.96	–	3.5	Categorical: 0.67 (95% CI 0.65 to 0.70) Continuous: 0.71 (95% CI 0.69 to 0.73)	Low
Friberg, 2012[122] Observational	48,599	Bleeding	–	–	–	0=0.6 1=1.7 2=2.2 3=3.0 4=4.4 5=6.0 6=7.1 7=9.6 8=19.3 9=0.0	1.4	0.63 (95% CI 0.61 to 0.64)	Low
Gage, 2006[185b] Observational	1,604	Bleeding	–	–	–	0=1.9 1=2.5 2=5.3 3=8.4 4=10.4 ≥5=12.3	0.82	0.67 (SE 0.04)	Low

Study Design	No. of Patients	Outcome	Low	Moderate	High	Event Rates for HEMORR$_2$HAGES Score (Continuous), %	Followup Period (Years)	C-statistic[a]	Risk of Bias
Jaspers Focks, 2016[190] Observational	1,157	Bleeding	4.1	7.0	8.4	–	2.5	Major bleeding = 0.57 (95% CI 0.50 to 0.63) Clinically relevant bleeding = 0.53 (95% CI 0.50 to 0.57) Any bleeding = 0.53 (95% CI 0.50 to 0.57)	Low
Lip, 2011[191] Observational	3,665	Bleeding	3.0	6.1	2.0	–	1.36	0.61 (95% CI 0.56 to 0.65)	Low
Lip, 2012[132] Observational	3,607	Bleeding	–	–	–	–	–	Categorical: 0.53 (95% CI 0.50 to 0.57) Continuous: 0.59 (95% CI 0.56 to 0.62)	Medium
Olesen, 2011[192] Observational	44,771	Bleeding	3.06	6.33	12.16	–	10	Categorical: 0.78 (95% CI 0.75 to 0.82) Continuous: 0.77 (95% CI 0.73 to 0.81)	High
Pisters, 2010[18] Observational	1,706	Bleeding	–	–	–	–	1	0.64 (95% CI 0.53 to 0.75)	Low

Study Design	No. of Patients	Outcome	Low	Moderate	High	Event Rates for HEMORR$_2$HAGES Score (Continuous), %	Followup Period (Years)	C-statistic[a]	Risk of Bias
Proietti 2017[201] Observational	18,113	Bleeding	54.6	41.6	3.8	–	2	0.62 (95% CI 0.61 to 0.64)	Low
Proietti, 2016[194] Observational	3,551	Bleeding	2.2	2.4	–	–	1.6	–	Low
Rivera-Caravaca, 2017[173] Observational	1,361	Bleeding	–	–	–	0=2.8 1=14.8 2=22 3=25.6 4=17.6 ≥5=17.2	6.5	0.54	Low

[a]C-statistics given are for categorical risk scores unless otherwise noted.
[b]Derivation study.
Abbreviations: CI=confidence interval; HEMORR$_2$HAGES=Hepatic or renal disease, Ethanol abuse, Malignancy, Older (age >75 years), Reduced platelet count or function, Re-bleeding risk (2 points), Hypertension (uncontrolled), Anemia, Genetic factors, Excessive fall risk, Stroke; No=number; SE=standard error

HAS-BLED

The HAS-BLED tool is calculated based on existence of the following clinical factors: Hypertension, abnormal renal (CrCl <50) or liver function (1 point each); stroke, bleeding history or predisposition, labile INR (TTR <60%), age >65, drugs of interest/alcohol (1 point each).[18] The HAS-BLED total score ranges from 0 to 9, with increasing scores corresponding to increasing bleeding risk, and is easy to calculate and apply in clinical practice. It is interpreted as low (0), moderate (1-2), high (≥3) risk of bleeding.

HAS-BLED was evaluated in 19 included studies among patients with AF with and without anticoagulation.[18,122,132,159,173,176,179,180,182,183,186,189-192,194-196,201,203] Fourteen of these studies compared HAS-BLED with at least one other risk score of interest. Of note, some studies excluded patients with labile INR and so quantified "labile INR"' as 0 for all patients;[122,186,195] these studies were, in effect, evaluating a modified HAS-BLED. Not all studies described in detail how they calculated the HAS-BLED score within their population. Inter-study differences in approach to calculating HAS-BLED limited our ability to compare data across populations.

Multiple studies presented major bleeding event rate data for HAS-BLED among patients on warfarin, either continuous or stratified by risk level (Table 26). Although different study populations had variable incidence of bleeding events, bleeding event rate generally increased with increased HAS-BLED in all studies for patients taking warfarin.

Among patients on warfarin, c-statistics for the categorical HAS-BLED ranged from 0.50 to 0.80, demonstrating moderate SOE for modest risk prediction ability (Table 26).[18,122,132,173,179,180,182,183,186,189-192,194-196] One study did not report the c-statistics for the HAS-BLED.[194] Eight studies presented c-statistics for HAS-BLED in other populations; for a mixed population of patients on warfarin or on dabigatran, c-statistics ranged from 0.62 to 0.66[176,201], for patients on aspirin alone, c-statistics ranged from 0.59 to 0.91,[18,122] while for patients not on antithrombotic therapy, c-statistics ranged from 0.60 to 0.81.[18,122,132,191,192]

Of note, one study provided event data for HAS-BLED ≤2 and ≥3 using a complicated matrix in which results were stratified by $CHADS_2$, CHA_2DS_2-VASc, and treatment status.[141] Because the primary goal of this analysis was to evaluate the net clinical benefit of antithrombotic treatment versus no treatment in different subgroups, these data are not presented here. Another study presented data for HAS-BLED and major bleeding event risk among patients status post coronary artery stents and showed no statistically significant association between major bleeding event rate and HAS-BLED score ≤2 versus ≥3. Because this was a specialized population, these data are not included in Table 26.

Table 26. Summary of results for studies evaluating HAS-BLED among patients on warfarin

Study Design	No. of Patients	Outcome	Low	Moderate	High	Event Rates for HAS-BLED Score (Continuous), %	Followup Period (Years)	C-statistic[a]	Risk of Bias
Apostolakis, 2012[179] Observational	4,576	Bleeding	1.3	–	3.1	0=1.1 1=0.6 2=1.8 3=2.9 4=3.4 ≥5=7.7	1.17	0.65 (95% CI 0.56 to 0.73)	Low
Apostolakis, 2013[180] Observational	2,293	Bleeding	–	–	–	0=6.7 1=8 2=10.6 3=16.4 4=14.6 ≥5=38.5	1.17	0.60 (95% CI 0.56 to 0.63)	Low
Barnes, 2014[182] Observational	2,600	Bleeding	1.3	2.0	6.6	–	1	0.69 (95% CI 0.63 to 0.75)	Low
Esteve-Pastor, 2016[183] Observational	1,276	Bleeding	1.7	3.2	6.2	–	1	0.63 (95% CI 0.56 to 0.71)	Low
Esteve-Pastor[204] Observational	1,120	Bleeding	2.16	–	3.74	–	6.5	0.583 (95% CI 0.554 to 0.612)	Low

Study Design	No. of Patients	Outcome	Low	Moderate	High	Event Rates for HAS-BLED Score (Continuous), %	Followup Period (Years)	C-statistic[a]	Risk of Bias
Friberg, 2012[122] Observational	48,599	Bleeding	–	–	–	0=0.0 1=0.7 2=1.9 3=2.4 4=3.4 5=5.7 6=15.5 7=0.0	1.4	0.61 (95% CI 0.59 to 0.62)	Low
Gallego, 2012[186] Observational	965	Bleeding	–	–	–	0=0.0 1=1.2 2=2.2 3=5.9 4=7.0 ≥5=19.4	2.36	0.70 (95% CI 0.64 to 0.76)	Medium
Hijazi, 2016[189] RCT	14,537 (ARISTOTLE) 8,461 (RE-LY)	Bleeding	0.36 0.62	1.56 1.67	3.75 4.87	–	1.7 (ARISTOTLE) 1.9 (RE-LY)	ARISTOTLE = 0.61 (95% CI 0.59 to 0.63) RE-LY= 0.62 (0.59 to 0.64)	Low
Jaspers Focks, 2016[190] Observational	1,157	Bleeding	4.1	7.3	7.7	–	2.5	Major bleeding = 0.57 (95% CI 0.50 to 0.63) Clinically relevant bleeding = 0.50 (95% CI 0.47 to 0.54) Any bleeding = 0.51 (95% CI 0.47 to 0.54)	Low

Study Design	No. of Patients	Outcome	Low	Moderate	High	Event Rates for HAS-BLED Score (Continuous), %	Followup Period (Years)	C-statistic[a]	Risk of Bias
Lip, 2011[191] Observational	3,665	Bleeding	0.9	3.7	6.7	0=0.9 1=3.4 2=4.1 3=5.8 4=8.9 5=9.1 6=0	1.36	0.66 (95% CI 0.61 to 0.70)	Low
Lip, 2012[132] Observational	3,607	Bleeding	–	–	–	–	–	Categorical: 0.58 (95% CI 0.55 to 0.61) Continuous: 0.61 (95% CI 0.58 to 0.65)	Medium
Lip, 2017[200]	57, 930	Bleeding	–	1.99	1.99	0=0.47 1=1.27 2=2.08 3=2.75 4=3.86 5=5.65 6=11.33	1	0.58 (95% CI 0.57 to 0.59)	Low
Olesen, 2011[192] Observational	44,771	Bleeding	2.66	5.54	8.11	–	10	Categorical: 0.80 (95% CI 0.76 to 0.83) Continuous: 0.80 (95% CI 0.76 to 0.83)	High
Pisters, 2010[18b] Observational	1,722	Bleeding	–	–	–	0=1.13 1=1.02 2=1.88 3=3.74 4=8.70 5=12.50 6=0.0	1	0.69 (95% CI 0.59 to 0.80)	Low

Study Design	No. of Patients	Outcome	Low	Moderate	High	Event Rates for HAS-BLED Score (Continuous), %	Followup Period (Years)	C-statistic[a]	Risk of Bias
Proietti 2017[201] Observational	18,113	Bleeding	69.7	–	30.3	–	2	0.62 (95% CI 0.60 to 0.63)	Low
Proietti, 2016[194] Observational	3,551	Bleeding	1.8	–	2.9	–	1.6	–	Low
Rivera-Caravaca, 2017[173] Observational	1,361	Bleeding	–	–	–	0=2 1=8 2=24.8 3=32.8 4=19.6 ≥5=12.8	6.5	0.62	Low
Roldan, 2012[195] Observational	937	Bleeding	–	–	–	0=0.0 1=0.8 2=1.9 3=5.7 4=5.6 ≥5=16.48	2.6	Categorical: 0.68 (95% CI 0.65 to 0.71) Continuous: 0.71 (95% CI 0.68 to 0.74)	Medium
Senoo, 2016[196] Observational	2,293	Bleeding	–	–	–	0=1.16 1=0.65 2=1.97 3=3.1 4=3.71 5=9.66 ≥6=not reported	–	0.65 (95% CI 0.56 to 0.73)	Low

Study Design	No. of Patients	Outcome	Low	Moderate	High	Event Rates for HAS-BLED Score (Continuous), %	Followup Period (Years)	C-statistic[a]	Risk of Bias
Yao, 2017[203] Observational	39,539	Bleeding	0.98	3.07	6.85	_	0.6	Categorical: 0.64 (95% CI 0.62 to 0.66) Continuous: 0.66 (95% CI 0.64 to 0.67)	Low

[a]C-statistics given are for categorical risk scores unless otherwise noted.
[b]Derivation study.
Abbreviations: ARISTOTLE= Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (trial); CI=confidence interval; HAS-BLED=Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (> 65 years), Drugs/alcohol concomitantly; N=number of participants; RE-LY=Randomized Evaluation of Long-Term Anticoagulation Therapy (trial)

ATRIA

The ATRIA tool is calculated based on existence of the following clinical factors: Anemia, renal disease (CrCl <30) (3 points each); age ≥75 (2 points); any prior bleeding, hypertension (1 point each).[184] The ATRIA total score ranges from 0 to 10, with increasing scores corresponding to increasing bleeding risk, and is easy to calculate and apply in clinical practice. It is interpreted as low (0-3), moderate (4), high (5-10) risk of bleeding.

ATRIA was evaluated in thirteen included studies among patients with AF with and without anticoagulation.[132,168,173,176,179,182,184,190,194-196,200,201,203] All of these studies compared ATRIA with other risk scores of interest. Multiple studies presented major bleeding event rate data for ATRIA stratified by risk level among patients on warfarin (Table 27). Although different study populations had variable incidence of bleeding events, bleeding event rate generally increased with increased ATRIA in all studies for patients taking warfarin.

Among patients on warfarin, c-statistics for the categorical ATRIA ranged from 0.51 to 0.74, but given the inconsistency and imprecision of the findings, there was insufficient evidence to determine the risk prediction abilities (Table 27).[132,173,179,182,184,190,194-196,200] Three studies presented c-statistics for HAS-BLED in a mixed population of patients on warfarin or on dabigatran, c-statistics ranged from 0.64 to 0.66.[168,176,201] One study presented c-statistics for ATRIA among patients not on antithrombotic therapy: 0.59 (continuous) and 0.47 (categorical).[132]

Table 27. Summary of results for studies evaluating ATRIA among patients on warfarin

Study Design	No. of Patients	Outcome	Low	Moderate	High	Event Rates for ATRIA score (Continuous), %	Followup Period (Years)	C-statistic[a]	Risk of Bias
Apostolakis, 2012[179] Observational	4,576	Bleeding	1.5	2.9	3.9	0=1.2 1=1.2 2=1.9 3=2.2 4=2.9 5=3.6 6=4.0 ≥7=0.0	1.17	0.61 (95% CI 0.51 to 0.70)	Low
Barnes, 2014[182] Observational	2,600	Bleeding	2.3	7.4	9.1	–	1	0.67 (95% CI 0.61 to 0.74)	Low
Fang, 2011[184b] Observational	3,063	Bleeding	0.83	2.41	9.1	0=0.48 1=0.58 2=0.78 3=1.27 4=2.41 5=4.18 6=5.11 7=3.56 8=23.11 9=10.13 10=16.34	3.5	Categorical: 0.69 (95% CI 0.66 to 0.71) Continuous: 0.74 (95% CI 0.72 to 0.76)	Low
Inohara, 2017[168] Observational	9,749	Bleeding	–	–	–	–	–	0.660 (95% CI 0.679 to 0.641)	Low

Study Design	No. of Patients	Outcome	Low	Moderate	High	Event Rates for ATRIA score (Continuous), %	Followup Period (Years)	C-statistic[a]	Risk of Bias
Jaspers Focks, 2016[190] Observational	1,157	Bleeding	5.4	7.9	8.7	–	2.5	Major Bleeding = 0.58 (95% CI 0.51 to 0.64) Clinically relevant bleeding = 0.52 (95% CI 0.49 to 0.56) Any bleeding = 0.53 (95% CI 0.50 to 0.57)	Low
Lip, 2012[132] Observational	3,607	Bleeding	–	–	–	–	–	Categorical: 0.55 (95% CI 0.52 to 0.59) Continuous: 0.60 (95% CI 0.56 to 0.63)	Medium
Lip, 2017[200]	57, 930	Bleeding	–	2.73	3.46	0=0.81 1=1.53 2=2.87 3=2.80 4=5.30 5=6.56 6=6.04 7=8.27 8=8.03 9-10=8.77	1	0.59 (95% CI 0.57 to 0.60)	Low
Proietti 2017[201] Observational	18,113	Bleeding	82.5	–	17.5	–	2	0.64 (95% CI 0.62 to 0.65)	Low
Proietti, 2016[194] Observational	3,551	Bleeding	2.5	–	3.4	–	–	–	Low

Study Design	No. of Patients	Outcome	Low	Moderate	High	Event Rates for ATRIA score (Continuous), %	Followup Period (Years)	C-statistic[a]	Risk of Bias
Rivera-Caravaca, 2017[173] Observational	1,361	Bleeding	–	–	–	0=5.6 1=22.4 2=8.4 3=34 4=10.8 ≥5=18.8	6.5	0.54	Low
Roldan, 2012[195] Observational	937	Bleeding	–	–	–	0=1.1 1=2.0 2=2.4 3=1.9 4=9.1 ≥5=6.5	2.6	Categorical: 0.59 (95% CI 0.55 to 0.62) Continuous: 0.68 (95% CI 0.65 to 0.71)	Medium
Senoo, 2016[196] Observational	2,293	Bleeding	–	–	–	0=1.2 1=1.27 2=1.97 3=2.47 4=3.6 5=4.09 ≥6=4.29	–	0.61 (95% CI 0.51 to 0.70)	Low
Yao, 2017[203] Observational	39,539	Bleeding	1.33	3.79	5.51	–	0.6	Categorical: 0.60 (95% CI 0.58 to 0.62) Continuous: 0.67 (95% CI 0.65 to 0.69)	Low

[a]C-statistics given are for categorical risk scores unless otherwise noted.
[b]Derivation study; bleeding event rate data presented is for validation cohort, c-statistic data provided for combined cohort only.
Abbreviations: CI=confidence interval; ATRIA=Anticoagulation and Risk Factors in Atrial Fibrillation; N=number of participants

ABC Bleeding Risk Score

The ABC bleeding risk score is calculated based on existence of the following clinical factors: Age, biomarkers (GDF-15, cTnT-hs, and haemoglobin), and clinical history (previous bleeding).[189] The ABC bleeding total score ranges from 0 to 28, with increasing scores corresponding to increasing bleeding risk, and is easy to calculate and apply in clinical practice. It is interpreted as 1-year and 3-years risk of bleeding by low <1%, medium 1-2%, high >2%.

One included study developed and evaluated the use of the ABC Bleeding Risk Score. The study initially derived the score in the ARISTOTLE study and then validated it in the RE-LY study.[107,189] The major bleeding rates were similar across the derivation and validation cohorts. The newly derived ABC risk score was compared to both the HAS-BLED and ORBIT bleeding risk scales. Among the full ARISTOTLE cohort the ABC Risk Score had a c-statistic of 0.68 (95% CI 0.66 to 0.70) and then had a c-statistic of 0.71 (95% CI 0.68 to 0.73) in the RE-LY cohort demonstrating low SOE for modest risk prediction abilities. The ABC bleeding score performed better than HAS-BLED and ORBIT scores indicating that it may be a useful score after further evaluation. A companion article to the Murcia AF Project[173] evaluated ABC Bleeding Risk Score among patients with AF with anticoagulation. In this study c-statistics for ABC Bleeding Risk Score in patients on warfarin was 0.518 (95% CI 0.488 to 0.548) (Table 28).[204]

Table 28. Summary of results for studies evaluating ABC Bleeding Risk Score among patients on warfarin

Study Design	N on Warfarin	Follow up	Bleeding Events Rate	C-statistics	Risk of Bias
Esteve-Pastor[204] Primary paper: Rivera-Caravaca, 2017[173] Observational	1,120	Median= 6.5yr	Major bleeding rates: Annual rate (%/year) Low-medium risk: 247% High Risk: 2.93%	0.518 (95% CI 0.488 to 0.548)	Low

Abbreviations: ABC=Age, biomarkers, clinical history; CI=confidence interval

Individual Risk Factors

Individual risk factors assessed and their major findings are presented in Table 29. Assessment of bleeding events based on individual risk factors was reported by 20 studies.[18,102,103,111,122,123,125,128,130,136,145,146,153,171,174,187,188,197,199,202] Nine studies evaluated the risk of major bleeding in patients with chronic kidney disease.[18,103,111,122,123,128,136,171,197] All these studies demonstrated that chronic kidney disease was associated with an increased risk of bleeding events (Table 29) although these studies did not specifically look at CKD risk as a tool for bleeding risk prediction. The differences in CKD subgroup definitions as well as the heterogeneity of the overall populations studied eliminated the possibility of a quantitative synthesis of this evidence; however, there was a moderate SOE for an increase in bleeding risk for patients with CKD.

One study examined the risk of dementia finding no statistically significant increase in risk among older females compared to males or following diagnosis.[146] Five studies[102,125,130,174,199] examined the risk of major bleeding among patients' INR levels, finding higher risk of major bleeding when not in therapeutic range. One study[173] evaluated the c-index of major bleeding scores among patients which INR levels were not in therapeutic range. One study[202] evaluated

the c-index of major bleeding scores among patients with previous history of TIA or ischemic stroke on oral anticoagulants (Table 29).

Table 29. Summary of results evaluating individual risk factors

Study Design	No. of Patients	Followup	Bleeding Risk	Risk of Bias
Presence and severity of CKD				
Apostolakis, 2013[103] Observational	2293	–	Major Bleeding Patients with more than mild CKD (CrCl 60 mL/min) had higher risk of major bleeding compare with patients with CrCl ≥60 mL/min: HR 1.58 (95% CI 1.05 to 2.39)[a]	Low
Bassand, 2018[171]	28,628	2 years	Major Bleeding HR 1.74 (95% CI 1.34 to 2.26)	Low
Friberg, 2015[123] Observational	283,969	Total: Median 2.1 years	Intracranial Bleeding Presence and severity of CKD: HR 1.50 (95% CI 1.28 to 1.74)[a] Any Bleeding Presence and severity of CKD: HR 2.24 (95% CI 2.14 to 2.35)[a]	Low
Jun, 2017[128] Observational	14,892	1 year	Compared to nonuse, warfarin therapy was not associated with higher risk for major bleeding except for those with eGFRs of 60 to 89 mL/min/1.73 m2 (HR 1.36; 95% CI 1.13 to 1.64)	Low
McAlister, 2017[136] Observational	58,451	Median 31 months	eGFR, mL/min/1.73^2 ≥60 = 1.00 45-59 = 1.13 (95% CI 1.04 to 1.22) 30-44 = 1.25 (95% CI 1.14 to 1.37) <30 = 1.50 (95% CI 1.33 to 1.68)	Low
Friberg, 2012[122] Observational	182,678	Total: Median 1.4 year (IQR 1.8)	Multivariable Analysis Major Bleeding HR 1.59 (95% CI 1.41 to 1.79)[a]	Low
Pisters, 2010[18] Observational	3456	1 year	Major Bleeding OR 2.86 (95% CI 1.33 to 6.18)[a]	Low
Sherwood, 2015[197] Observational	14,263	–	Creatinine clearance (for each 5-U decrease to <60 ml/min) HR 1.06 (95% CI 1.01 to 1.12)[a]	Low
Cognitive impairment				
Orkaby, 2017[146] Observational	2,572	Mean 2.2 person-years following diagnosis of dementia	After diagnosis of dementia no statistically significant decrease in risk of major bleeding (HR 0.78, 95% CI 0.61 to 1.01, P = .06)	Medium
INR				
An, 2017[102] Observational	32,074	Total: 5 years Median 3.8 years	Patients whose TTRs were < 65%, had a 2 times higher risk of major bleeding (HR 2.10, 95% CI 1.96 to 2.24) compared with patients with the highest TTR quartile (≥ 73%)	Low
Haas, 2016[125]	9,934	1 year	TTR <65% vs. ≥65% bleeding risk HR 1.54 (95% CI 1.04 to 2.26)	Low

Study Design	No. of Patients	Followup	Bleeding Risk	Risk of Bias
Observational				
Lind, 2012[130] Observational	19,179	34718.9 patient-years	The bleeding risk HR for the SDT_{INR} variable was 1.27 (95% CI 1.20 to 1.35), and the HR for TTR was 1.07 (95% CI 1.01 to 1.14)	High
Phelps, 2018[174] Observational	8,405	1 year	Major Bleeding OR 0.62 (95% CI 0.43 to 0.89)	Moderate
Rivera-Caravaca,2018[199] Observational	1,361	6 months Median follow-up 214 days	Major bleeding rates per year: TTR <20% = 1.47 and ≥20% = 2.93; TTR <65% = 3.03 and ≥65% = 2.10	Low
Age				
Bassand, 2018[171]	28,628	2 years	Major Bleeding (HRs) <65 = referent 65-69 = 1.30 (95% CI 0.86 to 1.96) 70-74=1.88 (95% CI 1.30 to 2.74) 75+=2.49 (95% CI 1.81 to 3.42)	Low
Friberg, 2012[122] Observational	182,678	Total: Median 1.4 year (IQR 1.8)	Multivariable Analysis Major Bleeding Age: 65-74 yr HR 2.33 (95% CI 1.96 to 2.77)[a] >75yr HR 3.28 (95% CI 2.80 to 3.83)a	Low
Goodman, 2014[187] Observational	14,264	–	Multivariable analysis Major Bleeding Age (per 5y increase) HR 1.17 (95% CI 1.12 to 1.23)[a]	Low
Hankey, 2014[188] Observational	14,264	–	Intracranial Bleeding Age: HR for 10 years increase 1.35 (95% CI 1.13 to 1.63)[a]	Medium
Olesen, 2012[145] Observational	6348	–	Major Bleeding Age <65: Event Rate 0.39 (0.16 to 0.94) Age 65-74y: Event Rate 1.34 (0.60 to 2.97) Age>75: Event Rate 1.98 (1.10 to 3.58)	Medium
Pisters, 2010[18] Observational	3456	1 year	Major Bleeding Age >65: OR 2.66 (1.33-5.32)a	Low
Renoux, 2017[153] Observational	147,622	Mean follow up period 2.9 years	Female vs. Male for Major Bleeding <75 = HR 0.91 (95% CI 0.88 to 0.95) ≥75 = HR 0.96 (95% CI 0.89 to 1.02)	Low
Sherwood, 2015[197] Observational	14,263	–	Major Bleeding (Gastrointestinal) Age (for each 5-yr increase): HR 1.11 (1.06 to 1.17)[a]	Low

Study Design	No. of Patients	Followup	Bleeding Risk	Risk of Bias
Prior stroke				
Bassand, 2018[171]	28,628	2-years	Major Bleeding HR 1.36 (95% CI 1.04 to 1.78)	Low
Friberg, 2012[122] Observational	182,678	Total: Median 1.4 year (IQR 1.8)	Multivariable Analysis Major Bleeding HR 1.14 (95% CI 1.04 to 1.24)[a]	Low
Hankey, 2014[188] Observational	14,264	–	Intracranial Bleeding HR 1.42 (95% CI 1.02 to 1.96)[a]	Medium
Pisters, 2010[18] Observational	3456	1 year	Major Bleeding Prior stroke: OR 0.94 (95% CI 0.32 to 2.86)	Low
Hilkens, 2017[202] Observational	3623	2 years	C-statistic (95% CI) of risk scores for major bleeding in patients with a TIA or stroke on oral anticoagulants at 2 years HEMORR2 HAGES 0.63 (0.59 to 0.66) HAS-BLED 0.62 (0.58 to 0.65) ATRIA 0.66 (0.62 to 0.69)	Low
Presence of heart disease				
Bassand, 2018[171]	28,628	2-years	Major Bleeding HR 1.07 (95% CI 0.84 to 1.36)	Low
Friberg, 2012[122] Observational	182,678	Total: Median 1.4 year (IQR 1.8)	Multivariable Analysis Major Bleeding Presence of heart disease (Heart Failure): HR 1.15 (95% CI 1.07 to 1.24)[a] (Hypertension) HR 1.25 (95% CI 1.16 to 1.33)[a]	Low
Goodman, 2014[187] Observational	14,264	–	Multivariable Model Major Bleeding Presence of heart disease (Hypertension): DBP >90 mm Hg (per 5-mm Hg increase) HR 1.28 (1.11 to 1.47)[a]	Low
Hankey, 2014[188] Observational	14,264	–	Intracranial Bleeding HR 0.65 (95% CI 0.47 to 0.89)[a]	Medium
Pisters, 2010[18] Observational	3456	1 year	Major Bleeding Presence of heart disease (PA>160mmHg): OR 0.60 (95% CI 0.21 to 1.72)	Low
Diabetes				
Bassand, 2018[171]	28,628	2-years	Major Bleeding HR 0.92 (95% CI 0.71 to 1.18)	Low

Study Design	No. of Patients	Followup	Bleeding Risk	Risk of Bias
Friberg, 2012[122] Observational	182,678	Total: Median 1.4 yr (IQR 1.8)	Multivariable Analysis Major Bleeding HR 1.01 (95% CI 0.92 to 1.11)	Low
Sex				
Bassand, 2018[171]	28,628	2 years	Major Bleeding HR (Women) 1.14 (95% CI 0.90 to 1.45)	Low
Friberg, 2012[122] Observational	182,678	Total: Median 1.4 yr (IQR 1.8)	Multivariable Analysis Major Bleeding Female HR 0.79 (95% CI 0.73 to 0.85)[a]	Low
Goodman, 2014[187] Observational	14,264	–	Multivariable Model Major Bleeding Female vs. Male HR 0.82 (95% CI 0.70 to 0.95)a	Low
Renoux, 2017[153] Observational	147,622	Mean follow up period 2.9 years	Female vs. Male for Major Bleeding <75 = HR 0.91 (95% CI 0.88 to 0.95) ≥75 = HR 0.96 (95% CI 0.89 to 1.02)	Low
Sherwood, 2015[197] Observational	14,263	–	Major Bleeding (Gastrointestinal) Male HR 1.21 (95% CI 1.01 to 1.44)[a]	Low
Cancer				
Friberg, 2012[122] Observational	182,678	Total: Median 1.4 yr (IQR 1.8)	Multivariable Analysis Major Bleeding Cancer <3 years: HR 1.15 (95% CI 1.04 to 1.27)[a]	Low
Race/Ethnicity				
Bassand, 2018[171]	28,628	2-years	Major Bleeding (HRs) Caucasian / Hispanic / Latino (referent) Asian = 0.61 (95% CI 0.44 to 0.84) Other = 0.51 (95% CI 0.16 to 1.61)	Low
Hankey, 2014[188] Observational	14,264	–	Intracranial Bleeding Asian HR 2.02 (95% CI1.39 to 2.94) Black HR 3.25 (95% CI 1.43 to 7.41)[a]	Medium

[a] p value <0.05

Abbreviations: ATRIA=Anticoagulation and Risk Factors in Atrial Fibrillation; BRI=Bleeding Risk Index; CI=confidence interval; CKD=chronic kidney disease; CrCl= creatinine clearance; eGFR=estimated glomerular filtration rate; HAS-BLED=Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (> 65 years), Drugs/alcohol concomitantly; HR=hazard ratio; $HEMORR_2HAGES$=Hepatic or renal disease, Ethanol abuse, Malignancy, Older (age >75 years), Reduced platelet count or function, Rebleeding risk (2 points), Hypertension (uncontrolled), Anemia, Genetic factors, Excessive fall risk, Stroke; SE=standard error; INR=international normalized ratio; TIA=transient ischemic attack; TTR=time in therapeutic range; SDTinr=standardized deviation of transformed INF

Comparison of Bleeding Risk Scores and Meta-Analysis Results for Major Bleeding

Comparison of risk scores between study populations was complicated by some studies' use of administrative data sources, for two main reasons. First, many of the included studies used different approaches to calculating the risk scores of interest due to unavailable data (e.g.,

genetic factors in HEMORR$_2$HAGES or data on INR lability for HAS-BLED). Second, some studies were unable to validate clinical bleeding events, which could have affected their estimates of the performance of these risk scores. We therefore did not attempt meta-analysis for bleeding risk score data.

Included studies consistently used c-statistics to characterize these risk prediction scores, so we have used it as the basis for comparing these scores within study populations, while also keeping in mind its limitations as a measure of prediction only. Table 30 provides a summary of available c-statistics for the risk scores of interest among AF patients on warfarin. Tables 31 and 32 provide the same for patients on aspirin alone and on no antithrombotic therapy, respectively. Fewer studies presented other means for comparing risk scores, such as NRI, but available data on NRI with different risk scores are presented in Table 33.

Among patients on warfarin, the five risk scores—BRI, HEMORR$_2$HAGES, HAS-BLED, ATRIA, and ABC—were evaluated in studies where direct comparison with one or more of the other four scores was possible (Table 30). Of note, as with bleeding event rate estimates, c-statistics for each score varied considerably by population, making comparisons across studies difficult. Within-study c-statistics for patients on warfarin differed significantly between scores (as indicated by a p value <0.05 or non-overlapping 95% CIs) in only four cases; in one study HAS-BLED had a statistically significantly higher c-statistic than BRI,[191] in a second study the categorical HAS-BLED had a statistically significantly higher c-statistic than the categorical ATRIA (Table 30).[195] A third study demonstrated a higher c-statistic for categorical HEMORR$_2$HAGES as compared to categorical BRI.[184] Finally, in the derivation study for the ABC risk score[189], the ABC score had a higher c-statistic compared to HAS-BLED within the ARISTOTLE derivation cohort. Note that this was not the case in the validation RE-LY cohort. Among patients on aspirin alone or no antithrombotic therapy, no study appeared to show any significant between-score differences in c-statistics (Tables 31 and 32).

Four studies provided data on NRI as a means for comparing bleeding risk scores (Table 33). Within studies, NRI for patients differed significantly between risk scores in only two cases. In one study,[195] HAS-BLED had a statistically significant positive NRI compared with ATRIA among patients on warfarin. In another study,[132] HAS-BLED had a statistically significant positive NRI in separate, two-way comparisons with BRI, HEMORR$_2$HAGES, and ATRIA; however, it should be noted that the reported NRI values were for a mixed population of patients on or off warfarin, and not reported separately for patients on warfarin alone.

Although some studies seem to suggest that HAS-BLED predicts major bleeding more effectively than other scores among AF patients on warfarin, the majority of included studies do not show statistically significant differences between risk scores in discrimination or NRI. Early findings from the ABC risk score are promising. Further studies comparing all available risk scores for predicting major bleeding should use consistent and appropriate statistical evaluations (hazard ratios, likelihood ratios, c-statistics, NRI, etc.) in independent cohorts to better establish whether any score is superior in any population (e.g., AF patients on warfarin, AF patients on direct oral antithrombotic agents, and AF patients off of anticoagulation therapy).

Table 30. C-statistics from studies comparing scores of interest for prediction of major bleeding risk among patients on warfarin[a]

Study	BRI	HEMORR$_2$HAGES	HAS-BLED	ATRIA	ABC
Apostolakis, 2012[179d]	–	0.60 (95% CI 0.51 to 0.69)	0.65 (95% CI 0.56 to 0.73)	0.61 (95% CI 0.51 to 0.70)	–
Barnes, 2014[182]	–	0.66 (95% CI 0.61-0.74)	0.69 (95% CI 0.63-0.75)	0.67 (95% CI 0.61 to 0.74)	–
Fang, 2011[184d,f]	Categorical: 0.59 (95% CI 0.58 to 0.61) Continuous: 0.68 (95% CI 0.65 to 0.70)	Categorical: 0.67 (95% CI 0.65 to 0.70) Continuous: 0.71 (95% CI 0.69 to 0.73)	–	Categorical: 0.69 (95% CI 0.66 to 0.71) Continuous: 0.74 (95% CI 0.72 to 0.76)	–
Friberg, 2012[122d]	–	0.63 (95% CI 0.61 to 0.64)	0.61 (95% CI 0.59 to 0.62)	–	–
Gage, 2006[185b,c]	0.65 (SE 0.03)	0.67 (SE 0.04)	–	–	–
Hijazi, 2016[189]	–	–	ARISTOTLE: 0.61 (0.58 to 0.63) RE-LY: 0.60 (0.56 to 0.64)	–	ARISTOTLE: 0.68 (0.65 to 0.70) RE-LY: 0.65 (0.61 to 0.70)
Jaspers Focks, 2016[190]	–	Major bleeding = 0.57 (95% CI 0.50 to 0.63) Clinically relevant bleeding = 0.53 (95% CI 0.50 to 0.57) Any bleeding = 0.53 (95% CI 0.50 to 0.57)	Major Bleeding = 0.57 (95% CI 0.50 to 0.63) Clinically relevant bleeding = 0.50 (95% CI 0.47 to 0.54) Any bleeding = 0.51 (95% CI 0.47 to 0.54)	Major Bleeding = 0.58 (95% CI 0.51 to 0.64) Clinically relevant bleeding = 0.52 (95% CI 0.49 to 0.56) Any bleeding= 0.53 (95% CI 0.50 to 0.57)	–
Lip, 2011[191d]	0.56 (95% CI 0.51 to 0.60)	0.61 (95% CI 0.56 to 0.65)	0.66 (95% CI 0.61 to 0.70)	–	–
Lip, 2012[132g]	Categorical: 0.56 (95% CI 0.53 to 0.59) Continuous: 0.60 (95% CI 0.56 to 0.63)	Categorical: 0.53 (95% CI 0.50 to 0.57) Continuous: 0.59 (95% CI 0.56 to 0.62)	Categorical: 0.58 (95% CI 0.55 to 0.61) Continuous: 0.61 (95% CI 0.58 to 0.65)	Categorical: 0.55 (95% CI 0.52 to 0.59) Continuous: 0.60 (95% CI 0.56 to 0.63)	–
Lip, 2017[200]	–	–	0.58 (95% CI 0.57-0.59)	0.59 (95% CI 0.57-0.60)	–

Study	BRI	HEMORR$_2$HAGES	HAS-BLED	ATRIA	ABC
Olesen, 2011[192d]	–	Categorical: 0.78 (95% CI 0.75 to 0.82) Continuous: 0.77 (95% CI 0.73 to 0.81)	Categorical: 0.80 (95% CI 0.76 to 0.83) Continuous: 0.80 (95% CI 0.76 to 0.83)	–	–
Pisters, 2010[18d,e]	–	0.64 (95% CI 0.53 to 0.75)	0.69 (95% CI 0.59 to 0.80)	–	–
Roldan, 2012[195h]	–	–	Categorical: 0.68 (95% CI 0.65 to 0.71) Continuous: 0.71 (95% CI 0.68 to 0.74)	Categorical: 0.59 (95% CI 0.55 to 0.62) Continuous: 0.68 (95% CI 0.65 to 0.71)	–
Senoo, 2016[196]	–	–	0.65 (95% CI 0.56 to 0.73)	0.61 (95% CI 0.51 to 0.70)	–

[a]C-statistics given are for categorical risk scores unless otherwise noted.
[b]Derivation study for HEMORR$_2$HAGES.
[c]P-value for 2-way between-score comparison not provided.
[d]P-value for between-score comparison not provided.
[e]Derivation study for HAS-BLED.
[f]Derivation study for ATRIA.
[g]P-values for all between-score comparisons >0.05 (not specified as <0.05 in source article).
[h]P=0.035 for comparison of between-score categorical c-statistics and p=0.356 for comparison of between-score continuous c-statistics.

Abbreviations: ABC=Age, biomarkers, clinical history; ARISTOTLE=Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (trial); ATRIA=Anticoagulation and Risk Factors in Atrial Fibrillation; BRI=Bleeding Risk Index; CI=confidence interval; HAS-BLED=Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (> 65 years), Drugs/alcohol concomitantly; HEMORR$_2$HAGES=Hepatic or renal disease, Ethanol abuse, Malignancy, Older (age >75 years), Reduced platelet count or function, Rebleeding risk (2 points), Hypertension (uncontrolled), Anemia, Genetic factors, Excessive fall risk, Stroke; SE=standard error; RE-LY=Randomized Evaluation of Long-Term Anticoagulation Therapy (trial)

Table 31. C-statistics from studies comparing scores of interest for prediction of major bleeding risk among patients on aspirin alone[a]

Study	BRI	HEMORR$_2$HAGES	HAS-BLED
Friberg, 2012[122e]	–	0.60 (95% CI 0.59 to 0.61)	0.59 (95% CI 0.58 to 0.60)
Gage, 2006[185b,c]	0.69 (SE 0.05)	0.72 (SE 0.05)[b]	–
Pisters, 2010[18d,e]	–	0.83 (95% CI 0.68 to 0.98)	0.91 (95% CI 0.83 to 1.00)

[a]C-statistics given are for categorical risk scores unless otherwise noted.
[b]Derivation study for HEMORR$_2$HAGES.
[c]P-value for 2-way between-score comparison not provided.
[d]Derivation study for HAS-BLED.
[e]P-value for between-score comparison not provided.

Abbreviations: BRI=Bleeding Risk Index; CI=confidence interval; HAS-BLED=Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (> 65 years), Drugs/alcohol concomitantly; HEMORR$_2$HAGES=Hepatic or renal disease, Ethanol abuse, Malignancy, Older (age >75 years), Reduced platelet count or function, Rebleeding risk (2 points), Hypertension (uncontrolled), Anemia, Genetic factors, Excessive fall risk, Stroke; SE=standard error

Table 32. C-statistics from studies comparing scores of interest for prediction of major bleeding risk among patients off antithrombotic therapy[a]

Study	BRI	HEMORR$_2$HAGES	HAS-BLED	ATRIA
Friberg, 2012[122e]	–	0.69 (95% CI 0.67 to 0.70)	0.66 (95% CI 0.65 to 0.68)	–
Gage, 2006[185b,c]	0.65 (SE 0.03)	0.66 (SE 0.04)	–	–
Lip, 2011[191d]	0.50 (95% CI 0.44 to 0.57)	0.62 (95% CI 0.52 to 0.72)	0.66 (95% CI 0.55 to 0.74)	–
Lip, 2012[132f]	Categorical: 0.58 (95% CI 0.54 to 0.62) Continuous: 0.60 (95% CI 0.56 to 0.64)	Categorical: 0.55 (95% CI 0.50 to 0.59) Continuous: 0.59 (95% CI 0.54 to 0.63)	Categorical: 0.60 (95% CI 0.54 to 0.64) Continuous: 0.60 (95% CI 0.56 to 0.64)	Categorical: 0.47 (95% CI 0.42 to 0.51) Continuous: 0.59 (95% CI 0.55 to 0.64)
Olesen, 2011[192d]	–	Categorical: 0.77 (95% CI 0.74 to 0.80) Continuous: 0.79 (95% CI 0.73 to 0.79)	Categorical: 0.82 (95% CI 0.79 to 0.84) Continuous: 0.81 (95% CI 0.78 to 0.83)	–
Pisters, 2010[18d,e]	–	0.81 (95% CI 0.00 to 1.00)	0.85 (95% CI 0.00 to 1.00)	–

[a]C-statistics given are for categorical risk scores unless otherwise noted.
[b]Derivation study for HEMORR$_2$HAGES.
[c]P-value for 2-way between-score comparison not provided.
[d]P-value for between-score comparison not provided.
[e]Derivation study for HAS-BLED.
[f]P values for all between-score comparisons >0.05 (not specified as <0.05 in source article).

Abbreviations: ATRIA=Anticoagulation and Risk Factors in Atrial Fibrillation; BRI=Bleeding Risk Index; CI=confidence interval; HAS-BLED=Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (> 65 years), Drugs/alcohol concomitantly; HEMORR$_2$HAGES=Hepatic or renal disease, Ethanol abuse, Malignancy, Older (age >75 years), Reduced platelet count or function, Rebleeding risk (2 points), Hypertension (uncontrolled), Anemia, Genetic factors, Excessive fall risk, Stroke; SE=standard error

Table 33. Net reclassification improvement from studies comparing scores of interest for predicting major bleeding risk among patients on warfarin (except as indicated)

Study	Referent	Comparison 1	Comparison 2	Comparison 3
Apostolakis, 2012[179]	HAS-BLED	+6.8% compared with HEMORR$_2$HAGES (p=0.42)	+9.0% compared with ATRIA (p=0.33)	–
	ATRIA	-2.2% compared with HEMORR$_2$HAGES (p=0.82)		
Fang, 2011[184a]	ATRIA	+50.5% compared with BRI (p=NR)	+28.9% compared with HEMORR$_2$HAGES (p=NR)	–
Lip, 2012[132b]	HAS-BLED	+11.2% compared with HEMORR$_2$HAGES (p<0.0001)	+9.1% compared with BRI (p<0.0001)	+6.6% compared with ATRIA (p=0.0007)
Roldan, 2012[195]	HAS-BLED	+13.6% compared with ATRIA (continuous) (p=0.04) +19.6% compared with ATRIA (categorical) (p=0.02)	–	–

[a]Derivation study for ATRIA.
[b]Population used to calculate NRI included both patients on warfarin and patients not taking warfarin.

Abbreviations: ATRIA=Anticoagulation and Risk Factors in Atrial Fibrillation; BRI=Bleeding Risk Index; CI=confidence interval; HAS-BLED=Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (> 65 years), Drugs/alcohol concomitantly; HEMORR$_2$HAGES=Hepatic or renal disease, Ethanol abuse, Malignancy, Older (age >75 years), Reduced platelet count or function, Rebleeding risk (2 points), Hypertension (uncontrolled), Anemia, Genetic factors, Excessive fall risk, Stroke; NR=not reported; SE=standard error

Sufficient data on homogeneous populations/scores/outcomes did not exist to permit quantitative meta-analysis of available risk scores of interest.

Although the 95% CIs on the c-statistics overlap between scores, many of the point estimates when given direct comparison of scores are better for HAS-BLED than for the other scores. In addition the net reclassification improvement data is promising for the HAS-BLED score. These led us to suggest a modest prediction ability of the HAS-BLED score albeit with moderate SOE/medium confidence. Note that the early evidence from the use of the ABC risk score suggests a potential benefit of that score as compared to HAS-BLED although this is only based on one study and the validation cohort in this study did not reach statistical significance.

Intracranial Hemorrhage (Intracerebral Hemorrhage, Subdural Hematoma)

Overview

Most available studies for KQ 2 included ICH within the outcome “major bleeding,” but three studies presented this outcome separately. One of these studies evaluated both HAS-BLED and HEMORR$_2$HAGES,[122] another study evaluated both HAS-BLED and ATRIA[203] and a third study evaluated INR.[127]

HEMORR$_2$HAGES

HEMORR$_2$HAGES was evaluated in one included study of patients with AF with and without anticoagulation.[122] This study compared HEMORR$_2$HAGES with one other risk score of interest, HAS-BLED. Of note, due to unavailability of information on genetic factors, this study left out the "genetic factors" component of the score and so was, in effect, evaluating a modified HEMORR$_2$HAGES.

This study presented ICH event rate data for the continuous HEMORR$_2$HAGES score among 48,599 patients on warfarin. ICH bleeding rate for a HEMORR$_2$HAGES score of 0 was 0.2 bleeding events per year: score 1=0.5, score 2=0.7, score 3=0.9, score 4=1.4, score 5=1.8, score 6=1.4, score 7=1.1, score 8=0, and score 9=0. Among patients on warfarin, the ICH c-statistic for HEMORR$_2$HAGES in this study was 0.62 (95% CI 0.60 to 0.64). This study also presented c-statistics for HEMORR$_2$HAGES in other populations; for patients on aspirin alone, the c-statistic was 0.58 (95% CI 0.55 to 0.60), while for patients not on antithrombotic therapy the c-statistic was 0.66 (95% CI 0.63 to 0.69).

HAS-BLED

HAS-BLED was evaluated in two included studies of patients with AF with and without anticoagulation.[122,189] One study compared HAS-BLED with the HEMORR$_2$HAGES[122] and the second study[189] compared to the ABC-bleeding score . Of note, the study by Friberg excluded patients with labile INR, so quantified "labile INR" as 0 for all patients; the study also excluded the "drugs" component of the HAS-BLED score. Because of these changes, the study was, in effect, evaluating a modified HAS-BLED.[122]

The Friberg study presented ICH event rate data for the continuous HAS-BLED score among 48,599 patients on warfarin. ICH bleeding rate for a HAS-BLED score of 0 was 0 bleeding events per year: score 1=0.2, score 2=0.6, score 3=0.7, score 4=1.2, score 5=1.6, score 6=0, and score 7=0. Among patients on warfarin, the ICH c-statistic for HAS-BLED in this study was 0.60 (95% CI 0.58 to 0.62). This study also presented c-statistics for HAS-BLED in other populations; for patients on aspirin alone, the c-statistic was 0.58 (95% CI 0.56 to 0.61), while for patients not on antithrombotic therapy, the c-statistic was 0.64 (95% CI 0.61 to 0.67).[122] The Hijazi study reported only the c-indices comparing the ABC-bleeding score to HAS-BLED for intracranial hemorrhage, 0.66 (95% CI 0.62 to 0.69) and 0.58 (95% CI 0.54 to 0.61), respectively.[189]

HAS-BLED was evaluated in one included studies of patients with AF and anticoagulation with novel oral anticoagulants.[203] This study compared HAS-BLED with ATRIA. The Yao study presented ICH event rate data for the categorical and continuous HAS-BLED score among 39,539 patients in use of novel oral anticoagulants. Among patients on NOACs, the ICH categorical c-statistic for HAS-BLED in this study was 0.63 (95% CI 0.58 to 0.69). This study also presented continuous c-statistics for HAS-BLED that was 0.64 (95% CI 0.58 to 0.70).[203]

ATRIA

ATRIA was evaluated in one included studies of patients with AF and anticoagulation with novel oral anticoagulants.[203] The Yao study presented ICH event rate data for the categorical and continuous ATRIA score among 39,539 patients in use of novel oral anticoagulants. Among patients on NOACs, the ICH categorical c-statistic for ATRIA in this study was 0.56 (95% CI 0.50 to 0.61). This study also presented continuous c-statistics for ATRIA that was 0.63 (95% CI 0.57 to 0.68).[203]

INR

A single study conducted among patients with AF evaluated the incidence of ICH by INR at the time of stroke.[127] This study suggested that at supratherapeutic INR ranges, ICH incidence was higher, but the study was not designed to truly evaluate the predictive accuracy of this risk factor. ICH rates per 100 patient-years were 0.5 for INR <1.5, 0.3 for INR 1.5–1.9, 0.3 for INR 2.0–2.5, 0.5 for INR 2.6–3.0, 0.6 for INR 3.1–3.5, 0.4 for INR 3.6–3.9, 2.7 for INR 4.0–4.5, and 9.4 for INR >4.5.

Comparison of Bleeding Risk Scores and Meta-Analysis Results for Intracranial Hemorrhage

The single included study comparing HAS-BLED and HEMORR$_2$HAGES did not show a statistically significant difference between the risk scores in prediction abilities for ICH in any patient population. No NRI data was available for comparing risk scores in predicting ICH. Further studies comparing all available risk scores for predicting ICH should use appropriate statistical evaluations (hazard ratios, likelihood ratios, c-statistics, NRI, etc.) in independent cohorts to better establish whether any score is superior in any population (e.g., AF patients on warfarin, AF patients on direct oral antithrombotic agents, and AF patients off of anticoagulation therapy). Better understanding ICH risk prediction will be particularly important, because this represents the most devastating variety of major bleeding event that patients on anticoagulation suffer.[178]

Minor Bleeding

Overview

A single study evaluated the impact of the BRI on estimating the risk of minor bleeding (not requiring transfusion, no major associated morbidity) in patients with AF on warfarin.[181]

BRI

A single study provided event rate data for incidence of minor bleeding by BRI risk category among patients on warfarin.[181] In this study, 8.3 percent of the low-risk group, 4.4 percent moderate-risk group, and 6.9 percent of the high-risk group experienced minor bleeding per patient-year. The BRI was not felt to be predictive of minor bleeding in this analysis.

Strength of Evidence

Table 34 summarizes the SOE for the bleeding risk prediction abilities of the included tools. This summary table represents only those studies that evaluated the risk prediction abilities of the tools using a c-statistic. Note we did not reduce the SOE for evaluating prediction of diagnostic tools through observational studies. We did allow for increased heterogeneity in findings when a greater number of studies were performed (e.g., HEMORR$_2$HAGES scores) and reduced our SOE if there were limited numbers of included studies (e.g., BRI).

Table 34. Bleeding risk instruments and strength of evidence domains for prediction of bleeding risk[a]

Outcome	Number of Studies (Subjects)	Risk of Bias	Consistency	Directness	Precision	SOE and Effect (95% CI)
BRI	4[132,184,185,191,198] (11,939)	Observational/ Moderate	Consistent	Direct	Precise	**SOE=Moderate** Limited risk discrimination ability (c-statistic ranging from 0.56 to 0.65)
HEMORR$_2$HAGES	10[18,122,132,179,182,184,185,190-192] (115,348)	Observational/ Moderate	Consistent	Direct	Imprecise	**SOE=Moderate** Limited risk discrimination ability (c-statistic ranging from 0.53 to 0.78)
HAS-BLED	11[18,122,132,179,182,189-192,195,196,200] (194,839)	Observational/ Moderate	Consistent	Direct	Imprecise	**SOE=Moderate** Modest risk discrimination ability (c-statistic ranging from 0.50 to 0.80)
ATRIA	7[132,179,182,184,190,195,196,200] (76,163)	Observational/ Moderate	Inconsistent	Direct	Imprecise	**SOE=Insufficient**
ABC	1[107] (22,998)	Observational/ Moderate	NA	Direct	Precise	**SOE=Low** Limited risk discrimination (c-statistic of 0.65 in validation study)
Major bleeding events among patients with AF on warfarin	13[18,122,132,179,182,184,185,189-192,195,196,200] (351,985)	Observational/ Moderate	Consistent	Direct	Imprecise	**SOE=Moderate** Favors HAS-BLED
Intracranial hemorrhage among patients with AF on warfarin	2[122,189] (71,597)	Observational/Moderate	NA	Direct	Precise	**SOE=Low** No evidence of a difference
Major bleeding events among patients with AF on aspirin alone	3[18,122,185] (177,538)	Observational/ Moderate	Inconsistent	Direct	Imprecise	**SOE=Low** No evidence of a difference
Major bleeding events among patients with AF not on antithrombotic therapy	6[18,122,132,185,191,192] (310,607)	Observational/ Moderate	Consistent	Direct	Imprecise	**SOE=Low** No evidence of a difference

[a]C-statistics given are for categorical risk scores unless otherwise noted.

Abbreviations: ABC=age, biomarkers, clinical history; AF=atrial fibrillation; ATRIA=Anticoagulation and Risk Factors in Atrial Fibrillation; BRI=Bleeding Risk Index; CI=confidence interval; HAS-BLED=Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (> 65 years), Drugs/alcohol concomitantly; HEMORR$_2$HAGES=Hepatic or renal disease, Ethanol abuse, Malignancy, Older (age >75 years), Reduced platelet count or function, Rebleeding risk (2 points), Hypertension (uncontrolled), Anemia, Genetic factors, Excessive fall risk, Stroke; KQ=Key Question; NA=not applicable; SOE=strength of evidence

Key Question 3. Interventions for Preventing Thromboembolic Events

KQ 3. What are the comparative safety and effectiveness of specific anticoagulation therapies, antiplatelet therapies, and procedural interventions for preventing thromboembolic events:

a) In patients with nonvalvular AF?

b) In specific subpopulations of patients with nonvalvular AF?

Key Points

- ASA versus VKA (warfarin): Based on 5 observational studies involving 251,578 patients, warfarin reduces the risk of nonfatal and fatal ischemic stroke compared with aspirin (moderate SOE); however, based on 3 studies involving 212,770 patients, warfarin is also associated with increased rates of major bleeding complications compared with aspirin (moderate SOE)
- ASA+clopidogrel versus ASA: In patients not eligible for warfarin, two good quality RCTs involving 8,147 patients showed lower rates of any stroke (HR 0.72, 95% CI 0.62 to 0.83) for combination therapy of aspirin and clopidogrel compared to ASA alone (moderate SOE). In the largest RCT (7,554 patients), the combination of aspirin and clopidogrel was associated with higher rates of major bleeding than aspirin alone (HR 1.57, 95% CI 1.29 to 1.92) (moderate SOE).
- Warfarin versus clopidogrel: Based on 1 large observational, good quality study involving 54,636 patients, warfarin reduces the risk of nonfatal and fatal ischemic stroke compared with clopidogrel monotherapy, with no evidence of differences in major bleeding (moderate SOE).
- ASA+clopidogrel versus Warfarin: Based on two large, good-quality RCTs involving 60,484 patients, warfarin is superior to aspirin plus clopidogrel for the prevention of stroke or systemic embolism (high SOE). In one good quality RCT of 6,706 patients, warfarin is superior to aspirin plus clopidogrel for the reduction in any minor bleeding (moderate SOE) however warfarin increased hemorrhagic stroke risk compared to ASA+ clopidogrel (moderate SOE). There was no evidence of a difference between therapies for MI, death from vascular causes or all-cause mortality (moderate SOE for both outcomes).
- Clopidogrel+warfarin versus warfarin: Clopidogrel+warfarin shows a trend toward a benefit on stroke prevention (low SOE) and is associated with increased risk of nonfatal and fatal bleeding compared with warfarin alone (moderate SOE). These findings are based on 1 good-quality observational study involving 52,349 patients.
- Warfarin+aspirin+clopidogrel versus warfarin: Triple therapy increases the risk of nonfatal and fatal bleeding (moderate SOE) and also shows a trend toward increased ischemic stroke (low SOE) compared with warfarin alone. These findings are based on 1 good-quality observational study involving 52,180 patients
- Thrombin inhibitors (dabigatran) versus warfarin: Based on 1 large good-quality RCT involving 18,113 patients and 35 observational studies involving 1,737,961 patients we found:

- Dabigatran at a 150mg dose is superior to warfarin in reducing the incidence of the composite outcome of stroke (including hemorrhagic) or systemic embolism (RR 0.66, 95% CI 0.53 to 0.82), with no statistically significant difference in the occurrence of major bleeding (RR 0.93, 95% CI 0.81 to 1.07) (high SOE for both outcomes), all-cause mortality(RR 0.88, 95% CI 0.77 to 1.00) (low SOE), or MI risk (low SOE).
- Dabigatran at a 110mg dose is similar to warfarin for the composite outcome of stroke or systemic embolism (RR 0.91, 95% CI 0.74 to 1.11) (moderate SOE). It is associated with a reduction in the risk of major bleeding (RR 0.80, 95% CI 0.69 to 0.93) when compared with warfarin (high SOE), but there is no evidence of a difference in all-cause mortality or MI risk (low SOE for both outcomes). Note the 110mg dose is currently not approved for stroke prevention in patients with AF in the US.
- Observational studies were inconsistent with RCT evidence for the outcomes of all-cause mortality (observational studies demonstrated a benefit for patients on dabigatran, while RCT studies suggested no evidence of a difference on either dose) and MI risk (observational studies did not show a difference, RCT studies suggested an increase with the 150mg dose of dabigatran).

- Xa inhibitor (apixaban) versus ASA: Apixaban is superior to aspirin in reducing the incidence of stroke or systemic embolism (HR 0.45, 95% CI 0.32 to 0.62) with similar major bleeding risk (HR 1.13, 95% CI 0.74 to 1.75), in patients who are not suitable for warfarin (moderate SOE for both outcomes). These findings are based on 1 good quality RCT involving 5,599 patients.
- Xa inhibitor (apixaban) versus warfarin: Apixaban is superior in reducing the incidence of (1) stroke or systemic embolism (HR 0.79, 95% CI 0.66 to 0.95) (high SOE), (2) the risk of major bleeding (0.69, 95% CI 0.60 to 0.80) (high SOE), and (3) all-cause mortality (low SOE) when compared with warfarin. These findings are based on 1 large good-quality RCT involving 18,201 patients, and 29 observational studies with 1,251,855 patients.
- Xa inhibitor (rivaroxaban) versus warfarin: Rivaroxaban is similar to warfarin in preventing stroke or systemic embolism (HR 0.88, 95% CI 0.74 to 1.03) (moderate SOE), with similar rates of major bleeding (low SOE) and all-cause mortality (moderate SOE). These findings are based on 1 large, good-quality RCT involving 14,264 patients and 26 observational studies with 1,483,949 patients. Inconsistent with the RCT findings, observational studies supported a reduction in stroke or systemic embolism and a trend towards a reduction in ischemic or uncertain stroke, while also providing evidence of a small increase in the risk of major bleeding.
- Xa inhibitor (edoxaban) versus warfarin: Edoxaban (either 60mg or 30mg dose) is superior in reducing hemorrhagic stroke (low dose HR 0.33, 95% CI 0.22 to 0.50; high dose HR 0.54, 95% CI 0.38 to 0.77) (moderate SOE) and the risk of major bleeding (moderate SOE) though did not differ in overall stroke risk (moderate SOE), myocardial infarction (moderate SOE) or all-cause mortality (moderate SOE for high dose). There was low SOE that low dose edoxaban (30 mg) reduced all-cause mortality. These findings are based on 1 large, good-quality RCT involving 21,105 patients. Note that the 60 mg once-daily dose of edoxaban is approved by the FDA to treat only NVAF patients with creatinine clearance (CrCL) >50 to ≤ 95 mL/min, while 30 mg once-daily dose of

edoxaban is approved to treat NVAF in patients with renal dysfunction (CrCL 15 to 50 mL/min).

- Percutaneous left atrial appendage (LAA) closure versus warfarin: LAA shows a trend toward a benefit over warfarin for all strokes (including ischemic or hemorrhagic) and all-cause mortality (low SOE for both outcomes). Although LAA with percutaneous closure results in less frequent major bleeding than warfarin (low SOE), it is also associated with a higher rate of adverse safety events such as pericardial effusion and device embolization (moderate SOE). These findings are based on 1 good-quality RCT involving 707 patients and 4 observational studies involved 1,430 patients.

Description of Included Studies

We identified 220 articles representing 117 studies relevant to KQ 3 (Appendix Table F-3).[23-26,112,113,115,124,127,134,141,169,177,179,187,188,197,207-408]

A total of 22 RCTs[23-26,113,115,215,219,232,233,250,276,288,289,315,320,321,339,354,358,366,371] and 95 observational studies[112,127,141,177,207,208,214,218,220,221,226-230,238,239,253,255,257-259,262,264,266-269,273,275,287,292-295,297-300,302-305,307-311,322,324,327,329,330,337,345-347,350-352,357,362,365,370,373,375,376,379-389,391-398,400-403,405-409] were included in our analyses. The included studies explored interventions in studies of diverse quality, funding, and geographical location. Additional study characteristics can be reviewed in Appendix Table F-3.

In regard to funding, 44 studies were sponsored solely by industry,[23-26,113,115,177,215,220,232,233,239,250,255,273,275,276,288,289,292,294,295,309,315,321,346,354,362,366,373,379,380,387,388,392,393,395,397,398,400,405-407,409] 12 by government,[127,214,221,257,268,269,357,376,381,386,396,403] 16 received funding from non-government, non-industry sources,[207,208,219,298,299,307,308,320,329,330,350-352,370,385,408] 26 received funding from multiple sources including government, industry, non-government and non-industry,[218,226,228-230,258,259,262,264,287,293,300,305,327,337,345,347,365,375,382,384,389,391,394,401,402] and 19 had either no sponsorship or this information was unclear.[112,141,227,238,253,266,267,297,302-304,310,311,322,324,339,358,371,383]

Among the 117 studies, 50 were performed in the UK or Europe,[112,141,215,219-221,227,230,238,250,253,257,258,262,264,266,267,273,275,287,292,295,297-299,302,307,308,311,315,320-322,324,329,339,345,351,352,354,358,371,381,385,389,391,397,398,401,408] 54 in the United States,[127,173,177,207,208,218,226,228,229,239,255,259,268,269,276,289,293,294,300,303-305,309,310,327,330,337,346,347,350,357,362,365,370,373,376,379,380,382-384,386-388,392,393,395,396,400,402,403,405-407,409] 2 in Canada,[214,394] and 9 were conducted on multiple continents.[23-26,113,232,233,288,375] Two studies were unclear or did not report a geographical location.[115,366]

Seventy-five studies were considered of good quality or had a low risk of bias rating,[23-26,112,113,115,127,173,177,207,208,214,218,219,228-230,232,233,250,255,258,259,267-269,275,276,287,288,293,294,297,299,300,303-305,310,311,320-322,327,329,330,339,346,347,362,365,366,370,373,376,379-382,387,388,391-393,395,396,398,400-402,405-409] 16 were considered fair quality or had a moderate risk of bias rating,[215,289,315,350,354,358,371,375,383-386,389,394,397,403] and 26 were of poor quality or had a high risk of bias rating.[141,220,221,226,227,238,239,253,257,262,264,266,273,292,295,298,302,307-309,324,337,345,351,352,357] Studies with increased risk of bias had potential limitations related to bias arising in the randomization process or due to confounding, bias due to missing data, and methodological limitations for studies that did not use propensity-matched controls.

Table 35 represents the direct treatment comparisons and study design types evaluated for this KQ. This table demonstrates how most of the included studies evaluated interventions compared to warfarin but did not compare directly between non-warfarin treatment strategies.

One exception is that there were many observational studies which compared Xa inhibitors to either dabigatran or another Xa inhibitor (21 and 17 observational studies respectively). Note that there were no RCTs which made such a direct comparison.

Table 35. Number and study design of specific comparisons within included studies

Comparators (across) / Interventions (down)	Warfarin	Aspirin	Antiplatelet	Clopidogrel	Clopidogrel+Aspirin	Clopidogrel+Warfarin	Clopidogrel+Warfarin+ Aspirin	Thrombin Inhibitor (Dabigatran)	Thrombin Inhibitor (Dabigatran)+Aspirin	Factor Xa Inhibitors	Factor Xa Inhibitors (idraparinux)	DOACs (Unspecified)	VKAs (General)	Percutaneous LAA Closure Devices
Aspirin	1 RCT 4 Obs													
Warfarin+Aspirin	4 Obs													
Antiplatelet	1 Obs													
Clopidogrel	1 Obs													
Clopidogrel+Aspirin	1 RCT 1 Obs	2 RCTs												
Clopidogrel+Warfarin	1 Obs													
Clopidogrel+Warfarin+Aspirin	1 Obs													
Thrombin Inhibitor (Dabigatran)	1 RCT 35 Obs													
Thrombin Inhibitor (Dabigatran)+Aspirin	1 RCT													
Factor Xa Inhibitors	4 RCTs 38 Obs	1 RCT						21 Obs		17 Obs				
Factor Xa Inhibitors (idraparinux)	1 RCT													
VKAs (General)												7 Obs		
Percutaneous LAA Closure Devices	1 RCT 3 Obs													5 Obs

Abbreviations: DOAC=direct oral anticoagulant; LAA=left atrial appendage; Obs=observational; RCT=randomized controlled trial; VKA=vitamin K antagonist

Detailed Synthesis

One hundred and seventeen studies looked explicitly at the comparative safety and effectiveness of specific anticoagulation therapies, antiplatelet therapies, and procedural interventions for preventing thromboembolic events in patients with nonvalvular AF. Below we describe each of these studies categorized by the treatment comparisons represented, and within each comparison grouped by thromboembolic outcomes, bleeding outcomes, and other clinical outcomes. Many of these studies also focused on specific subgroups of interest. These studies are not combined with the more general AF population studies, but instead are discussed separately at the end of this section categorized by specific subgroup.

1. Aspirin Versus VKA (Warfarin)

In 2014, a good-quality RCT (comparion article to the study by Mant and colleagues[320]) provided the first evidence on the effect of anticoagulation on cognitive function in elderly patients with AF.[323] A total of 973 patients aged ≥75 years with AF were recruited from primary care and randomly assigned to warfarin (n=488; target international normalized ratio [INR] 2-3) or aspirin (n=485; 75mg/d). Neither participants nor investigators were masked to group assignment. Followup was for a mean of 2.7 years (SD 1.2). Cognitive outcome was assessed using the Mini-Mental State Examination at 9-, 21-, and 33-month followup. Participants who had a stroke were censored from the analysis, which was by intention to treat (ITT) with imputation for missing data. There was no evidence of a difference between mean Mini-Mental State Examination scores in people assigned to warfarin or aspirin at 9 or 21 months. At 33-months followup, there was a nonsignificant difference in MMSE scores of 0.56 in favor of warfarin that decreased to 0.49 (95% CI -0.01 to 0.98) after imputation.

We identified one good-quality observational study involving 98,460 patients[275] that compared aspirin with warfarin. One additional retrospective study[215] evaluated aspirin and warfarin compared with no therapy (we concentrate on the aspirin vs. warfarin findings here). The latter included a population-based cohort analysis of 70,766 patients with a first-ever diagnosis of chronic AF conducted within the United Kingdom to estimate the risk of ischemic stroke and intracranial hemorrhage associated with the use of warfarin and aspirin.[215] Two additional observational studies performed within Europe did not use propensity-matched controls[307,308] and therefore were also not synthesized quantitatively.

Thromboembolic Outcomes

Ischemic Stroke

This outcome was assessed in 4 studies. In the first study,[275] treatment with aspirin was associated with increased risk of nonfatal and fatal ischemic stroke when compared with warfarin (HR 1.83; 95% CI 1.73 to 1.94). The second study[215] showed that warfarin use was associated with decreased risk of ischemic stroke compared with no use of any antithrombotic therapy (adj RR 0.65, 95% CI 0.59 to 0.71). On the other hand, treatment with aspirin was not associated with a decreased risk of ischemic stroke (adj RR 1.05, 95% CI 0.98 to 1.13) corresponding to a relative risk of 1.66 for aspirin versus warfarin. In a Spanish retrospective cohort study, the rate of stroke per 1000 person-years for those using an antiplatelet agent was 20.1 (95% CI 18.0 to 22.6) compared with 11.1 (95% CI 9.8 to 12.7) in those using VKA therapy.[264] In the final observational study there was no evidence of a difference between

treatments (HR 1.06, 95% CI 0.80 to 1.40).[308] There was moderate SOE that warfarin therapy reduced stroke as compared with aspirin.

Cerebral Infarction, Unspecified Stroke, or Transient Ischemic Attack

A Danish study showed there was an increased risk of stroke when comparing aspirin to VKA therapy (IRR 2.0, 95% CI 1.88 to 2.12).[302]

Bleeding Outcomes

Bleeding was assessed in three studies. In one observational study,[275] the risk of nonfatal and fatal bleeding was lower in the aspirin group (HR 0.93; 95% CI 0.88 to 0.98). A Danish study showed no evidence of a difference in rates of bleeding requiring hospitalization between those on aspirin or VKA therapy (IRR 0.95, 95% CI 0.90 to 1.01).[302] Finally in a Spanish retrospective cohort study, the rate of all bleeding events per 1000 person-years for those using an antiplatelet agent was 22.0 (95% CI 19.7 to 24.5) compared to 27.8 (95% CI 25.5 to 30.2) in those using VKA therapy.[264] There was moderate SOE that warfarin increased rates of bleeding compared with aspirin.

Cerebral Bleeding

In a Spanish retrospective cohort study, the rate of cerebral bleeding events per 1000 person-years for those using an antiplatelet agent was 2.7 (95% CI 2.0 to 3.6) compared with 3.4 (95% CI 2.7 to 4.3) in those using VKA therapy.[264]

Gastrointestinal Bleeding

In a Spanish retrospective cohort study, the rate of gastrointestinal bleeding all-cause mortality per 1000 person-years for those using an antiplatelet agent was 12.2 (95% CI 10.5 to 14.1) compared with 10.4 (95% CI 9.0 to 11.9) in those using VKA therapy.[264]

Other Clinical Outcomes

All-Cause Mortality

Two studies explored all-cause mortality. In one study evaluating a Spanish retrospective cohort study, the rate of all-cause mortality per 1000 person-years for those using an antiplatelet agent was 76.2 (95% CI 72.0 to 80.8) compared with 31.4 (95% CI 29.1 to 34.0) in those using VKA therapy.[264] In the observational study[308] there was no evidence of a difference in treatment arms (HR 1.03, 95% CI 0.87 to 1.22). Given the heterogeneity in populations and findings there was insufficient evidence to determine the impact of warfarin and aspirin on all-cause mortality.

Myocardial Infarction

In a Danish study, the incidence of first-time MI in patients without a history of coronary artery disease (CAD) was found to be higher in patients taking aspirin when compared with vitamin K antagonist (VKA) therapy (warfarin or phenprocoumon) (incidence rate ratio [IRR] 1.54; 95% CI 1.40 to 1.68).[302] In the VKA therapy group, 4 percent were taking phenprocoumon while 96 percent were taking warfarin.

Strength of Evidence

Table 36 summarizes the SOE for outcomes of interest for this comparison.

Table 36. Strength of evidence—aspirin versus warfarin

Outcome	Number of Studies (Subjects)	Risk of Bias	Consistency	Directness	Precision	Reporting Bias	SOE and Effect (95% CI)
Ischemic stroke	5[215,264,275,308,410] (251,578)	Moderate	Consistent	Direct	Precise	Suspected	**SOE=Moderate** Reduction in stroke with warfarin
Bleeding	4[264,275,302] (212,770)	Moderate	Consistent	Direct	Precise	Suspected	**SOE=Moderate** Warfarin associated with increased rates of bleeding
All-cause mortality	3[264,308,410] (62,206)	High	Inconsistent	Direct	Imprecise	Suspected	**SOE=Insufficient**

Abbreviations: CI=confidence interval; SOE=strength of evidence

2. VKA (Warfarin) and Aspirin Versus VKA (Warfarin) Alone

One good-quality retrospective cohort study compared warfarin+aspirin (18,345 patients) with warfarin monotherapy (50,919 patients).[275] This study demonstrated increased risks of both stroke and bleeding in the combination arm compared with warfarin monotherapy. One poor-quality nationwide observational study using the Danish Nationwide patient registry evaluated VKA therapy alone (37,539 patients) compared to dual therapy with VKA and aspirin (8,962 patients).[302] Another retrospective, multicenter cohort study (n=40,449) using Swedish registries examined complications of warfarin treatment alone compared to warfarin therapy with aspirin.[221] Lastly, a secondary analysis of data from the Stroke Prevention using an Oral Thrombin Inhibitor in Patients with Atrial Fibrillation (SPORTIF) III and V trials (good quality) assessed 3,624 patients enrolled in the warfarin arms of the trials for whom information on use of aspirin was available.[374] Four groups were created for comparison (no aspirin + warfarin, time in therapeutic range [TTR] ≧65%; aspirin + TTR ≥ 65%; no aspirin + TTR < 65%; and aspirin + TTR < 65%).

Thromboembolic Outcomes

Ischemic Stroke

In the study by Hansen and collagues the combined aspirin and VKA (warfarin) therapy was associated with statistically significant increased risk of nonfatal and fatal ischemic stroke when compared with VKA (warfarin) monotherapy (HR 1.27; 95% CI 1.14 to 1.40) (moderate SOE).[275]

Cerebral Infarction, Unspecified Stroke, or Transient Ischemic Attack

The nationwide Danish study showed that the incidence of cerebral infarction, unspecified stroke, or TIA was higher in those on combined aspirin and VKA (warfarin) in comparison to VKA monotherapy (IRR 1.30; 95% CI 1.18 to 1.43).[302] Given the high risk of bias with this study the SOE was rated as insufficient.

Stroke or Systemic Embolism

From the secondary analysis of the SPORTIF III and V trial data, the rates of stoke or systemic embolism not statistically significantly different in the four groups; 1.9%, 2.9%, 3.0%,

and 3.2%, respectively (no aspirin + TTR ≥65%; aspirin + TTR ≥ 65%; no aspirin + TTR < 65%; and aspirin + TTR < 65%) (low SOE).[374]

Bleeding Outcomes

In this study the risk of nonfatal and fatal bleeding was almost twice as high among patients on combined aspirin and VKA (warfarin) therapy than among patients receiving VKA (warfarin) monotherapy (HR 1.83; 95% CI 1.72 to 1.96) (moderate SOE).[275] Another study also showed that the risk of bleeding was significantly higher in the dual therapy with aspirin and VKA (warfarin) group relative to VKA (warfarin) monotherapy (IRR 1.93; 95% CI 1.81 to 2.07).[302]

Major Bleeding

In a Swedish retrospective multicenter study, there was a higher risk of major bleeding for those on combined aspirin and VKA (warfarin) compared to those on warfarin monotherapy (adj HR 1.36, 95% CI 1.17 to 1.58).[221] From the secondary analysis of the SPORTIF III and V trial data, patients without aspirin + TTR < 65% (HR 1.93; 95% CI 1.29 to 2.87) and those with aspirin + TTR < 65% (HR 2.24; 95% CI 1.28 to 3.93) were statistically significantly more likely to have major bleeding than patients without aspirin + TTR ≥ 65%. There was no statistically significant difference between those with aspirin + TTR ≥ 65% and those without aspirin + TTR ≥ 65% (HR 1.32; 95% CI 0.72 to 2.40) (low SOE).[374]

Intracranial Bleeding

In the Swedish study, there was no evidence of a difference in risk of intracranial bleeding for those on combined aspirin and VKA (warfarin) compared to those on VKA (warfarin) monotherapy (adj HR 1.28, 95% CI 0.91-1.80).[221] Given the high risk of bias with this study the SOE was rated as insufficient.

Gastrointestinal Bleeding

In the Swedish study, there was a higher risk of gastrointestinal bleeding for those on combined aspirin and VKA (warfarin) compared to those on VKA (warfarin) monotherapy (adj HR 1.59, 95% CI 1.24-2.02).[221] Given the high risk of bias with this study the SOE was rated as insufficient.

Other Clinical Outcomes

All-Cause Mortality

From the secondary analysis of the SPORTIF III and V trial data, patients without aspirin + TTR < 65% (HR 1.80; 95% CI 1.31 to 2.47) and those with aspirin + TTR < 65% (HR 1.74; 95% CI 1.12 to 2.72) were statistically significantly more likely to die than patients without aspirin + TTR ≥ 65%. There was no statistically significant difference between those with aspirin + TTR ≥ 65% and those without aspirin + TTR ≥ 65% (HR 0.78; 95% CI 0.45 to 1.37) (low SOE).[374]

Myocardial Infarction

The nationwide Danish study showed that the incidence of first time myocardial infarction was higher in the dual therapy group in comparison to the VKA therapy alone group (IRR 1.22; 95% CI 1.06 to 1.40).[302] Given the high risk of bias with this study the SOE was rated as insufficient.

Strength of Evidence

Table 37 summarizes the SOE for outcomes of interest for this comparison.

Table 37. Strength of evidence—warfarin+aspirin versus warfarin alone

Outcome	Number of Studies (Subjects)	Risk of Bias	Consistency	Directness	Precision	Reporting Bias	SOE and Effect (95% CI)
Ischemic stroke	1[275] (69,264)	Moderate	NA	Direct	Precise	Suspected	**SOE=Moderate** Increased with warfarin+ASA (HR 1.27 (95% CI 1.14 to 1.40)
Cerebral Infarction, Unspecified Stroke, or Transient Ischemic Attack	1[302] (71,959)	High	NA	Direct	Precise	None	**SOE = insufficient**
Stroke or Systemic Embolism	1[374] (3,624)	Low	NA	Direct	Imprecise	None	**SOE=Low** No evidence of differences between those with or without ASA regardless of TTR
Bleeding	2[275,302] (141,223)	Moderate	Consistent	Direct	Precise	Suspected	**SOE=Moderate** Increased with warfarin+ASA
Major Bleeding	1 RCT[374] 1 Obs[221] (32,770)	Moderate	Consistent	Direct	Imprecise	None	**SOE=Low** Increased with TTR < 65% without ASA (HR 1.93; 95% CI 1.29 to 2.87) or with ASA (HR 2.24; 95% CI 1.28 to 3.93) as compared to no ASA + TTR≥65%;
Intracranial Bleeding	1 Obs[221] (29,146)	High	NA	Direct	Imprecise	None	**SOE = insufficient**
GI Bleeding	1 Obs[221] (29,146)	High	NA	Direct	Imprecise	None	**SOE = insufficient**
All Cause Mortality	1[374] (3,624)	Low	NA	Direct	Imprecise	None	**SOE=Low** Increased with TTR < 65% without ASA (HR 1.80; 95% CI 1.31 to 2.47) or with ASA (HR 1.74; 95% CI 1.12 to 2.72) as compared to no ASA + TTR≥65%;
Myocardial Infarction	1[302] (71,959)	High	NA	Direct	Imprecise	None	**SOE=Insufficient**

Abbreviations: ASA=aspirin; CI=confidence interval; HR=hazard ratio; Obs=observational; NA=not applicable; RCT=randomized controlled trial; SOE=strength of evidence; TTR=time in therapeutic range

3. VKA (Warfarin)Therapy Versus Antiplatelet or No Treatment

An Italian retrospective observational cohort study conducted over 7 years compared patients who did and did not receive VKA therapy.[238] A total of 6,138 patients were included. The VKA group was further subdivided into those with time in the therapeutic range (TTR) <65 percent and TTR ≥65 percent. The non-VKA group was subdivided into those taking an antiplatelet medication and those not taking an antiplatelet.

Thromboembolic Outcomes

Any Stroke

In this study, there was a significantly decreased risk of stroke with VKA therapy compared with no VKA or an antiplatelet agent (TTR <65%: HR 0.786; 95% CI 0.629 to 0.982; p=0.034; TTR ≥65%: HR 0.594; 95% CI 0.435 to 0.810; p=0.001).[238] There was no evidence of a difference in risk of stroke when comparing those in the non-VKA group with those not taking an antiplatelet medication (p=0.483).

Other Clinical Outcomes

Medication Adherence

In this study, 1,820 patients (37%) in the VKA therapy group discontinued treatment within 6 months.[238]

4. Clopidogrel+Aspirin Versus Aspirin Alone

Two good-quality RCTs involving 8,147 patients analyzed the combination of clopidogrel+aspirin compared with aspirin alone in patients with AF.[233,276] Both reported intention-to-treat (ITT) analyses. Given the size and quality of the larger RCT of 7,554 patients,[233] the findings of the smaller study involving 593 patients[276] are presented here, but our findings and SOE rating are based mainly on the larger RCT. Note that this larger RCT also recently reported a follow up study detailing additional outcomes.[372]

Thromboembolic Outcomes

Any Stroke

The findings of these two studies differed in terms of the impact of treatment on all strokes. The larger study showed lower rates of stroke in the group treated with clopidogrel+aspirin (2.4% per year vs. 3.3% per year for clopidogrel+aspirin and aspirin alone, respectively; HR 0.72; 95% CI 0.62 to 0.83; p<0.001).[233] Rates of any stroke did not, however, differ between groups in the smaller study (2.2% per year vs. 2.1% per year for clopidogrel+aspirin and aspirin alone, respectively; HR 1.03; 95% CI 0.49 to 2.13; p=0.94).[276] Based on the large study, but reflecting the inconsistent findings, there was moderate SOE that combined treatment lowered the risk of any stroke.

Ischemic Stroke

Rates of ischemic stroke were higher in the aspirin group in the larger study (1.9% per year for clopidogrel+aspirin vs. 2.8% per year for aspirin alone; HR 0.68; 95% CI 0.57 to 0.80),[233] and similar across groups in the smaller study (2.0% per year for clopidogrel+aspirin vs. 2.1%

per year for aspirin alone; HR 0.96; 95% CI 0.46 to 2.01; p=0.91).[276] Based on the large study, but reflecting the inconsistent findings, there was low SOE that combined therapy lowered the risk of ischemic stroke.

Hemorrhagic Stroke

Rates of hemorrhagic stroke were similar between the groups in both studies (moderate SOE).[233,276]

Systemic Embolism

Only the larger study involving 7,554 patients reported the rates of systemic embolism, which were similar between the groups (0.4% per year for clopidogrel+aspirin vs. 0.4% per year for aspirin alone; HR 0.96; 95% CI 0.66 to 1.40; p=0.84) (moderate SOE).[233]

Bleeding Outcomes

Major Bleeding

The combination of clopidogrel+aspirin was associated with higher rates of major bleeding when compared with aspirin alone in the larger study involving 7,554 patients (2.0% per year for clopidogrel+aspirin vs. 1.3% per year for aspirin alone; HR 1.57; 95% CI 1.29 to 1.92; p<0.001) (high SOE).[233] The smaller study did not report rates of major bleeding.[276]

Minor Bleeding

Rates of minor bleeding were higher in the clopidogrel+aspirin group compared with aspirin alone in the larger study involving 7,554 patients (3.5% per year for clopidogrel+aspirin vs. 1.4% per year for aspirin alone; HR 2.42; 95% CI 2.03 to 2.89; p<0.001) (high SOE).[233] The other smaller study did not report this outcome.

Intracranial Bleeding

Rates of intracranial bleeding were higher in the clopidogrel+aspirin group in the larger study involving 7,554 patients (0.4% per year for clopidogrel+aspirin vs. 0.2% per year for aspirin alone; HR 1.87; 95% CI 1.19 to 2.94; p=0.006),[233] and similar between therapies in one small study involving 593 patients (3 patients in the clopidogrel+aspirin group vs. 1 patient in the aspirin alone group; p=0.62).[276] Based on the larger study, but reflecting the inconsistent and imprecise findings, there was low SOE that combined therapy increased intracranial bleeding.

Extracranial Bleeding

Rates of extracranial bleeding were higher with clopidogrel+aspirin than with aspirin alone in both studies. In the larger study involving 7,554 patients, rates were 1.6% per year for clopidogrel+aspirin vs. 1.1% per year for aspirin alone (HR 1.51; 95% CI 1.21 to 1.88; p<0.001).[233] The small study involving 593 patients found 2% extracranial bleeding in the clopidogrel+aspirin group vs. 1% in the aspirin alone group but did not reach statistical significance (p=0.51).[276] Given the inconsistent findings and low number of events, there was insufficient SOE that combined therapy increased extracranial bleeding.

Other Clinical Outcomes

All-Cause Mortality

All-cause mortality did not differ between the groups in either study (in the larger study, 6.4% per year for clopidogrel+aspirin vs. 6.6% per year for aspirin alone; HR 0.98; 95% CI 0.89 to1.08; p=0.69[233] and in the smaller study, 29 patients in the clopidogrel+aspirin vs. 25 patients in aspirin alone group; HR 1.12; 95% CI 0.65 to 1.90; p=0.69[276]) (moderate SOE). In a followup study to the larger study,[372] using all deaths that occurred until the end of all available followup (median followup of 3.7 years), there was still no evidence of a difference between the groups (HR 0.99; 95% CI 0.90 to 1.10).

Death From Vascular Causes

Death from vascular causes also did not differ between the groups in the larger study (4.7% per year for clopidogrel+aspirin vs. 4.7% per year for aspirin alone; HR 1.00; 95% CI 0.89 to 1.12; p=0.97[233]); however, in the smaller study there was a trend toward a benefit of aspirin alone (21 patients in the clopidogrel+aspirin vs. 12 patients in aspirin alone group; HR 1.68; 95% CI 0.83 to 3.42; p=0.15[276]), reducing the SOE (low SOE).

Myocardial Infarction

Myocardial infarction did not differ between treatment groups in the larger study (0.7% per year for clopidogrel+aspirin vs. 0.9% per year for aspirin alone; HR 0.78; 95% CI 0.59 to 1.03; p=0.08)[233]) however, in the smaller study there was a trend toward a benefit of aspirin alone (9 patients in the clopidogrel+aspirin group vs. 6 patients in the aspirin alone group; HR 1.43; 95% CI 0.51 to 4.01; p=0.50[276]), reducing the SOE (low SOE).

Hospitalization

Only the smaller study involving 593 patients reported rates of rehospitalization, which were similar between the two groups (41 patients in the clopidogrel+aspirin group vs. 43 patients in the aspirin alone group; HR 0.89; 95% CI 0.58 to 1.37; p=0.60).[276] Given the small size of the study and the imprecision of the findings, there was insufficient SOE to determine the impact of combined therapy on hospitalization.

Strength of Evidence

Table 38 summarizes the SOE for outcomes of interest for this comparison.

Table 38. Strength of evidence—clopidogrel+aspirin versus aspirin alone

Outcome	Number of Studies (Subjects)	Risk of Bias	Consistency	Directness	Precision	Reporting Bias	SOE and Effect (95% CI)
Any stroke	2[233,276] (8,147)	Low	Inconsistent	Direct	Precise	None	**SOE=Moderate** Lower rates with combined therapy (HR 0.72; 95% CI 0.62 to 0.83)
Ischemic stroke	2[233,276] (8,147)	Low	Inconsistent	Direct	Imprecise	None	**SOE=Low** Lower rates with combined therapy (HR 0.68; 95% CI 0.57 to 0.80)

Outcome	Number of Studies (Subjects)	Risk of Bias	Consistency	Directness	Precision	Reporting Bias	SOE and Effect (95% CI)
Hemorrhagic stroke	2[233,276] (8,147)	Low	Consistent	Direct	Imprecise	None	**SOE=Moderate** Similar between therapies in both studies
Systemic embolism	1[233] (7,554)	Low	NA	Direct	Imprecise	None	**SOE=Moderate** Similar between therapies (HR 0.96; 95% CI 0.66 to 1.40)
Major bleeding	1[233] (7,554)	Low	NA	Direct	Precise	None	**SOE=Moderate** Clopidogrel+ASA associated with higher rates (HR 1.57; 95% CI 1.29 to 1.92)
Minor bleeding	1[233] (7,554)	Low	NA	Direct	Precise	None	**SOE=Moderate** Clopidogrel+ASA associated with higher rates (HR 2.42; 95% CI 2.03 to 2.89)
Intracranial bleeding	2[233,276] (8,147)	Low	Inconsistent	Direct	Imprecise	None	**SOE=Low** Higher rate with clopidogrel+ASA (HR 1.87; 95% CI 1.19 to 2.94)
Extracranial bleeding	2[233,276] (8,147)	Low	Inconsistent	Direct	Imprecise	None	**SOE=Insufficient**
All-cause mortality	2[233,276] (8,147)	Low	Consistent	Direct	Imprecise	None	**SOE=Moderate** No evidence of a difference (HR 0.98 [95% CI 0.89 to 1.08] in one study; HR 1.12 [95% CI 0.65 to 1.90] in other study)
Death from vascular causes	2[233,276] (8,147)	Low	Inconsistent	Direct	Imprecise	None	**SOE=Low** No evidence of a difference based on large RCT (HR 1.00; 95% CI 0.89 to 1.12), although a smaller study showed a trend toward a benefit of ASA alone (HR 1.68; 95% CI 0.83 to 3.42)

Outcome	Number of Studies (Subjects)	Risk of Bias	Consistency	Directness	Precision	Reporting Bias	SOE and Effect (95% CI)
Myocardial infarction	2[233,276] (8,147)	Low	Inconsistent	Direct	Imprecise	None	**SOE=Low** No evidence of a difference based on large RCT (HR 0.78; 95% CI 0.59 to 1.03), although a smaller study showed a trend toward a benefit of ASA alone (HR 1.43; 95% CI 0.51 to 4.01)
Hospitalization	1[276] (593)	Low	NA	Direct	Imprecise	None	**SOE=Insufficient**

Abbreviations: ASA=aspirin; CI=confidence interval; HR=hazard ratio; NA=not applicable; RCT=randomized controlled trial; SOE=strength of evidence

5. Clopidogrel Versus VKA (Warfarin)

One good-quality retrospective cohort study compared clopidogrel (3,717 patients) with warfarin (50,919 patients).[275]

Ischemic Stroke

This study demonstrated that treatment with clopidogrel was associated with increased risk of nonfatal and fatal ischemic stroke when compared with warfarin (HR 1.86; 95% CI 1.52 to 2.27) (moderate SOE).[275]

Bleeding

This study found that the risk of nonfatal and fatal bleeding was similar between groups (HR 1.06; 95% CI 0.87 to1.29) (moderate SOE).[275]

Strength of Evidence

Table 39 summarizes the SOE for outcomes of interest for this comparison.

Table 39. Strength of evidence—clopidogrel versus warfarin

Outcome	Number of Studies (Subjects)	Risk of Bias	Consistency	Directness	Precision	Reporting Bias	SOE and Effect (95% CI)
Ischemic stroke	1[275] (54,636)	Moderate	NA	Direct	Precise	Suspected	**SOE=Moderate** Increased risk with clopidogrel (HR 1.86; 95% CI 1.52 to 2.27)
Bleeding	1[275] (54,636)	Moderate	NA	Direct	Precise	Suspected	**SOE=Moderate** Similar between therapies (HR 1.06; 95% CI 0.87 to 1.29)

Abbreviations: CI=confidence interval; HR=hazard ratio; NA=not applicable; SOE=strength of evidence

6. Clopidogrel+Aspirin Versus Warfarin

Two studies compared clopidogrel+aspirin with warfarin in ITT analyses.[232,275] One study was a good-quality retrospective analysis involving 2,859 patients on clopidogrel+aspirin

treatment and 50,919 patients on warfarin monotherapy.[275] The other study was a good-quality RCT involving 6,706 patients which was stopped early because of the clear evidence of superiority of the warfarin strategy.[232]

Thromboembolic Outcomes

Stroke or Systemic Embolism

In both studies, treatment with clopidogrel+aspirin was associated with increased risk of nonfatal and fatal ischemic stroke when compared with warfarin (HR 1.56; 95% CI 1.17 to 2.10;[275] and HR 1.72; 95% CI 1.24 to 2.37; p=0.001[232]) (high SOE).

Hemorrhagic Stroke

The RCT involving 6,706 patients reported rates of hemorrhagic stroke, which were higher in the warfarin group (0.12% per year vs. 0.36% per year for clopidogrel+aspirin and warfarin, respectively; HR 0.34; 95% CI 0.12 to 0.93; p=0.036)[232] (moderate SOE).

Bleeding Outcomes

Major Bleeding

The RCT reported no evidence of differences in major bleeding rates, including severe and fatal bleeding (2.42% per year vs. 2.21% per year for clopidogrel+aspirin and warfarin, respectively; HR 1.10; 95% CI 0.83 to 1.45; p=0.53).[232] The other large retrospective study reported that the risk of nonfatal and fatal bleeding was higher in the clopidogrel+aspirin group (HR 1.66; 95% CI 1.34 to 2.04).[275] Given the inconsistent findings, but the similar rates found in the RCT, there was low SOE of similar rates of major bleeding between therapies.

Minor Bleeding

Only the RCT study reported rates of minor bleeding, which were higher in the clopidogrel+aspirin group (13.58% per year vs. 11.45% per year for clopidogrel+aspirin and warfarin, respectively; HR 1.23; 95% CI 1.09 to 1.39; p=0.0009) (moderate SOE).[232]

Intracranial Bleeding

Intracranial bleeding, including subdural hematoma, was reported by the RCT and was more common with warfarin therapy; however, this difference did not reach statistical significance and had low numbers of events (p=0.08) (insufficient SOE).[232]

Other Clinical Outcomes

All-Cause Mortality

All-cause mortality was reported by the RCT, and there was no evidence of a difference between the two therapies (3.8% per year vs. 3.76% per year for clopidogrel+aspirin and warfarin, respectively; HR 1.01; 95% CI 0.81 to 1.26; p=0.91) (moderate SOE).[232]

Death From Vascular Causes

Death from vascular causes was reported by the RCT. Rates were slightly higher with clopidogrel+aspirin; however, the difference did not reach statistical significance (2.87% per

year vs. 2.52% per year for clopidogrel+aspirin and warfarin, respectively; HR 1.14; 95% CI 0.88 to 1.48; p=0.34) (moderate SOE).[232]

Myocardial Infarction

Within the RCT,[232] MI occurred at rates of less than one percent per year in both groups and was not statistically different between the treatments. Rates of MI were not reported in the other study[275] (moderate SOE).

Strength of Evidence

Table 40 summarizes the SOE for outcomes of interest for this comparison.

Table 40. Strength of evidence—clopidogrel+aspirin versus warfarin

Outcome	Number of Studies (Subjects)	Risk of Bias	Consistency	Directness	Precision	Reporting Bias	SOE and Effect (95% CI)
Stroke or systemic embolism	2[232,275] (60,484)	Low	Consistent	Direct	Precise	None	**SOE=High** Increased risk with clopidogrel+ASA in both studies (HR 1.56 [95% CI 1.17 to 2.10] in one study; HR 1.72 [95% CI 1.24 to 2.37] in other study)
Hemorrhagic stroke	1[232] (6,706)	Low	NA	Direct	Imprecise	None	**SOE=Moderate** Increased risk with warfarin (HR 0.34 [95% CI 0.12 to 0.93])
Major bleeding	2[232,275] (60,484)	Low	Inconsistent	Direct	Imprecise	Suspected	**SOE=Low** Similar rates between therapies (HR 1.10; 95% CI 0.83 to 1.45),
Minor bleeding	1[232] (6,706)	Low	NA	Direct	Precise	None	**SOE=Moderate** Increased risk with clopidogrel+ASA (HR 1.23; 95% CI 1.09 to 1.39)
Intracranial bleeding	1[232] (6,706)	Low	NA	Direct	Imprecise	None	**SOE=Insufficient**
All-cause mortality	1[232] (6,706)	Low	NA	Direct	Precise	None	**SOE=Moderate** No evidence of a difference (HR 1.01; 95% CI 0.81 to 1.26)
Death from vascular causes	1[232] (6,706)	Low	NA	Direct	Imprecise	None	**SOE=Moderate** No evidence of a difference (HR 1.14; 95% CI 0.88 to 1.48)

Outcome	Number of Studies (Subjects)	Risk of Bias	Consistency	Directness	Precision	Reporting Bias	SOE and Effect (95% CI)
Myocardial infarction	1[232] (6,706)	Low	NA	Direct	Imprecise	None	**SOE=Moderate** No evidence of a difference (myocardial infarction occurred at rates of <1% per year with both therapies)

Abbreviations: ASA=aspirin; CI=confidence interval; HR=hazard ratio; NA=not applicable; RCT=randomized controlled trial; SOE=strength of evidence

7. Warfarin+Clopidogrel Versus Warfarin Alone

One good-quality retrospective study compared warfarin+clopidogrel (1,430 patients) with warfarin monotherapy (50,919 patients).[275] While the risk of ischemic stroke was similar across the two treatments, the risk of bleeding was greatly increased in patients receiving warfarin+clopidogrel compared with those receiving warfarin monotherapy.

Thromboembolic Outcomes

Ischemic Stroke

In the one included study, there was a trend toward benefit of warfarin+clopidogrel for nonfatal and fatal ischemic stroke (HR 0.70; 95% CI 0.35 to 1.40) (low SOE).[275]

Bleeding Outcomes

The risk of nonfatal and fatal bleeding was three-fold higher for patients receiving warfarin+clopidogrel as compared with patients receiving warfarin monotherapy (HR 3.08; 95% CI 2.32 to 3.91) (moderate SOE).[275]

Strength of Evidence

Table 41 summarizes the SOE for outcomes of interest for this comparison.

Table 41. Strength of evidence—warfarin+clopidogrel versus warfarin alone

Outcome	Number of Studies (Subjects)	Risk of Bias	Consistency	Directness	Precision	Reporting Bias	SOE and Effect (95% CI)
Ischemic stroke	1[275] (52,349)	Moderate	NA	Direct	Imprecise	Suspected	**SOE=Low** Trend toward benefit of warfarin+ clopidogrel (HR 0.70; 95% CI 0.35 to 1.40)
Bleeding	1[275] (52,349)	Moderate	NA	Direct	Precise	Suspected	**SOE=Moderate** Higher for patients on warfarin+ clopidogrel (HR 3.08; 95% CI 2.32 to 3.91)

Abbreviations: CI=confidence interval; HR=hazard ratio; NA=not applicable; SOE=strength of evidence

8. Warfarin Alone Versus Warfarin+Aspirin+Clopidogrel

One good-quality retrospective study compared warfarin monotherapy (50,919 patients) with the triple therapy of warfarin+aspirin+clopidogrel (1,261 patients).[275]

Thromboembolic Outcomes

Ischemic Stroke

The rates of nonfatal and fatal ischemic stroke were similar between groups (HR 1.45; 95% CI 0.84 to 2.52), although there was a trend toward an increase in the triple therapy arm (low SOE).[275]

Bleeding Outcomes

Triple therapy was associated with a large and statistically significant increased risk of nonfatal and fatal bleeding (HR 3.70; 95% CI 2.89 to 4.76) (moderate SOE).[275]

Strength of Evidence

Table 42 summarizes the SOE for outcomes of interest for this comparison.

Table 42. Strength of evidence—warfarin alone versus warfarin+aspirin+clopidogrel

Outcome	Number of Studies (Subjects)	Risk of Bias	Consistency	Directness	Precision	Reporting Bias	SOE and Effect (95% CI)
Ischemic stroke	1[275] (52,180)	Moderate	NA	Direct	Imprecise	Suspected	**SOE=Low** Trend toward being higher for patients on triple therapy (HR 1.45; 95% CI 0.84 to 2.52)
Bleeding	1[275] (52,180)	Moderate	NA	Direct	Precise	Suspected	**SOE=Moderate** Higher for patients on triple therapy (HR 3.70; 95% CI 2.89 to 4.76)

Abbreviations: CI=confidence interval; HR=hazard ratio; NA=not applicable; SOE=strength of evidence

9. Thrombin Inhibitor (Dabigatran) Versus Warfarin

One large, good-quality, noninferiority RCT of 18,113 patients (RE-LY) compared a thrombin inhibitor (dabigatran) with warfarin in nonvalvular AF patients in ITT analyses.[23] Patients receiving dabigatran were randomized to one of two doses (110mg and 150mg). Note that the 110mg dose is not currently approved by the FDA for atrial fibrillation within the US. It is however approved for other uses and so can be used off-label for AF patients. The 150mg dose is FDA-approved and indicated for AF patients.

With the RE-LY trial,[23] patients receiving the 110mg dose had similar rates of stroke and systemic embolism to those associated with warfarin, but lower rates of major hemorrhage. Patients who received 150mg of dabigatran had lower rates of stroke and systemic embolism than patients in the warfarin group, but similar rates of major hemorrhage.

The observational study Long-term Multicenter Extension of Dabigatran Treatment in Patients with Atrial Fibrillation (RELY-ABLE) was designed to provide additional information on the long-term effects of the two doses of dabigatran in patients completing RE-LY by extending the followup of patients on dabigatran from a mean of 2 years at the end of RE-LY by an additional 2.25 years.[234] Patients randomly assigned to dabigatran in RE-LY were eligible for RELY-ABLE if they had not permanently discontinued study medication at the time of their final RE-LY study visit. Enrolled patients continued to receive the double-blind dabigatran dose received in RE-LY for up to 28 months of followup after RE-LY (median followup, 2.3 years).

There were 5851 patients enrolled, representing 48 percent of patients originally randomly assigned to receive dabigatran in RE-LY and 86 percent of RELY-ABLE–eligible patients.

This comparison was also assessed in 35 observational studies.[112,177,214,218,220,258,268,273,287,297-300,309-311,324,329,346,347,351,352,357,362,370,373,376,384,387,392,395,398,402,403,408]

Thromboembolic Outcomes

Hemorrhagic or Ischemic Stroke

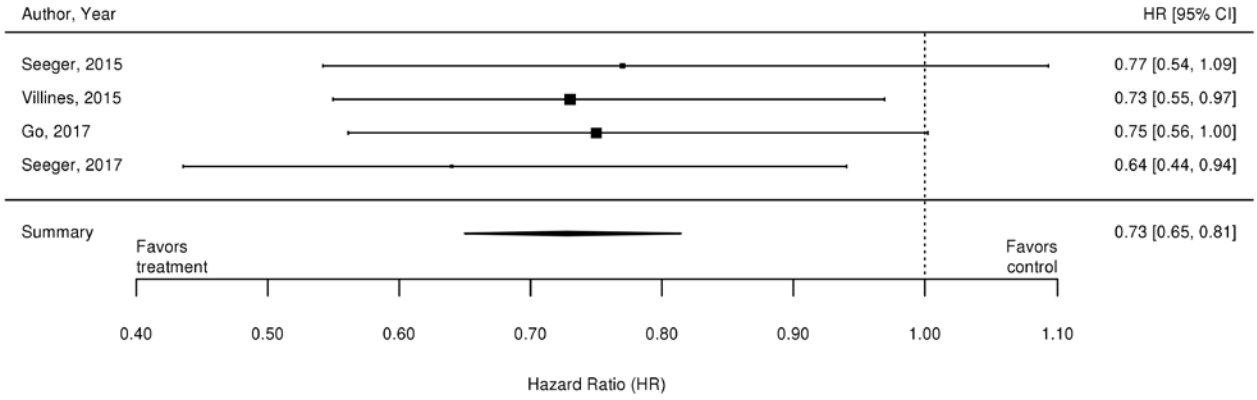
Four observational studies compared dabigatran with warfarin and evaluated hemorrhagic or ischemic stroke. These findings are summarized in Table 43 and in Figure 9. Consistent with RCT evidence, they demonstrate a reduction in stroke for patients on dabigatran compared with warfarin (HR 0.73; 95% CI 0.65 to 0.81, I^2 = 0%, Q = 0.6, p=0.90).

Table 43. Observational studies: hemorrhagic or ischemic stroke—dabigatran 150mg or 110mg versus warfarin

Database	Location	Risk Estimate (95% CI) Dabigatran vs. Warfarin
Analysis With Propensity-Matched Controls		
MarketScan, Truven and Clinformatics, Optum[346]	US	0.77 (0.54 to 1.09)
Department of Defense (DoD) database[362]	US	0.73 (0.55 to 0.97)
MarketScan, Truven and Clinformatics, Optum[347]	US	0.64 (0.44 to 0.95)
FDA's Sentinel Distributed Database[376]	US	0.75 (0.56 to 1.00)

Abbreviations: CI=confidence interval; FDA=Food and Drug Administration

Figure 9. Forest plot for hemorrhagic or ischemic stroke—dabigatran 150mg or 110mg (treatment) versus warfarin (control) (observational)



Abbreviation: CI=confidence interval

Stroke or Systemic Embolism, or Major Bleeding

Within the RELY-ABLE study[234] rates of stroke or systemic embolism were 1.46 percent and 1.60 percent per year on dabigatran 150mg and 110mg twice daily, respectively (HR 0.91; 95% CI 0.69 to 1.20).

The retrospective propensity-matched CARBOS study used a German claims database to compare risk of stroke, systemic embolism, or major bleeding between those initiated on apixaban, dabigatran or rivaroxaban versus the VKA of phenprocoumon.[287] In this study, there was no statistically significant difference in risk between users of dabigatran versus phenprocoumon (HR 0.80; 95% CI 0.61 to 1.04; p=0.095).

Stroke or Systemic Embolism

In the RCT,[23] dabigatran at a 110mg dose was similar to warfarin in preventing stroke and systemic embolism (1.53% per year vs. 1.69% per year for dabigatran and warfarin, respectively; relative risk [RR] 0.91; 95% CI 0.74 to 1.11; p<0.001 for noninferiority and 0.34 for superiority) (moderate SOE for no evidence of a difference). Dabigatran at 150mg was superior to warfarin in reducing the incidence of stroke (including hemorrhagic stroke) and systemic embolism by 34 percent (1.11% per year vs. 1.69% per year; RR 0.66; 95% CI 0.53 to 0.82; p<0.001) (high SOE that dabigatran reduced risk).

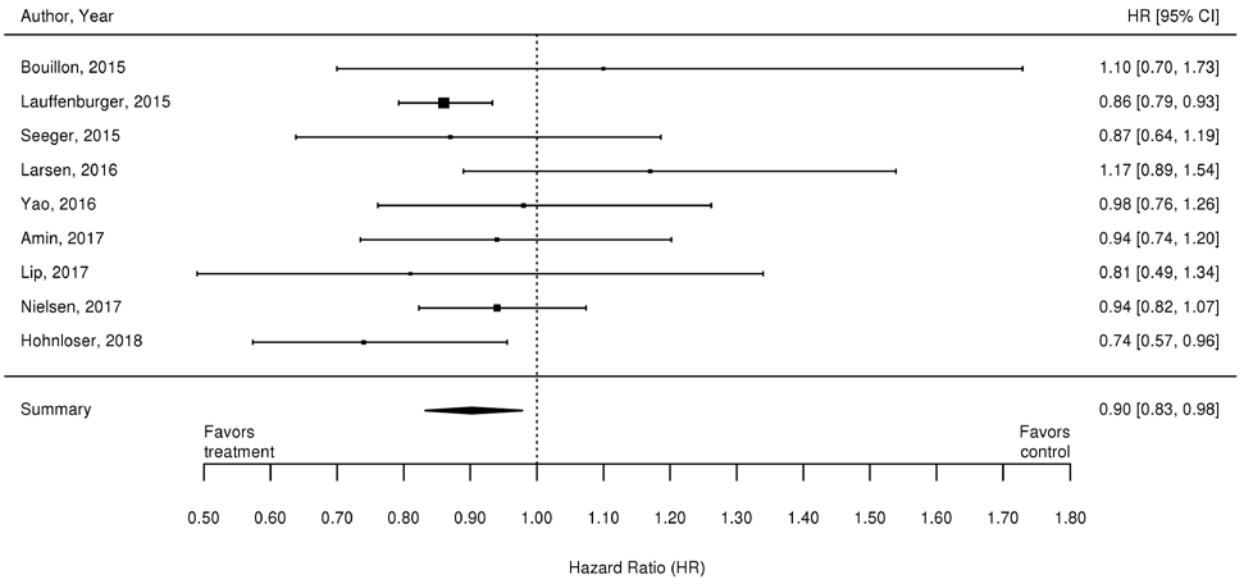
This outcome was also assessed in 10 observational studies. These findings are summarized in Table 44 and the 9 studies that use propensity matching methods are synthesized quantitatively in Figure 10. As the figure demonstrates, consistent with the RCT evidence for the high dose dabigatran, these studies demonstrate that dabigatran reduces risk of stroke or systemic embolism compared with warfarin (HR 0.90; 95% CI 0.83 to 0.98, I^2 = 9.8%, Q = 8.9, p=0.35) although several individual observational studies do not demonstrate a statistically significant reduction.

Table 44. Observational studies: stroke or systemic embolism—dabigatran 150mg or 110mg versus warfarin

Database	Location	Risk Estimate (95% CI) Dabigatran vs. Warfarin
Analysis With Propensity-Matched Controls		
Danish national prescription registry, Danish civil registration system, Danish national patient register[329]	Europe	0.94 (0.82 to 1.07) Age ≥80: 0.98 (0.82 to 1.17)Age ≥80 and/or renal disease: 0.93 (0.79 to 1.10)
Danish national prescription registry, Danish civil registration system, Danish national patient register[299]	Europe	1.17 (0.89 to 1.54) Age ≥65: 1.20 (0.87 to 1.67) Age <65: 1.00 (0.78 to 1.29)
Observational cohort study of Danish citizens[311]	Europe	0.81 (0.49 to 1.34) Age >65: 0.96 (0.53 to 1.76) Hypertension: 0.83 (0.31 to 2.23) Men: 0.90 (0.49 to 1.66) Women: 0.72 (0.28 to 1.84)
MarketScan, Truven and Clinformatics, Optum[346]	US	0.87 (0.64 to 1.19)
OptumLabs Data Warehouse (OLDW)[370]	US	0.98 (0.76 to 1.26)
Truven Health MarketScan Commercial Claims and Encounters and Medicare supplement databases[300]	US	0.86 (0.79 to 0.93)
French national health-insurance database (Système National d'Information Inter-Régimes de l'Assurance Maladie [SNIIRAM][112]	Europe	1.10 (0.70 to 1.73) p=0.70 Switched to dabigatran 75-110mg vs. maintained on VKA therapy: 1.13 (0.71 to 1.81) p=0.62Switched to dabigatran 150mg vs. maintained on VKA therapy: 0.80 (0.16 to 4.12) p=0.79
US Center for Medicare and Medicaid Services (CMS) data[395]	US	0.94 (0.74 to 1.21) Reduced: 1.41 (0.86 to 2.30) Standard: 0.84 (0.63 to 1.12)
German Applied Health Research Database[398]	Europe	0.74 (0.57 to 0.95)
Analysis Without Propensity-Matched Controls		
Danish National Patient Registry[352]	Europe	0.97 (0.84 to 1.13)

Abbreviations: CI=confidence interval; VKA=vitamin K antagonist

Figure 10. Forest plot for stroke or systemic embolism—dabigatran 150mg or 110mg (treatment) versus warfarin (control) (observational)



Abbreviation: CI=confidence interval

Ischemic Stroke, Systemic Embolism, or Death

One study examined a sample of the Medicare database and compared the composite outcome of ischemic stroke, systemic embolism, or death in users of dabigatran versus warfarin[384] This study found a significantly lower risk of this composite outcome among dabigatran users compared with warfarin with an adj HR (95% CI) of 0.73 (0.63, 0.86).

Ischemic or Uncertain Stroke

In the RCT,[23] the rates of ischemic or uncertain stroke were similar between dabigatran 110mg and warfarin (1.34% per year for dabigatran 110mg vs. 1.20% per year for warfarin; RR 1.11; 95% CI 0.89 to 1.40; p=0.35) (high SOE). Dabigatran 150mg was associated with lower rates of ischemic or uncertain stroke when compared with warfarin (0.92% per year for dabigatran 150mg vs. 1.20% per year for warfarin; RR 0.76; 95% CI 0.60 to 0.98; p=0.03) (moderate SOE).

This outcome was also assessed in 15 observational studies. These studies are summarized in Table 45 and the studies that used propensity matching methods are synthesized in Figure 11. The dosing of 110mg and 150mg were not consistently evaluated among these trials but within this set of studies a reduction for the outcome of ischemic or uncertain stroke (HR 0.86, 95% CI 0.76 to 0.98, I^2 = 59%, Q = 26.8, p=0.005) was found with dabigatran as compared to warfarin.

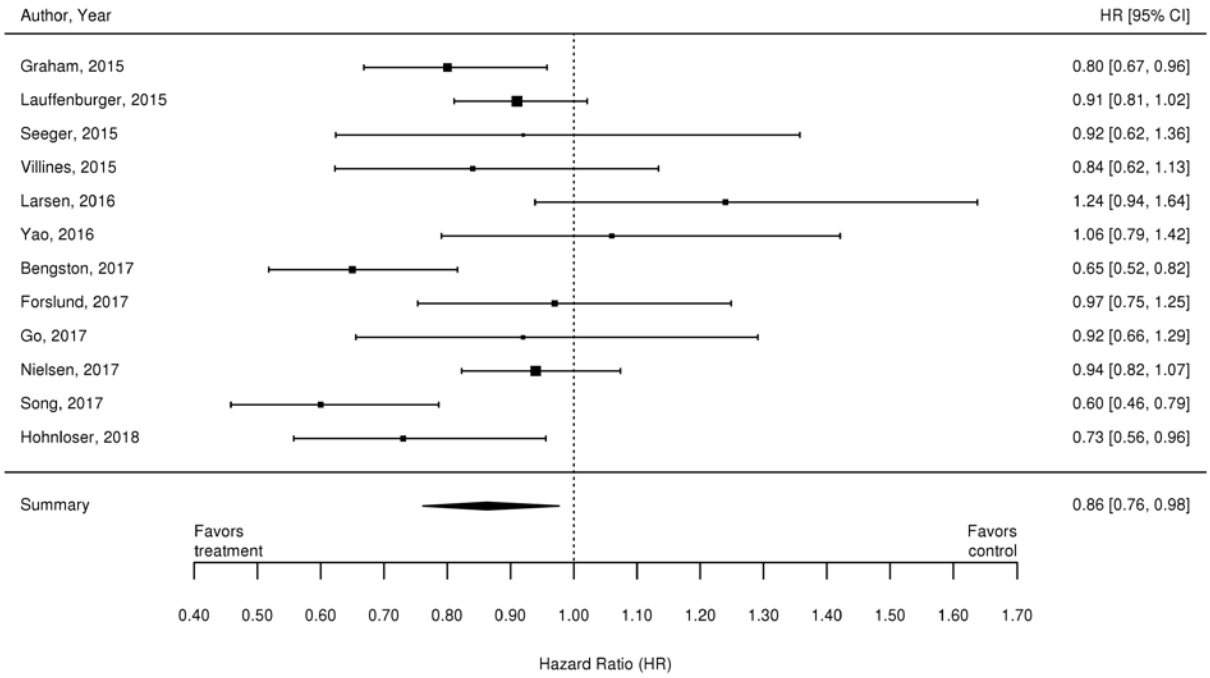
Table 45. Observational studies: ischemic or uncertain stroke—dabigatran 150mg or 110mg versus warfarin

Database	Location	Risk Estimate (95% CI) Dabigatran vs. Warfarin
Analysis With Propensity-Matched Controls		
Danish national prescription registry, Danish civil registration system, Danish national patient register[329]	Europe	0.94 (0.82 to 1.07) Age ≥80: 0.97 (0.81, 1.16) Age ≥80 and/or renal disease: 0.93 (0.78 to 1.11)

Database	Location	Risk Estimate (95% CI) Dabigatran vs. Warfarin
Danish national prescription registry, Danish civil registration system, Danish national patient register[299]	Europe	1.24 (0.94 to 1.64) Age <65: 1.12 (0.87 to 1.46) Age ≥65: 1.26 (0.91 to 1.76)
Truven Health MarketScan1 Commercial Claims and Encounters Database and the Medicare Supplemental and Coordination of Benefits Database[218]	US	0.65 (0.52 to 0.82)Early (<90 days): 0.32 (0.22 to 0.47) Later (≥90 days): 0.99 (0.75 to 1.31)
Maintenance et Exploitation des Données pour l'Étude de la Clientèle Hospitalière—Med-Echo and the provincial physician and prescription claims database (la Régie de l'assurance maladie du Quebec)[214]	Canada	Men dabigatran 110mg: 1.08 (0.89 to 1.31)Men dabigatran 150mg:0.98 (0.78 to 1.23)Women dabigatran 110mg: 1.06 (0.89 to 1.24)Women dabigatran 150mg: 0.79 (0.56 to 1.04)
MarketScan, Truven and Clinformatics, Optum[346]	US	0.92 (0.62 to 1.35)
Department of Defense (DoD) database[362]	US	0.84 (0.62 to 1.13)
Truven Health MarketScan Commercial Claims and Encounters and Medicare supplement databases[300]	US	0.91 (0.81 to 1.02)
Medicare database[268]	US	0.80 (0.67 to 0.96)
Health data register of the Stockholm Region (Va˚rdanalysdatabasen, VAL)[258]	Europe	0.97 (0.76 to 1.26)
Danish National Prescription Registry; Danish National Patient Register; Danish Civil Registration System[297]	Europe	Among patients with prior VKA experience: Dabigatran 110mg: adj HR 1.54 (1.11 to 2.13) Dabigatran 150mg: adj HR 1.79 (1.25 to 2.56) Among VKA-naïve patients: Dabigatran 110mg: adj HR 0.67 (0.52 to 0.86) Dabigatran 150mg: adj HR 1.02 (0.80 to 1.30)
OptumLabs Data Warehouse (OLDW)[370]	US	1.06 (0.79 to 1.42)
FDA's Sentinel Distributed Database[376]	US	HR 0.92 (0.65 to 1.28)
MarketScan[177]	US	HR 0.60 (0.46 to 0.79)
German Applied Health Research Database[398]	Europe	0.73 (0.56 to 0.96)
Analysis Without Propensity-Matched Controls		
Danish National Patient Registry[352]	Europe	0.89 (0.72 to 1.09)

Abbreviations: adj=adjusted; CI=confidence interval; HR=hazard ratio; VKA=vitamin K antagonist

Figure 11. Forest plot for ischemic or uncertain stroke—dabigatran 150mg or 110mg (treatment) versus warfarin (control) (observational)



Abbreviation: CI=confidence interval

Ischemic Stroke or Intracranial Hemorrhage

A U.S. study used MarketScan[392] to look at risk of intracranial hemorrhagic or ischemic stroke in patients with nonvalvular atrial fibrillation and a history of previous stroke or transient ischemic attack (REAFFIRM study). In a propensity-matched analysis, dabigatran had no evidence of a difference in risk compared to warfarin (HR 0.53, 95% CI 0.26 to 1.07).

Ischemic Stroke

A U.S. study used MarketScan[392] to look at risk ischemic stroke in patients with nonvalvular atrial fibrillation and a history of previous stroke or transient ischemic attack (REAFFIRM study). In a propensity-matched analysis, dabigatran had no evidence of a difference in risk compared to warfarin (HR 0.60, 95% CI 0.28-1.27). A second U.S. propensity-matched study using CMS data found a nonsignificant difference in risk of ischemic stroke when comparing dabigatran users to warfarin users (HR 1.24, 95% CI 0.93 to 1.65).[395] This was similarly seen in a German propensity-matched study (adj HR 0.86, 95% CI 0.64 to 1.15, p=0.297).[398] A fourth U.S. propensity-matched study using data from the U.S. Food and Drug Administration Sentinel network examined the risk of ischemic stroke between dabigatran and warfarin users.[376] There was no statistically significant difference between dabigatran and warfarin in incidence of ischemic stroke (HR 0.92, 95% CI 0.65 to 1.28). All four studies support no evidence of a difference in ischemic stroke risk between dabigatran and warfarin (moderate SOE).

Bleeding Outcomes

Hemorrhagic Stroke

In the RCT,[23] both doses of dabigatran were associated with lower rates of hemorrhagic stroke when compared with warfarin (0.12% per year for dabigatran 110mg vs. 0.38% per year for warfarin; RR 0.31; 95% CI 0.17 to 0.56; p<0.001; 0.10% per year for dabigatran 150mg versus 0.38% per year for warfarin; RR 0.26; 95% CI 0.14 to 0.49; p<0.001) (high SOE that dabigatran reduced risk with both doses). Within the RELY-ABLE study[234] rates of major hemorrhage were 3.74 percent and 2.99 percent per year on dabigatran 150mg and 110mg (HR 1.26; 95% CI 1.04 to 1.53).

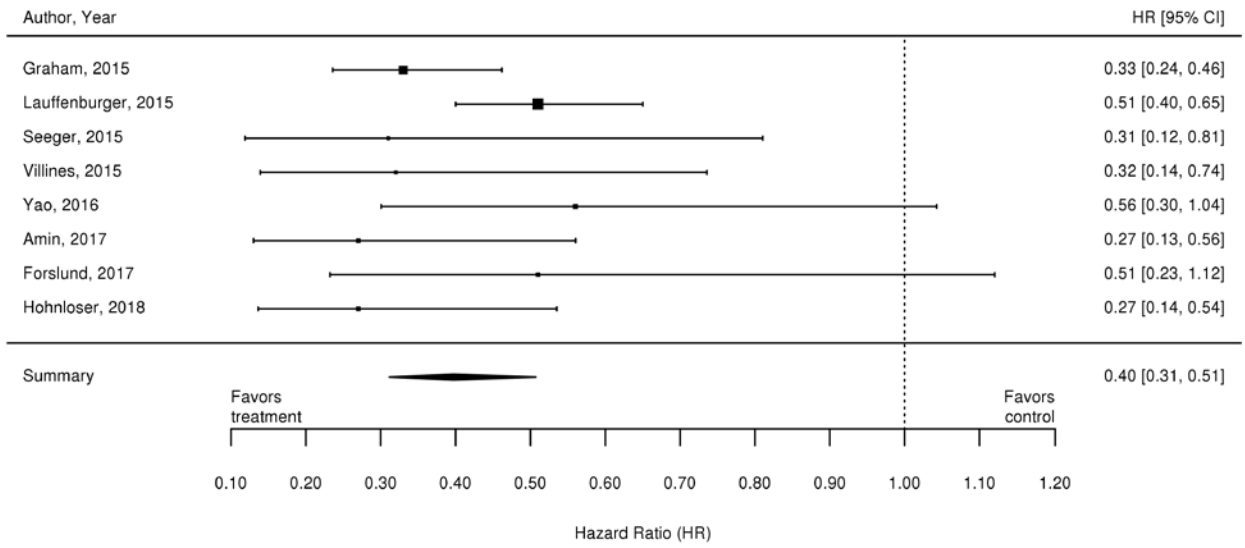
Hemorrhagic stroke was also evaluated in 8 observational studies. Table 46 and Figure 12 summarize these findings and consistent with the RCT evidence demonstrate a reduction in hemorrhagic stroke with dabigatran as compared with warfarin (HR 0.40, 95% CI 0.31 to 0.51, I^2 = 24.6%, Q = 9.3, p=0.23).

Table 46. Observational studies: hemorrhagic stroke—dabigatran 150mg or 110mg versus warfarin

Database	Location	Risk Estimate (95% CI) Dabigatran vs. Warfarin
Analysis With Propensity-Matched Controls		
MarketScan, Truven and Clinformatics, Optum[346]	US	0.31 (0.12 to 0.82)
Department of Defense (DoD) database[362]	US	0.32 (0.14 to 0.74)
Truven Health MarketScan Commercial Claims and Encounters and Medicare supplement databases[300]	US	0.51 (0.40 to 0.65)
Medicare database[268]	US	0.33 (0.24 to 0.47)
Health data register of the Stockholm Region (Va˚rdanalysdatabasen, VAL)[258]	Europe	0.51 (0.23 to 1.11)
OptumLabs Data Warehouse (OLDW)[370]	US	0.56 (0.30 to 1.04)
US Center for Medicare and Medicaid Services (CMS) data[395]	US	0.27 (0.13 to 0.56)
German Applied Health Research Database[398]	Europe	0.27 (0.14 to 0.55)

Abbreviation: CI=confidence interval

Figure 12. Forest plot: hemorrhagic stroke—dabigatran 150mg or 110mg (treatment) versus warfarin (control) (observational)



Abbreviation: CI=confidence interval

Major Bleeding

In the RCT,[23] dabigatran 110mg was associated with a 20 percent relative risk reduction in major bleeding when compared with warfarin (2.71% per year for dabigatran 110mg vs. 3.36% per year for warfarin; RR 0.80; 95% CI 0.69 to 0.93; p=0.003) (high SOE), while no evidence of a difference was seen between dabigatran 150mg and warfarin in regard to major bleeding (3.11% per year for dabigatran 150mg vs. 3.36% per year for warfarin; RR 0.93; 95% CI 0.81 to 1.07; p=0.31) (high SOE).

Major bleeding was also evaluated in 18 observational studies. These findings are summarized in Table 47 and the studies that used propensity matching are synthesized quantitatively in Figure 13. Most observational studies were not evaluated for dabigatran doses separately, but similar to the RCT evidence for the 110mg, the observational studies demonstrated a reduction in major bleeding (HR 0.77, 95% CI 0.70 to 0.86, I^2 = 75.8%, Q = 57.9, p<0.001).

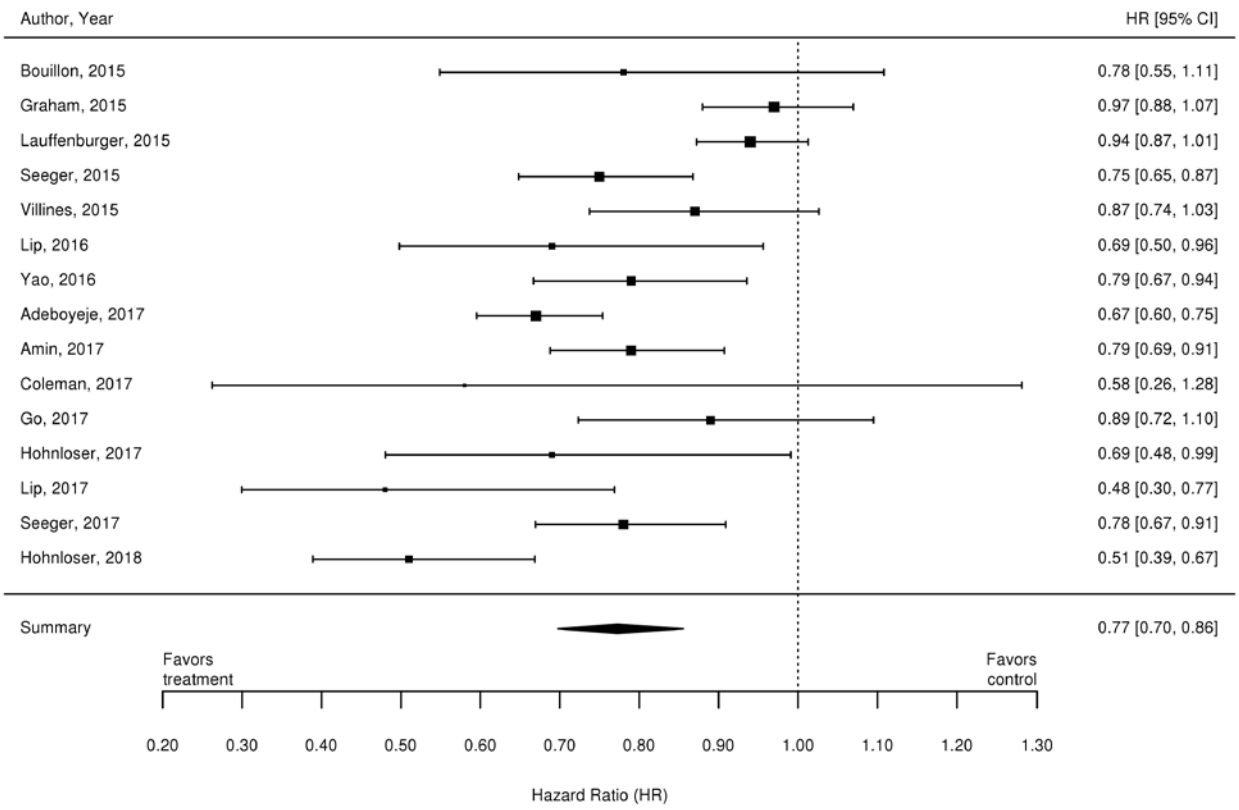
Table 47. Observational studies: major bleeding—dabigatran 150mg or 110mg versus warfarin

Database	Location	Risk Estimate (95% CI) Dabigatran vs. Warfarin
Analysis With Propensity-Matched Controls		
Observational cohort study of Danish citizens[311]	Europe	0.48 (0.30 to 0.77)
Maintenance et Exploitation des Données pour l'Étude de la Clientèle Hospitalière—Med-Echo and the provincial physician and prescription claims database (la Régie de l'assurance maladie du Quebec)[214]	Canada	Men dabigatran 110mg: 0.87 (0.77 to 0.98) Men dabigatran 150mg:0.73 (0.64 to 0.84) Women dabigatran 110mg: 1.00 (0.89 to 1.12) Women dabigatran 150mg: 0.85 (0.71 to 1.01)
MarketScan, Truven and Clinformatics, Optum[346]	US	0.75 (0.65 to 0.87)
MarketScan, Truven and Clinformatics, Optum[347]	US	0.78 (0.67 to 0.91)

Database	Location	Risk Estimate (95% CI) Dabigatran vs. Warfarin
Truven MarketScan® Commercial Claims and Encounter and Medicare Supplemental and Coordination of Benefits Databases[310]	US	0.69 (0.50 to 0.96)
OptumLabs Data Warehouse (OLDW)[370]	US	0.79 (0.67 to 0.94) p<0.01
Department of Defense (DoD) database[362]	US	0.87 (0.74 to 1.03)
Truven Health MarketScan Commercial Claims and Encounters and Medicare supplement databases[300]	US	0.94 (0.87 to 1.01)
Medicare database[268]	US	0.97 (0.88, 1.07) p=0.50
French national health-insurance database (Système National d'Information Inter-Régimes de l'Assurance Maladie [SNIIRAM][112]	Europe	0.78 (0.54 to 1.09) p=0.15
CARBOS study based on data from the Health Risk Institute (HRI)[287]	US	0.69 (0.48 to 0.99) p=0.042
HealthCore Integrated Research Environment (HIRE)[387]	US	0.67 (0.60, 0.76)
FDA's Sentinel Distributed Database[376]	US	0.89 (0.72 to 1.09)
US Center for Medicare and Medicaid Services (CMS) data[395]	US	0.79 (0.69 to 0.91) Reduced dose: 0.96 (0.74 to 1.25) Standard dose: 0.75 (0.64 to 0.89)
German Applied Health Research Database[398]	Europe	0.51 (0.39 to 0.67)
Analysis Without Propensity-Matched Controls		
Norwegian Patient Registry[273]	Europe	0.67 (0.52 to 0.88)
Truven MarketScan[309]	US	0.88 (0.64 to 1.21)
Larsen, 2014[298]	Europe	110mg dose 0.91 (0.73 to 1.14) 150mg dose 0.67 (0.53 to 0.85)

Abbreviation: CI=confidence interval

Figure 13. Forest plot for major bleeding—dabigatran 150mg or 110mg (treatment) versus warfarin (control) (observational)



Abbreviation: CI=confidence interval

Minor Bleeding

In the RCT,[23] overall, the rates of minor bleeding were higher in the warfarin group compared with both doses of dabigatran (13.16% per year for dabigatran 110mg vs. 16.37% per year for warfarin; RR 0.79; 95% CI 0.74 to 0.84; p<0.001; and 14.84% per year for dabigatran 150mg vs. 16.37% per year for warfarin; RR 0.91; 95% CI 0.85 to 0.97; p=0.005) (moderate SOE that dabigatran reduced risk with the or 110mg dose). Gastrointestinal bleeding was more common with higher dose dabigatran than with warfarin.

Any Bleeding

The retrospective CARBOS study[287] used a German claims database to evaluate risk of bleeding major bleeding, GI bleeding or any bleeding in patients newly initiated on apixaban, dabigatran or rivaroxaban versus the VKA of phenprocoumon. In their sensitivity analysis using propensity matching, there was no evidence of a difference in risk of any bleeding between dabigatran and phenprocoumon users (adj HR 0.90, 95% CI 0.76 to 1.08; p=0.267) (Table 48).

A nationwide study using the Norwegian patient registry[273] found a significantly lower risk of bleeding with dabigatran compared to warfarin (HR 0.74, 95% CI 0.66 to 0.84; p<0.001). A third study within the U.S. which also did not use propensity-matched controls[357] found an increase in any bleeding (HR 1.27, 95% CI 1.03 to 1.56). Finally, a study using a nationwide Danish prescription and patient registry demonstrated a reduction in any bleeding for patients on

either 110mg or 150mg doses of dabigatran (HR 0.72, 95% CI 0.59 to 0.88 and HR 0.67, 95% CI 0.55 to 0.83 respectively).[298]

One study examined a sample of the Medicare database and compared the outcome of any bleeding in users of dabigatran versus warfarin.[384] This study found a lower risk of any bleeding among dabigatran users compared with warfarin which was not statistically significant with an adj HR (95% CI) of 0.91 (0.80 to 1.04).

A retrospective propensity-matched study using MarketScan found a lower risk of bleeding in dabigatran users versus warfarin users over a 12 month followup period (adj HR 0.76, 95% CI 0.64 to 0.91).[177] This was similarly seen in a retrospective propensity-matched study using a German database (adj HR 0.82, 95% CI 0.71 to 0.93, p=0.003).[398]

Three of five studies found a significant lower risk of any bleeding with dabigatran compared to warfarin; one study found a significantly higher risk of any bleeding with dabigatran compared to warfarin, while one study showed no evidence of a difference.

Table 48. Observational studies: any bleeding—dabigatran 150mg or 110mg versus warfarin

Database	Location	Risk Estimate (95% CI) Dabigatran vs. Warfarin
Analysis With Propensity-Matched Controls		
CARBOS study[287]	Europe	adj HR 0.90 (0.76 to 1.08); p=0.267 (dabigatran and phenprocoumon)
Analysis Without Propensity-Matched Controls		
Norwegian patient registry[273]	Europe	HR 0.74 (0.66 to 0.84); p<0.001
VA database[357]	US	HR 1.27 (1.03 to 1.56); p=0.02
Danish prescription and patient registry[298]	Europe	Dabigatran 110mg vs. warfarin: HR 0.72, (0.59 to 0.88) and Dabigatran 150mg vs. warfarin HR 0.67 (0.55 to 0.83)
Medicare database[384]	US	0.91 (0.80 to 1.04)

Abbreviations: adj=adjusted: CI=confidence interval; HR=hazard ratio; VA=Veterans Affairs

Intracranial Bleeding

In the RCT,[23] both doses of dabigatran were associated with lower rates of intracranial bleeding (0.23% per year for dabigatran 110mg vs. 0.74% per year for warfarin; RR 0.31; 95% CI 0.20 to 0.47; p<0.001; 0.30% per year for dabigatran 150mg vs. 0.74% per year for warfarin; RR 0.40; 95% CI 0.27 to 0.60; p<0.001) (high SOE that dabigatran reduced risk with both doses).

A substudy[277] of the RE-LY trial[23] analyzed intracranial hemorrhages occurring during anticoagulation in all three groups (warfarin, dabigatran 110mg, and dabigatran 150mg). During a mean of 2.0 years of followup, 154 intracranial hemorrhages occurred in 153 participants, with a 30-day mortality of 36 percent. Intracranial hemorrhages included: 46 percent intracerebral (49% mortality), 45 percent subdural (24% mortality), and 8 percent subarachnoid (31% mortality). The rates of intracranial hemorrhage were 0.76 percent, 0.31 percent, and 0.23 percent per year among those assigned to warfarin, dabigatran 150mg, and dabigatran 110mg, respectively (p<0.001 for either dabigatran dose versus warfarin). There were no statistically significant differences in mortality rates of intracranial hemorrhages comparing warfarin with either dose of dabigatran for any site (mortality associated with intracranial hemorrhage was 36% warfarin, 35% dabigatran 150mg, and 41% dabigatran 110mg). Fewer fatal intracranial hemorrhages occurred among those assigned to dabigatran 150mg and 110mg (n=13 and n=11, respectively) versus warfarin (n=32; P <0.01 for both). Fewer traumatic intracranial hemorrhages occurred among those assigned to dabigatran (11 patients with each dose) compared with

warfarin (24 patients; p<0.05 for both dabigatran doses versus warfarin). Fatal traumatic intracranial hemorrhages occurred in 5 patients, 3 patients, and 3 patients assigned to warfarin, dabigatran 150mg, and dabigatran 110mg, respectively. The rate of spontaneous intracerebral hemorrhage was 0.36% per year (n=42) among those assigned to warfarin and was substantially lower for those assigned to dabigatran 150mg (0.09% per year, n=11; RR, 0.26; 95% CI 0.13 to 0.50) and dabigatran 110mg (0.08% per year, n=10; RR, 0.23; 95% CI 0.12 to 0.47). The mortality associated with spontaneous intracerebral hemorrhage averaged 52 percent, with no statistically significant differences between treatment arms. Fatal spontaneous intracerebral bleeding occurred in 19 patients assigned to warfarin versus 7 patients each with dabigatran 150mg and 110mg (p<0.01 for both comparisons with warfarin). Subdural hematomas accounted for 45 percent of intracranial hemorrhages and were associated with trauma in 44 percent of warfarin-assigned (16/36) and dabigatran-assigned (15/34) participants. The rate of subdural hematoma was 0.31, 0.20, and 0.08 percent per year among those assigned to warfarin, dabigatran 150mg (RR, 0.65; 95% CI 0.39 to 1.1; p=0.10) and dabigatran 110mg (RR, 0.27; 95% CI 0.12 to 0.55; p<0.001), respectively. The rate of subdural hematomas was significantly higher with dabigatran 150mg compared with the 110mg dosage (RR, 2.4; 95% CI 1.1 to 5.0; p=0.02). Fatal subdural bleeding occurred in 10, 5, and 2 patients assigned to warfarin, dabigatran 150mg, and dabigatran 110mg respectively (p<0.05 for dabigatran 110mg compared with warfarin).

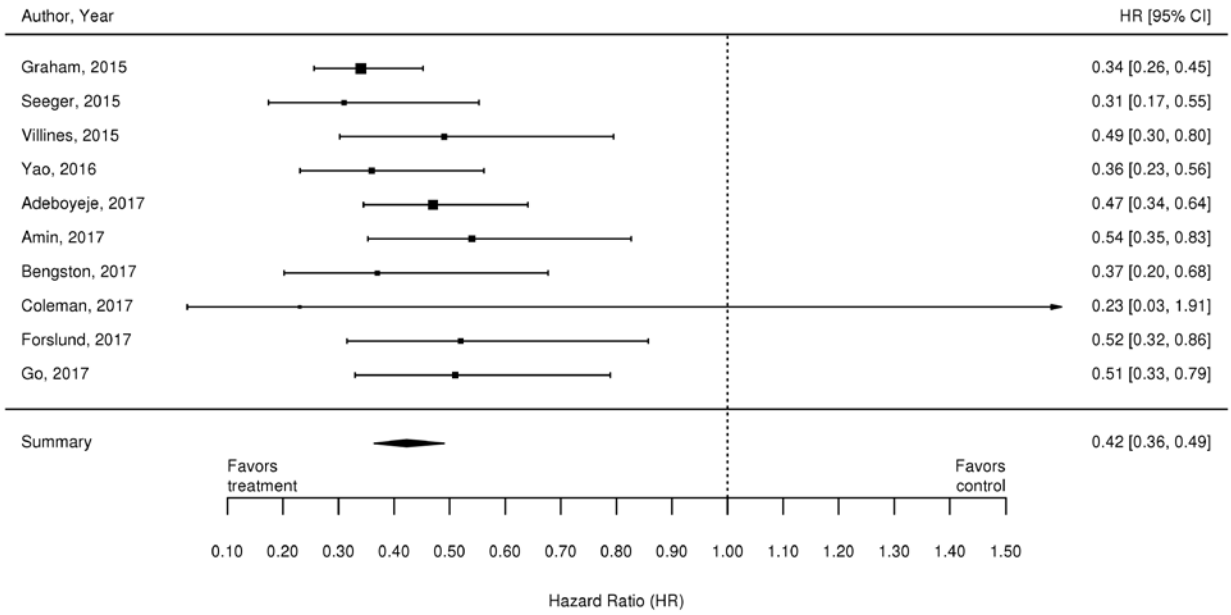
Intracranial bleeding was also evaluated in 15 observational studies. Table 49 summarizes theses and findings and the 9 observational studies which used propensity matching are synthesized in Figure 14. Consistent with the RCT evidence, dabigatran reduced intracranial bleeding compared with warfarin (HR 0.42, 95% CI 0.36 to 0.49, I^2 = 0%, Q = 7.8, p=0.55).

Table 49. Observational studies: intracranial bleeding—dabigatran 150mg or 110mg versus warfarin

Database	Location	Risk Estimate (95% CI) Dabigatran vs. Warfarin
Analysis With Propensity-Matched Controls		
Truven Health MarketScan1 Commercial Claims and Encounters Database and the Medicare Supplemental and Coordination of Benefits Database[218]	US	0.37 (0.20 to 0.67)
MarketScan, Truven and Clinformatics, Optum[346]	US	0.31 (0.17 to 0.54)
OptumLabs Data Warehouse (OLDW)[370]	US	0.36 (0.23 to 0.56) p<0.001
Department of Defense (DoD) database[362]	US	0.49 (0.30 to 0.79)
Medicare database[268]	US	0.34 (0.26 to 0.46) p<0.001
Health data register of the Stockholm Region (Va˚rdanalysdatabasen, VAL)[258]	Europe	0.52 (0.32 to 0.87)
HealthCore Integrated Research Environment (HIRE)[387]	US	0.47 (0.35, 0.65)
FDA's Sentinel Distributed Database[376]	US	0.51 (0.33 to 0.79)
US Center for Medicare and Medicaid Services (CMS) data[395]	US	0.54 (0.35 to 0.82)
Analysis Without Propensity-Matched Controls		
Danish National Patient Registry[352]	Europe	0.37 (0.27 to 0.52)
Norwegian Patient Registry[273]	Europe	0.46 (0.30 to 0.70)
Vaughan Sarrazin 2014[357]	US	0.86 (0.21 to 3.53)
Larsen, 2014[298]	Europe	110mg dose 0.31 (0.17 to 0.55) 150mg dose 0.32 (0.16 to 0.63)
Hernandez, 2017[384]	US	0.46 (0.23, 0.95)
German Applied Health Research Database[398]	Europe	0.41 (0.24 to 0.69)

Abbreviation: CI=confidence interval

Figure 14. Forest plot for intracranial bleeding—dabigatran 150mg or 110mg (treatment) versus warfarin (control) (observational)



Abbreviation: CI=confidence interval

Gastrointestinal Bleeding

Gastrointestinal (GI) bleeding was assessed in 18 observational studies. These findings are summarized in Table 50 and the 13 studies which used propensity matching are synthesized quantitatively in Figure 15. These studies demonstrate a trend towards an increase in GI bleeding with warfarn as compared to dabiagatan (HR 1.08, 95% CI 1.00 to 1.17, I^2 = 45.5%, Q = 22, p=0.037) (low SOE).

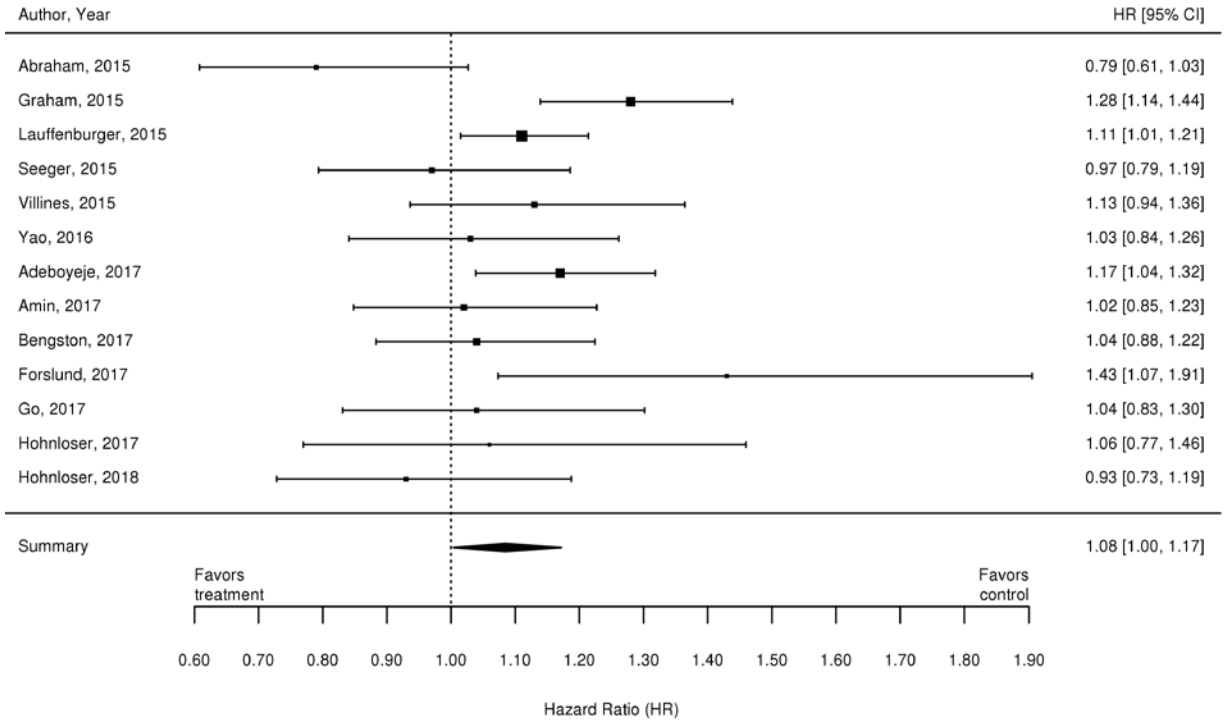
Table 50. Observational studies, GI bleeding—dabigatran 150mg or 110mg versus warfarin

Database	Location	Risk Estimate (95% CI) Dabigatran vs. Warfarin
Analysis With Propensity-Matched Controls		
Truven Health MarketScan1 Commercial Claims and Encounters Database and the Medicare Supplemental and Coordination of Benefits Database[218]	US	1.04 (0.88 to 1.22)
MarketScan, Truven and Clinformatics, Optum[346]	US	0.97 (0.79 to 1.18)
OptumLabs Data Warehouse (OLDW)[370]	US	1.03 (0.84 to 1.26) p=0.78
Department of Defense (DoD) database[362]	US	1.13 (0.94 to 1.37)
Optum Labs Data Warehouse[207]	US	0.79 (0.61 to 1.03)
Truven Health MarketScan Commercial Claims and Encounters and Medicare supplement databases[300]	US	1.11 (1.02 to 1.22)
Medicare database[268]	US	1.28 (1.14 to 1.44)
Health data register of the Stockholm Region (Va˚rdanalysdatabasen, VAL)[258]	Europe	1.43 (1.07 to 1.90)
CARBOS study based on data from the Health Risk Institute (HRI)[287]	Europe	1.06 (0.77 to 1.46)
HealthCore Integrated Research Environment (HIRE)[387]	US	1.17 (1.04, 1.32)
FDA's Sentinel Distributed Database[376]	US	1.04 (0.83 to 1.30)
US Center for Medicare and Medicaid Services (CMS) data[395]	US	1.02 (0.85 to 1.23)
German Applied Health Research Database[398]	Europe	0.93 (0.73 to 1.19)

Database	Location	Risk Estimate (95% CI) Dabigatran vs. Warfarin
Analysis Without Propensity-Matched Controls		
Norwegian Patient Registry[273]	Europe	1.26 (1.01 to 1.57)
Vaughan Sarrazin 2014[357]	US	1.54 (1.20 to 1.97)
Danish National Patient Registry[351]	Europe	110mg dose 0.90 (0.32 to 2.52) 150mg dose 1.43 (0.58 to 3.52)
Larsen, 2014[298]	Europe	110mg dose 0.91 (0.73 to 1.14) 150mg dose 1.37 (0.81 to 2.31)
Hernandez, 2017[384]	US	0.95 (0.75, 1.19)

Abbreviation: CI=confidence interval

Figure 15. Forest plot for gastrointestinal bleeding—dabigatran 150mg or 110mg (treatment) versus warfarin (control) (observational)



Abbreviation: CI=confidence interval

Other Clinical Outcomes

All-Cause Mortality

In the RCT,[23] all-cause mortality did not differ between warfarin and either dose of dabigatran (3.75% per year for dabigatran 110mg vs. 4.13% per year for warfarin; RR 0.91; 95% CI 0.80 to 1.03; p=0.13; 3.64% per year for dabigatran 150mg vs. 4.13% per year for warfarin; RR 0.88; 95% CI 0.77 to 1.00; p=0.051) although for this latter dose was just under the threshold for statistical significance. Within the RELY-ABLE study[234] rates of death were 3.02 percent and 3.10 percent per year (HR 0.97; 95% CI 0.80 to 1.19).

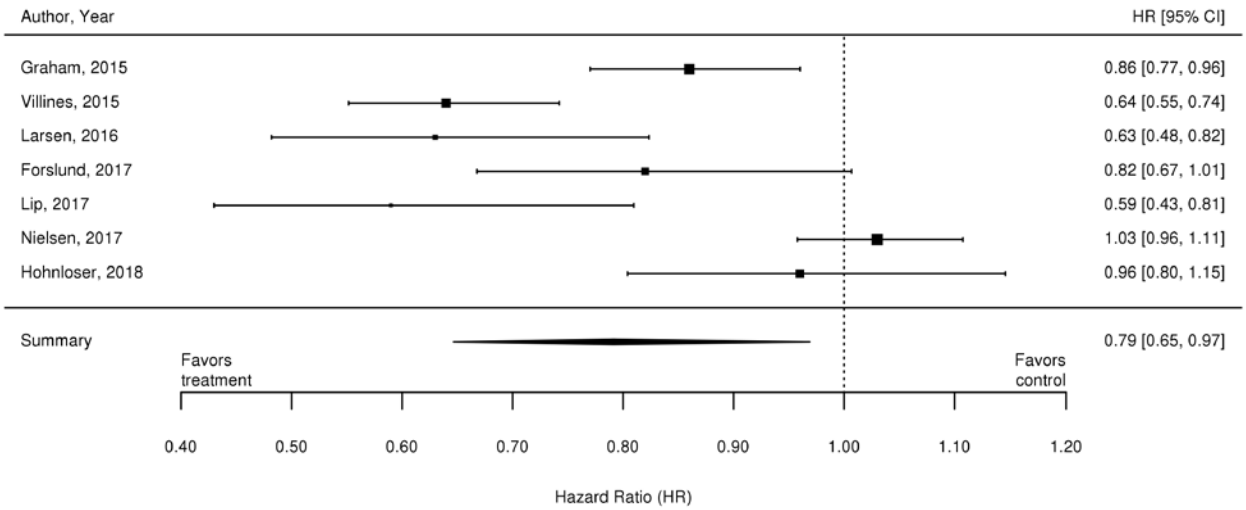
All-cause mortality was also evaluated in 8 observational studies. Table 51 summarizes these findings and Figure 16 synthesizes these studies quantitatively. Differing from the RCT evidence, the observational studies did demonstrate a benefit in all-cause mortality for patients on dabigatran compared with warfarin (HR 0.79, 95% CI 0.65 to 0.97, I^2 = 87.8%, Q = 49.1, p<0.001). This resulted in an overall low SOE for no evidence of a difference between either dose of dabigatran and warfarin.

Table 51. Observational studies: all-cause mortality—dabigatran 150mg and 110mg versus warfarin

Database	Location	Risk Estimate (95% CI) Dabigatran vs. Warfarin
Analysis With Propensity-Matched Controls		
Danish national prescription registry, Danish civil registration system, Danish national patient register[329]	Europe	1.03 (0.96 to 1.11) Age ≥80 and/or renal disease: 0.93 (0.84 to 1.02) Age ≥80: 1.00 (0.91 to 1.10)
Health data register of the Stockholm Region (Va˚rdanalysdatabasen, VAL)[258]	Europe	0.82 (0.67 to 1.01)
Danish national prescription registry, Danish civil registration system, Danish national patient register[299]	Europe	0.63 (0.48 to 0.82) Age <65: 0.58 (0.43 to 0.78) Age ≥ 65: 0.62 (0.46 to 0.84)
Observational cohort study of Danish citizens[311]	Europe	0.59 (0.43 to 0.81)
Department of Defense (DoD) database[362]	US	0.64 (0.55 to 0.74)
Medicare database[268]	US	0.86 (0.77 to 0.96) p=0.006
German Applied Health Research Database[398]	Europe	0.96 (0.80 to 1.14)
Analysis Without Propensity-Matched Controls		
Vaughan Sarrazin 2014[357]	US	0.76 (0.49 to 1.17)

Abbreviation: CI=confidence interval

Figure 16. Forest plot for all-cause mortality—dabigatran 150mg and 110mg (treatment) versus warfarin (control) (observational)



Abbreviations: CI=confidence interval

Death From Vascular Causes

In the RCT,[23] death from vascular causes was lower with the higher dose of dabigatran (moderate SOE) but there was no evidence of a difference at the lower dose (moderate SOE)

(2.43% per year for dabigatran 110mg vs. 2.69% per year for warfarin; RR 0.90; 95% CI 0.77 to 1.06; p=0.21; 2.28% per year for dabigatran 150mg vs. 2.69% per year for warfarin; RR 0.85; 95% CI 0.72 to 0.99; p=0.04).

Myocardial Infarction

In the RCT,[23] the rates of MI were higher with both dabigatran doses as compared with warfarin, although these results did not reach statistical significance with the lower dose (0.72% per year for dabigatran 110mg vs. 0.53% per year for warfarin; RR 1.35; 95% CI 0.98 to 1.87; p=0.07; 0.74% per year for dabigatran 150mg vs. 0.53% per year for warfarin; RR 1.38; 95% CI 1.00 to 1.91; p=0.048).

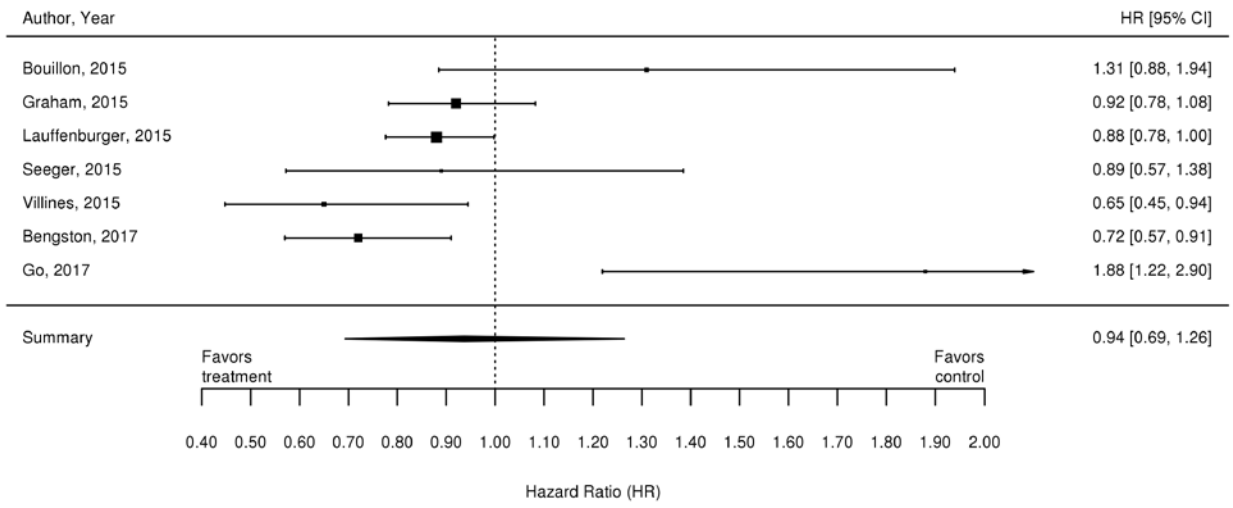
Myocardial infarction was also evaluated in 10 observational studies (Table 52). Eight studies which used propensity matching were synthesized quantitatively and did not demonstrate a difference in myocardial infarction between patients on dabigatran and those on warfarin (Figure 17) (HR 0.94, 95% CI 0.69 to 1.26, I^2 = 71.7%, Q = 21.2, p=0.002). Combined this resulted in low SOE of no evidence of a difference in risk of MI.

Table 52. Observational studies: myocardial infarction—dabigatran 150mg or 110mg versus warfarin

Database	Location	Risk Estimate (95% CI) Dabigatran vs. Warfarin
Analysis with Propensity-Matched Controls		
Truven Health MarketScan1 Commercial Claims and Encounters Database and the Medicare Supplemental and Coordination of Benefits Database[218]	US	0.72 (0.57, 0.91)
Maintenance et Exploitation des Données pour l'Étude de la Clientèle Hospitalière—Med-Echo and the provincial physician and prescription claims database (la Régie de l'assurance maladie du Quebec)[214]	Canada	Men dabigatran 110mg: 1.17 (0.89 to 1.53) Men dabigatran 150mg: 1.27 (0.94 to 1.71) Women dabigatran 110mg: 1.05 (0.80 to 1.38) Women dabigatran 150mg: 0.77 (0.47 to 1.25)
MarketScan, Truven and Clinformatics, Optum[346]	US	0.89 (0.57 to 1.38)
Department of Defense (DoD) database[362]	US	0.65 (0.45 to 0.95)
Truven Health MarketScan Commercial Claims and Encounters and Medicare supplement databases[300]	US	0.88 (0.77 to 0.99)
Medicare database[268]	US	0.92 (0.78 to 1.08)
French national health-insurance database (Système National d'Information Inter-Régimes de l'Assurance Maladie [SNIIRAM][112]	Europe	1.31 (0.88 to 1.93) p=0.19
FDA's Sentinel Distributed Database[376]	US	1.88 (1.22 to 2.90)
Analysis Without Propensity-Matched Controls		
VigiBase[324]	Europe	Reporting Odds Ratio 3.39 (2.01 to 5.7)
Danish nationwide database[408]	Europe	VKA experienced, dabigatran 110mg: 1.45 (0.98 to 2.15) VKA experienced, dabigatran 150mg: 1.30 (0.84 to 2.01) VKA naive, dabigatran 110mg: 0.71 (0.47 to 1.07) VKA naive, dabigatran 150mg: 0.93 (0.62 to 1.41)

Abbreviations: CI=confidence interval; VKA=vitamin K antagonist

Figure 17. Forest plot for myocardial infarction—dabigatran 150mg or 110mg (treatment) versus warfarin (control) (observational)



Abbreviation: CI=confidence interval

Hospitalization/Health Care Utilization

In the RCT,[23] hospitalization rates were lower with dabigatran 110mg (high SOE), and there was no evidence of a difference between the higher dose and warfarin (19.4% per year for dabigatran 110mg vs. 20.8% per year for warfarin; RR 0.92; 95% CI 0.87 to 0.97; p=0.003; 20.2% per year for dabigatran 150mg vs. 20.8% per year for warfarin; RR 0.97; 95% CI 0.92 to 1.03; p=0.34) (moderate SOE).

One observational study assessed length of stay during initial admission for AF.[255] This study, using propensity matching, found that those initiated on dabigatran had a shorter mean length of stay with 4.8 days compared to those treated with warfarin who had a mean LOS of 5.5 days; p<0.001.[255] Inpatient costs for this initial hospital admission were lower for those initiated on dabigatran $14,794 vs. $16,826, P=0.007.[255] A subset of these patients were analyzed for 30-days hospital readmission rate. Among this subset, the adjusted OR (95% CI) for 30 day hospital readmission was similar between groups. Compared to warfarin, those on dabigatran had an OR ((%% CI) of 30-day hospital readmission of 0.987 (0.65-1.49), P=0.951. Hospital costs for those re-admitted within 30 days did not differ significantly: costs for 30-days hospital readmission for those on dabigatran vs. warfarin were $10,403 vs. $11,911, with difference of $1,507, P=0.375.[255]

Another observational study utilizing the HealthCore Integrated Research Database (HIRD) compared measures related to healthcare utilization for patients with NVAF on dabigatran and warfarin.[373] In this database, the number of inpatient hospitalizations and visits to the emergency department were not statistically different between these 2 groups. However, the per-patient-per-month all-cause physician office visits and outpatient visits were significantly lower for those on dabigatran compared to warfarin; (for physician visits: dabigatran: mean 1.29 [SD±0.95] vs. warfarin: 2.02 [SD±1.53], P<0.001); for outpatient visits: dabigatran: (mean 2.17 [SD±2.90] vs. warfarin: 3.52 [SD±3.32], P<0.001. Both overall and AF-related pharmacy costs were significantly higher in the dabigatran group compared to warfarin (p<0.001 for both); however, overall medical costs were not statistically significantly different between treatment groups.

An observational propensity-matched study using MarketScan compared all cause healthcare utilization and readmission during a 12 month followup period between dabigatran and warfarin users.[177] Compared to warfarin users, dabigatran users had significantly ($p<0.001$ for all values) fewer hospitalizations (0.04 vs. 0.05), fewer outpatient visits (3.98 vs. 5.87) and fewer ER visits (0.12 vs. 0.16). Among those hospitalized, mean hospital length of stay was lower for dabigatran users (3.86 days vs. 4.43 days, $p<0.001$), lower rate of 30 day-readmission (14.5% vs. 17.4%, $p<0.001$) and a higher likelihood of being discharge home (86% vs. 84.1%, $p<0.001$). Among those hospitalized specifically for stroke, the average length of stay was lower for patients treated with dabigatran versus warfarin (4.7 days vs. 5.7 days, $p<0.001$). Among those hospitalized specifically for a bleeding event, the average length of stay was significantly lower for patients treated with dabigatran (4.3 days vs. 4.6 days, $p<0.001$).

A retrospective matched study to examine health care utilization over a 12 month period was conducted using the Humana Incorporated administrative claims database between dabigatran and warfarin users.[393] Dabigatran users had significantly less mean per patient per year hospitalization (0.92 vs. 1.13, $p=0.0124$), ER visits (1.32 vs. 1.56, $p=0.0011$) and physician office visits (21.43 vs. 29.41, $p<0.0001$).

Medication Adherence

A retrospective propensity-matched cohort analysis of U.S. MarketScan claims[228] examined medication persistence and discontinuation rates. Medication persistence was defined as absence of refill gap > 60 days and discontinuation was defined as no additional refill for >90 days and through to end of followup. Dabigatran demonstrated significantly higher levels of persistence compared with warfarin (HR 1.05, 95% CI 1.01 to 1.10). Another retrospective propensity-matched study using MarketScan[177] examined medication persistence. Persistence was defined as a gap in drug supply of no more than 30 days. Over the 12-month followup period, medication persistence was greater for the dabigatran cohort (37.9% vs. 33.7%, $p < 0.0001$) compared to the warfarin cohort. However, the mean number of days to nonpersistence were similar across the two treatment cohorts (145.8 vs. 146.6 days, $p = 0.494$).

A German retrospective analysis[220] examined medication persistence. At 180 days, dabigatran demonstrated a higher persistence compared with VKAs (60.3 vs. 58.1%; $p=0.235$), but not statistically significant. At 360 days, dabigatran demonstrated a statistically significant higher persistence compared to VKAs (47.3 vs. 25.5%; $p<0.001$).

A French cohort study using the IMS Longitudinal Patient Database compared medication non-persistence, defined as treatment discontinuation (no prescription for > 60 days) or switch, between dabigatran and warfarin initiators.[397] Nonpersistence was higher with dabigatran compared to warfarin (HR 1.42, 95% CI 1.20-1.69).

Finally, an administrative database study performed with Sweden with high risk of bias demonstrated warfarin having higher treatment persistence at 12 months compared to dabigatran (odds ratio = 1.81, 95% CI 1.57 to 2.10).[257]

Adverse Events

In the RCT,[23] dyspepsia was more common with dabigatran (11.8% patients with 110mg, 11.3% patients with 150mg compared with 5.8% with warfarin; $p <0.001$ for both) (moderate SOE with both doses). No evidence of differences in liver function or other adverse events were seen between the groups.

Quality of Life Outcomes

A substudy of the RE-LY trial[325] derived health-related quality-of-life estimates for AF patients receiving warfarin or dabigatran etexilate (dabigatran) during one year of stable treatment, i.e. in the absence of outcome events, such as strokes or major bleedings. Utilities ranged from 0.805 (dabigatran 150mg bid) to 0.811 (dabigatran 110mg bid) at baseline, and did not change over the one year observation period. No evidence of differences between the dabigatran groups and warfarin were statistically significant except for the dabigatran 150mg bid group at 3 months. Similarly, none of the within-group or between-group differences in VAS scores were statistically significant.3

Strength of Evidence

Table 53 summarizes the SOE for outcomes of interest for these comparisons. Note that we weighted the evidence from RCTs more importantly than the observational studies if their findings differed.

Table 53. Strength of evidence—thrombin inhibitor (dabigatran) versus warfarin

Outcome	Number of Studies (Subjects)	Risk of Bias	Consistency	Directness	Precision	Reporting Bias	SOE and Effect (95% CI)
Stroke or systemic embolism	1 RCT[23] (12,098) 10 Obs[112,299,300,311,329,346,352,370,395,398] (662,920)	Low	Consistent	Direct	Precise	None	**SOE=High** Dabigatran reduced risk (RR 0.66; 95% CI 0.53 to 0.82)
Ischemic or uncertain stroke	1 RCT[23] (12,098) 15 Obs[177,214,218,258,268,297,299,300,329,346,352,362,370,376,398] (963,214)	Low	Consistent	Dir3ect	Imprecise	None	**SOE=Moderate** Dabigatran reduced risk (RR 0.76; 95% CI 0.60 to 0.98)
Hemorrhagic stroke	1 RCT[23] (12,098) 8 Obs[258,268,300,346,362,370,395,398] (653,067)	Low	Consistent	Direct	Precise	None	**SOE=High** Dabigatran reduced risk (RR 0.26; 95% CI 0.14 to 0.49)
Major bleeding	1 RCT[23] (12,098) 20 Obs[112,214,268,273,287,298,300,309-311,346,347,362,370,376,392,395,398,402] (692,782)	Low	Consistent	Direct	Precise	None	**SOE=High** No evidence of a difference (RR 0.93; 95% CI 0.81 to 1.07)
Minor bleeding	1 RCT[23] (12,098)	Low	NA	Direct	Imprecise	None	**SOE=Moderate** Dabigatran reduced risk (RR 0.91; 95% CI 0.85 to 0.97)

Outcome	Number of Studies (Subjects)	Risk of Bias	Consistency	Directness	Precision	Reporting Bias	SOE and Effect (95% CI)
Intracranial bleeding	1 RCT[23] (12,098) 16 Obs[218,258,268,273,298,346,352,357,362,370,376,384,387,392,395,398] (1,037,632)	Low	Consistent	Direct	Precise	None	**SOE=High** Dabigatran reduced risk (RR 0.40; 95% CI 0.27 to 0.60)
GI Bleeding	18 Obs[207,218,258,268,273,287,298,300,346,351,357,362,370,376,384,387,395,398] (1,222,594)	Medium	Consistent	Direct	Imprecise	None	**SOE=Low** Increase in GI bleeding with warfarin as compared to dabigatran (HR 1.08, 95% CI 1.00 to 1.17)
All-cause mortality	1 RCT[23] (12,098) 8 Obs[258,268,299,311,329,357,362,398] (460,089)	Low	Inconsistent	Direct	Imprecise	None	**SOE=Low** No evidence of a difference (RR 0.88; 95% CI 0.77 to 1.00)
Death from vascular causes	1 RCT[23] (12,098)	Low	NA	Direct	Imprecise	None	**SOE=Moderate** Dabigatran reduced risk (RR 0.85; 95% CI 0.72 to 0.99)
Myocardial infarction	1 RCT[23] (12,098) 10 Obs[112,214,218,268,300,324,346,362,376,408] (689,413)	Low	Inconsistent	Direct	Imprecise	None	**SOE=Low** No evidence of a difference
Hospitalization	1 RCT[23] (12,098) 4 Obs[177,255,373,393] (74,029)	Low	Inconsistent	Direct	Precise	None	**SOE=Moderate** No evidence of a difference (RR 0.97; 95% CI 0.92 to 1.03)
Medication adherence	5 Obs[177,220,228,257,397] (126,955)	Low	Inconsistent	Direct	Imprecise	None	**SOE=Insufficient**
Adverse events	1 RCT[23] (12,098)	Low	NA	Direct	Imprecise	None	**SOE=Moderate** Dyspepsia more common with dabigatran (11.3% of patients with dabigatran 150mg vs. 5.8% with warfarin, p<0.001). No evidence of differences in liver function or other adverse events between therapies.

Outcome	Number of Studies (Subjects)	Risk of Bias	Consistency	Directness	Precision	Reporting Bias	SOE and Effect (95% CI)
Stroke or systemic embolism	1 RCT[23] (12,098) 10 Obs[112,299,300,311,329,346,352,370,395,398] (662,920)	Low	Inconsistent	Direct	Precise	None	**SOE=Moderate** No evidence of a difference (RR 0.91; 95% CI 0.74 to 1.11)
Ischemic or uncertain stroke	1 RCT[23] (12,098) 15 Obs[177,214,218,258,268,297,299,300,329,346,352,362,370,376,398] (963,214)	Low	Consistent	Direct	Precise (RCT), Imprecise (Obs)	None	**SOE=High** No evidence of a difference (RR 1.11; 95% CI 0.89 to 1.40)
Hemorrhagic stroke	1 RCT[23] (12,098) 8 Obs[258,268,300,346,362,370,395,398] (653,067)	Low	Consistent	Direct	Precise	None	**SOE=High** Dabigatran reduced risk (RR 0.31; 95% CI 0.17 to 0.56)
Major bleeding	1 RCT[23] (12,098) 20 Obs[112,214,268,273,287,298,300,309-311,346,347,362,370,376,392,395,398,402] (692,782)	Low	Consistent	Direct	Precise	None	**SOE=High** Dabigatran reduced risk (RR 0.80; 95% CI 0.69 to 0.93)
Minor bleeding	1 RCT[23] (12,098)	Low	NA	Direct	Precise	None	**SOE=Moderate** Dabigatran reduced risk (RR 0.79; 95% CI 0.74 to 0.84)
Intracranial bleeding	1 RCT[23] (12,098) 16 Obs[218,258,268,273,298,346,352,357,362,370,376,384,387,392,395,398] (1,037,632)	Low	Consistent	Direct	Precise	None	**SOE=High** Dabigatran reduced risk (RR 0.31; 95% CI 0.20 to 0.47)
GI Bleeding	18 Obs[207,218,258,268,273,287,298,300,346,351,357,362,370,376,384,387,395,398] (1,222,594)	Medium	Consistent	Direct	Imprecise	None	**SOE=Low** Increase in GI bleeding with warfarin as compared to dabigatran (HR 1.08, 95% CI 1.00 to 1.17)

Outcome	Number of Studies (Subjects)	Risk of Bias	Consistency	Directness	Precision	Reporting Bias	SOE and Effect (95% CI)
All-cause mortality	1 RCT[23] (12,098) 8 Obs[258,268,299,311,329,357,362,398] (460,089)	Low	Inconsistent	Direct	Imprecise	None	**SOE=Low** No evidence of a difference (RR 0.91; 95% CI 0.80 to 1.03)
Death from vascular causes	1 RCT[23] (12,098)	Low	NA	Direct	Imprecise	None	**SOE=Moderate** No evidence of a difference (RR 0.90; 95% CI 0.77 to 1.06)
Myocardial infarction	1 RCT[23] (12,098) 10 Obs[112,214,218,268,300,324,346,362,376,408] (689,413)	Low	Inconsistent	Direct	Imprecise	None	**SOE=Low** No evidence of a difference in risk. SOE was reduced given conflicting evidence between RCT and observational studies
Hospitalization	1 RCT[23] (12,098) 4 Obs[177,255,373,393] (74,029)	Low	Consistent	Direct	Precise	None	**SOE=High** Dabigatran reduced risk (RR 0.92; 95% CI 0.87 to 0.97)
Medication adherence	5 obs[177,220,228,257,397] (126,955)	Low	Inconsistent	Direct	Imprecise	None	**SOE=Insufficient**
Adverse events	1 RCT[23] (12,098)	Low	NA	Direct	Imprecise	None	**SOE=Moderate** Dyspepsia more common with dabigatran (11.8% of patients with dabigatran 110mg vs. 5.8% with warfarin, p<0.001). No evidence of differences in liver function or other adverse events between therapies.

Abbreviations: CI=confidence interval; NA=not applicable; Obs=observational; RCT=randomized controlled trial; RR=relative risk; SOE=strength of evidence

10. Thrombin Inhibitor (Dabigatran) ± Aspirin Versus Warfarin

One good-quality RCT (PETRO) involving 502 patients evaluated different doses of the thrombin inhibitor dabigatran with and without concomitant aspirin at different doses and compared with warfarin alone.[250]

Thromboembolic Outcomes

Thromboembolic events were limited to the 50mg dabigatran dose groups (there were 2 patients with systemic thromboembolic events, both of whom received 50mg dabigatran twice daily [1.96%]).

Bleeding Outcomes

Major Bleeding

Sixty four patients received 300mg dabigatran twice daily and aspirin, while 105 patients received the same dose of dabigatran without aspirin. Major hemorrhages were limited to the group treated with 300mg dabigatran twice daily and aspirin (4 of 64 such patients), and the rate was statistically different compared with the group treated with dabigatran 300mg twice daily without aspirin (0 of 105 such patients; $p<0.02$). There was also a significant difference in major and clinically relevant bleeding episodes (11 of 64 vs. 6 of 105; $p=0.03$) and total bleeding episodes (25 of 64 vs. 14 of 105; $p=0.0003$) between 300mg dabigatran twice daily+aspirin and 300mg dabigatran twice daily without aspirin.

The frequency of bleeding in the group treated with 50mg dabigatran twice daily was significantly lower than that in the warfarin group (7 of 107 vs. 12 of 70; $p=0.044$). When the doses of dabigatran were compared with each other, irrespective of aspirin assignment, there were differences in total bleeding episodes in the 300mg twice daily and 150mg twice daily groups versus the 50mg twice daily group (37 of 169 and 30 of 169 vs. 7 of 107; $p=0.0002$ and $p=0.01$, respectively).

Total bleeding events were more frequent in the 300mg (23%) and 150mg (18%) dabigatran groups compared with the 50mg groups (7%).

Other Clinical Outcomes

Myocardial Infarction

Seven patients reported angina. Two of these patients were classified as having acute coronary syndrome. One patients was treated with 50mg dabigatran twice daily+81mg aspirin and the other treated with 300mg dabigatran twice daily+81mg aspirin.

Adverse Events

Adverse events were more frequent in the dabigatran groups than in warfarin-treated patients. The most commonly reported adverse events were gastrointestinal disorders such as diarrhea, nausea, or vomiting (26%), followed by general system disorders such as fatigue or edema (12%), dizziness and headache (12%), and infections. Most of these were mild and required no change in treatment. No adverse events were found in the warfarin group.

11. Factor Xa Inhibitors (Apixaban, Rivaroxaban, or Edoxaban) Versus Warfarin

Four RCTs compared various factor Xa inhibitors with warfarin. These included:

- A good-quality RCT (ARISTOTLE) involving 18,201 patients comparing apixaban with warfarin[25]
- A good-quality RCT involving 1,146 patients comparing edoxaban with warfarin[366]

- A good-quality RCT including 21,105 patients (ENGAGE AF) comparing two different dosage levels of edoxaban to warfarin[26]
- A good-quality RCT (ROCKET-AF) involving 14,264 patients comparing rivaroxaban (20mg once daily) with warfarin[24]

Although each of these RCTs compared an Xa inhibitor with warfarin, they differed in significant ways. The ROCKET AF, ENGAGE AF, and ARISTOTLE studies were Phase III trials of DOACs. The study by Wietz and colleagues,[366] however, was a Phase II trial. Another difference between these larger trials, preventing direct comparisons of results, is the time in therapeutic range (TTR) for the participants in the warfarin arms of the study. TTRs for those on warfarin were, in general, greater for participants in the ARISTOTLE trial. TTRs for participants in the ROCKET trial were reported as lower than other trials; however, compared to "real-world" settings, TTRs for those on warfarin in the ROCKET trial were comparable and therefore relevant to clinical practice. These trials also differed related to the included populations baseline risk of stroke. Of note, the mean $CHADS_2$ score in ROCKET AF was 3.48, reflecting a high stroke risk, whereas it was 2.1 in ARISTOTLE and 2.8 in ENGAGE. In ROCKET AF, 87% of patients had $CHADS_2$ score of $\geq$3, compared to 30% in ARISTOTLE and 53% in ENGAGE AF. Thus, ROCKET AF reflects a much higher risk population than ARISTOTLE and ENGAGE, which would be expected to have higher rates of both bleeding and strokes. Finally, these trials also differed in terms of the underlying comorbidities in the populations. The ROCKET-AF trial had more patients with comorbidities, thus reflecting a more complex population. The ROCKET-AF trial included a substantially higher number of patients with prior stroke/TIA (55%) compared with ARISTOTLE (20%) and ENGAGE (29%). Moreover, the ROCKET-AF trial included a higher proportion of patients with comorbidities such as diabetes (ROCKET 40%; ARISTOTLE 25%, ENGAGE 36%) and congestive heart failure (ROCKET 63%; ARISTOTLE 35%, ENGAGE 58%).

We consider only the evidence from the ROCKET-AF, ENGAGE-AF, and ARISTOTLE trials similar enough to warrant meta analysis (Table 54) although given the differences between the trial populations and their lack of direct comparisons evaluate their SOE separately by individual drug.

In addition to the RCT evidence, 38 observational studies evaluated Xa inhibitors compared with warfarin.[112,207,218,220,228-230,257,258,267,273,287,292,293,295,299,304,305,309-311,324,327,329,352,365,370,379,380,384,392,395-398,400,402,409]

Table 54. Outcomes of interest within randomized controlled trials evaluating factor Xa inhibitors: apixaban, rivaroxaban, or edoxaban versus warfarin

Outcome or Subgroup of Interest	ARISTOTLE (Apixaban vs. Warfarin) (N=18,201)	ROCKET AF (Rivaroxaban vs. Warfarin) (N=14,264)	ENGAGE AF (High-Dose Edoxaban vs. Warfarin) (N=14,071)	ENGAGE AF (Low-Dose Edoxaban vs. Warfarin) (N=14,070)
Stroke or Systemic Embolism	In the ITT population: 1.27% of patients per year with apixaban, 1.60% of patients per year in the warfarin group (HR 0.79; 95% CI 0.66 to 0.95, p=0.01) NNT = 167/2 years	In the ITT population: 2.1% of patients per year in the rivaroxaban group and 2.4% of patients per year with warfarin (HR 0.88; 95% CI 0.7 to 1.03; p<0.001 for noninferiority; p=0.12 for superiority) In the per-protocol population,: 1.7% per year in the rivaroxaban group and 2.2% with warfarin (noninferiority HR 0.79; 95% CI 0.66 to 0.96; p<0.001; superiority HR 0.79; 95% CI 0.65 to 0.95; p=0.01)	In the ITT analysis in the overall study period, event rates were higher in all groups and there were no statistically significant differences (1.80% per year for warfarin, 1.57%/year for high dose edoxaban [HR 0.87; 97.5% CI 0.73-1.04 as compared to warfarin]) In the modified ITT: 1.5% of patients per year with warfarin, 1.18% of patients per year in the high-dose edoxaban group (HR 0.79; 97.5% CI 0.63-0.99, p < 0.001 for noninferiority and p=0.02 for superiority)	In the ITT analysis in the overall study period, event rates were higher in all groups and there were no statistically significant differences (2.04%/year for low dose edoxaban [HR 1.13; 97.5% CI 0.96 to 1.34 as compared to warfarin]) In the modified ITT: 1.61% of patients per year in the low-dose edoxaban group (HR1.07; 97.5% CI 0.87 to 1.31, p=0.005 for noninferiority and p=0.44 for superiority).
Ischemic or Uncertain Stroke	0.97% per year for apixaban and 1.05% per year for warfarin HR 0.92; 95% CI 0.74 to 1.13; p=0.42	1.34 per 100 patient-years for rivaroxaban and 1.42% per year for warfarin HR 0.94; 95% CI 0.75 to 1.17; p=0.58	1.25% per year for warfarin and 1.25% per year for edoxaban, HR1.00; 95% CI 0.83 to 1.19	1.77% per year for edoxaban and 1.25% per year for warfarin, HR 1.41; 95% CI 1.19 to 1.67
Hemorrhagic Stroke	0.24% per year for apixaban and 0.47% per year for warfarin HR 0.51; 95% CI 0.35 to 0.75; p<0.001	0.26% per year for rivaroxaban and 0.44% per year for warfarin HR 0.59; 95% CI 0.37 to 0.93; p=0.024	0.26% of patients per year, HR 0.54; 95% CI 0.38 to 0.77 0.47% patients per year for warfarin	0.16% of patients per year, HR 0.33; 95% CI 0.22 to 0.50 0.47% patients per year for warfarin
Any Stroke or TIA	NA	NA	**Any Stroke:** 1.49% of patients per year, HR 0.88; 95% CI 0.75 to 1.03 1.69% patients per year for warfarin	**Any Stroke:** 1.91% of patients per year, HR 1.13; 95% CI 0.97 to 1.31 1.69% patients per year for warfarin

Outcome or Subgroup of Interest	ARISTOTLE (Apixaban vs. Warfarin) (N=18,201)	ROCKET AF (Rivaroxaban vs. Warfarin) (N=14,264)	ENGAGE AF (High-Dose Edoxaban vs. Warfarin) (N=14,071)	ENGAGE AF (Low-Dose Edoxaban vs. Warfarin) (N=14,070)
Systemic Embolism	0.09% per year for apixaban and 0.10% per year for warfarin HR 0.87; 95% CI 0.44 to 1.75; p=0.70	0.04% per year for rivaroxaban and 0.19% per patient per year for warfarin HR 0.23; 95% CI 0.09 to 0.61; p=0.003	0.08% of patients per year, HR 0.65; 95% CI 0.34-1.20 0.12% of patients per year for warfarin Subanalysis: Geller, 2015[263]: there was no difference in nonfatal systemic embolic or fatal events between high dose edoxaban compared with warfarin.	0.15% of patients per year, HR 1.24; 95% CI 0.72 to 2.15 0.12% of patients per year for warfarin Subanalysis: Geller, 2015[263]: there was no difference in nonfatal systemic embolic or fatal events between low dose edoxaban compared with warfarin.
Major Bleeding	2.13% per year for apixaban and 3.09% per year for warfarin HR 0.69; 95% CI 0.60 to 0.80; p<0.001	3.6% per year for rivaroxaban and 3.4% per year for warfarin HR 1.04; 95% CI 0.90 to 1.20; p=0.58	2.75% of patients per year, HR 0.80; 95% CI 0.71-0.91 3.43% patients per year for warfarin	1.61% of patients per year, HR 0.47; 95% CI 0.41-0.55 3.43% patients per year for warfarin
Major, NMCR and Minor Bleeding	**Major or NMCR bleeding:** 4.07% per year in the apixaban group and 6.01% per year in the warfarin group HR 0.68; 95% CI 0.61 to 0.75 **Non-major bleeding:** 6.4% per year for apixaban, 9.4% per year for warfarin HR 0.69; 95% CI 0.63 to 0.75	**Major or NMCR bleeding:** 14.9% per year in the rivaroxaban group and 14.5% per year for warfarin HR 1.03; 95% CI 0.96 to 1.11 **NMCR bleeding:** 11.8% per year in the rivaroxaban group and 11.4% per year for warfarin HR 1.04; 95% CI 0.96 to 1.13	**Major or NMCR bleeding**: 11.1% of patients per year, HR 0.86; 95% CI 0.80 to 0.92 13.02% patients per year for warfarin **Minor Bleeding:**4.12% of patients per year, HR 0.84; 95% CI 0.76 to 0.94 4.89% patients per year for warfarin	**Major or NMCR bleeding**: 7.97% of patients per year, HR 0.62; 95% CI 0.57 to 0.67 13.02% patients per year for warfarin **Minor Bleeding:**3.52% of patients per year, HR 0.72; 95% CI 0.65 to 0.81 4.89% patients per year for warfarin
Gastrointestinal Bleeding	NA	3.61% per year for rivaroxaban and 2.6% per year for warfarin; HR 1.42; 95% CI 1.22 to 1.66	NA	NA
Intracranial Bleeding	Lower intracranial bleeding in patients treated with apixaban compared to warfarin HR 0.42; 95% CI 0.30 to 0.58; p<0.001	Overall event rate of 0.67% per year Lower intracranial bleeding in patients treated with rivaroxaban compared to warfarin HR 0.67; 95% CI 0.47 to 0.93; p=0.023	0.39% of patients per year, HR 0.47; 95% CI 0.34 to 0.63 0.85% patients per year for warfarin	0.26% of patients per year, HR 0.30; 95% CI 0.21 to 0.43 0.85% patients per year for warfarin

Outcome or Subgroup of Interest	ARISTOTLE (Apixaban vs. Warfarin) (N=18,201)	ROCKET AF (Rivaroxaban vs. Warfarin) (N=14,264)	ENGAGE AF (High-Dose Edoxaban vs. Warfarin) (N=14,071)	ENGAGE AF (Low-Dose Edoxaban vs. Warfarin) (N=14,070)
All-Cause Mortality	3.52% per year for apixaban and 3.94% per year in the warfarin group HR 0.89; 95% CI 0.80 to 0.998; p=0.047	In the ITT analysis: 4.5% per year in the rivaroxaban group and 4.9% per year for warfarin HR 0.92; 95% CI 0.82 to 1.03; p=0.15 In treatment per protocol analysis: 1.9% per year for rivaroxaban and 2.2% per year for warfarin HR 0.85; 95% CI 0.70 to 1.02; p=0.07	3.99% of patients per year, HR 0.92; 95% CI 0.83 to 1.01 4.35% patients per year for warfarin	3.80% of patients per year, HR 0.87; 95% CI 0.79 to 0.96 4.35% patients per year for warfarin
Death from Cardiovascular Causes	1.8% per year for apixaban and 2.02% per year for the warfarin group HR 0.89; 95% CI 0.76 to 1.04	1.53% per year for the rivaroxaban group and 1.71% per year for warfarin HR 0.89; 95% CI 0.73 to 1.10; p=0.289	2.74 % patients per year, HR 0.86; 95% CI 0.77 to 0.97 3.17% patients per year for warfarin	2.71% patients per year, HR 0.85; 95% CI 0.76 to 0.96 3.17% patients per year for warfarin
Myocardial Infarction	0.53% per year for apixaban and 0.61% per year for warfarin HR 0.88; 95% CI 0.66 to 1.17; p=0.37	0.9% per year for rivaroxaban and 1.1% per year in the warfarin group HR 0.81; 95% CI 0.63 to 1.06; p=0.12	0.70% of patients per year, HR 0.94; 95% CI 0.74 to 1.19 0.75% patients per year for warfarin	0.89% of patients per year, HR 1.19; 95% CI 0.95 to 1.49 0.75% patients per year for warfarin
Prior Stroke	Easton 2012[244]—No statistically significant interaction was found between prior stroke/TIA and treatment for stroke or systemic embolism, cardiovascular death, disabling or fatal stroke, all-cause mortality, major bleeding.	Hankey 2012[274]—No statistically significant interaction was found between prior stroke/TIA and treatment for stroke or systemic embolism, major or non-major clinically relevant bleeding.	Rost 2016[342]—No statistically significant interaction was found between prior stroke/TIA and treatment (high dose edoxaban vs. warfarin) for stroke or systemic embolic event, any stroke, hemorrhagic stroke, ischemic stroke, any cause death, or cardiovascular death.	NA

Outcome or Subgroup of Interest	ARISTOTLE (Apixaban vs. Warfarin) (N=18,201)	ROCKET AF (Rivaroxaban vs. Warfarin) (N=14,264)	ENGAGE AF (High-Dose Edoxaban vs. Warfarin) (N=14,071)	ENGAGE AF (Low-Dose Edoxaban vs. Warfarin) (N=14,070)
Aspirin Treatment	Alexander 2014[209]—No statistically significant interactions between treatment and use of aspirin vs. none on stroke or systemic embolism, ischemic stroke, MI, death, major bleeding, hemorrhagic stroke, major or clinically-relevant non-major bleeding or any bleeding.	Shah 2016[348]—No statistically significant interactions between treatment and use of aspirin versus none on stroke or systemic embolism, major bleeding or all-cause death.	Xu 2016[368]—No statistically significant interactions between treatment and use of single antiplatelet drug vs. none on stroke or systemic embolic events, ischemic stroke, hemorrhagic stroke, MI, cardiovascular death, major bleeding, intracranial bleeding, or any bleeding.	Xu 2016[368]—No statistically significant interactions between treatment and use of single antiplatelet drug vs. none on stroke or systemic embolic events, ischemic stroke, hemorrhagic stroke, MI, cardiovascular death, major bleeding, intracranial bleeding, or any bleeding.

Abbreviations: CI=confidence interval; HR=hazard ratio; ITT=intention to treat; NA=not available; NMCR=non-major clinically relevant; NNT =number needed to treat

Thromboembolic Outcomes

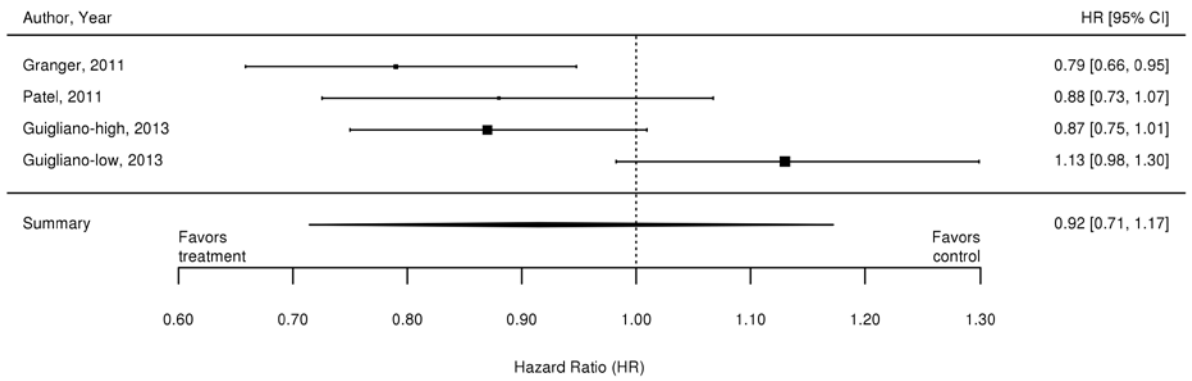
Stroke or Systemic Embolism

Three RCTs explored the impact of Xa inhibitors versus warfarin on stroke or systemic embolism. In one study,[25] in the ITT population, apixaban was shown to be superior to warfarin in preventing stroke and systemic embolism (1.27% per year vs. 1.60% per year for apixaban and warfarin, respectively; HR 0.79; 95% CI 0.66 to 0.95; p=0.01). In a second study,[24] among all randomized patients in the ITT analysis, primary events occurred in 2.1 percent per year in the rivaroxaban group and in 2.4 percent per year in the warfarin group (HR 0.88; 95% CI 0.74 to 1.03; p<0.001 for noninferiority; p=0.12 for superiority). However, in the per-protocol population, a prespecified secondary analysis, rivaroxaban was shown to be noninferior to warfarin in preventing stroke and systemic embolism (1.7% per year vs. 2.2% per year for rivaroxaban and warfarin, respectively; HR 0.79; 95% CI 0.66 to 0.96; p<0.001 for noninferiority; 1.7% per year vs. 2.2% per year for rivaroxaban and warfarin, respectively; HR 0.79; 95% CI 0.65 to 0.95; p=0.01 for superiority).

In another study,[26,265] the primary outcome of hemorrhagic stroke, ischemic stroke, or systemic emboli in the ITT analysis in the overall study period, event rates were higher in all groups and there were no statistically significant differences (1.80% per year for warfarin, 1.57% per year for high-dose edoxaban [HR 0.87; 97.5% CI 0.73 to 1.04; p=0.08 as compared to warfarin], and 2.04% per year for low dose edoxaban [HR 1.13; 97.5% CI 0.96 to 1.34; p=0.10 as compared to warfarin]). Note that in this study, if an edoxaban dosing regimen met the prespecified criteria for noninferiority, that dose was then compared with warfarin in a test of superiority with the use of data from the intention-to-treat population, with all primary-end-point events that occurred during the overall study period (i.e., from randomization to the end of the treatment period) considered in the analysis. In clinical practice, if CrCl is > 50 to 95 ml/min, then the dose of edoxaban is 60 mgs once a day. If the CrCl is 15 to 50 ml/min, then the appropriate dose of edoxaban is 30 mgs once a day. If CrCl >95 mL/min, then edoxaban should not be used. Note also that in the ENGAGE-AF trial, patients were randomized to 60 mg vs. 30 mg (not based on the renal function) vs. warfarin.

We performed a meta-analysis which combined the findings from the three RCTs and Figure 18 shows the forest plot for this analysis demonstrating that across the studies Xa inhibitors did not reduce the risk of stroke or systemic embolism (HR 0.92, 95% CI 0.71 to 1.17, I^2 = 74.2%, Q = 11.6, p=0.009). There was high SOE that apixaban reduced risk of stroke or systemic embolism compared with warfarin. There was low SOE that there was no evidence of a difference in stroke risk between rivaroxaban or edoxaban and warfarin. The SOE was reduced for rivaroxaban given the reduction demonstrated in the observational studies.

Figure 18. Forest plot for stroke or systemic embolism—Xa inhibitors (treatment) versus warfarin (control) (randomized controlled trials)



Abbreviation: CI=confidence interval

This outcome was also evaluated in 12 observational studies. Table 55 summarizes these findings and Figure 19 combines all of the studies that used propensity-matched controls across all Xa inhibitors. This combined analysis demonstrated a reduction in stroke risk between Xa inhibitors and warfarin (HR 0.78, 95% CI 0.68 to 0.90, I^2 = 78.8%, Q = 75.5, p<0.001). We also synthesized the findings for individual drugs. Figure 20 demonstrates that the observational studies combining evidence from the individual drugs a reduction in stroke or systemic embolism for rivaroxaban versus warfarin (HR 0.81, 95% 0.71 to 0.93, I^2 = 39.4%, Q = 13.2, p=0.11) and a trend towards a reduction for patients on apixaban versus warfarin (Figure 21) (HR 0.76, 95% CI 0.57 to 0.99, I^2 = 88.7%, Q = 61.7, p<0.001).

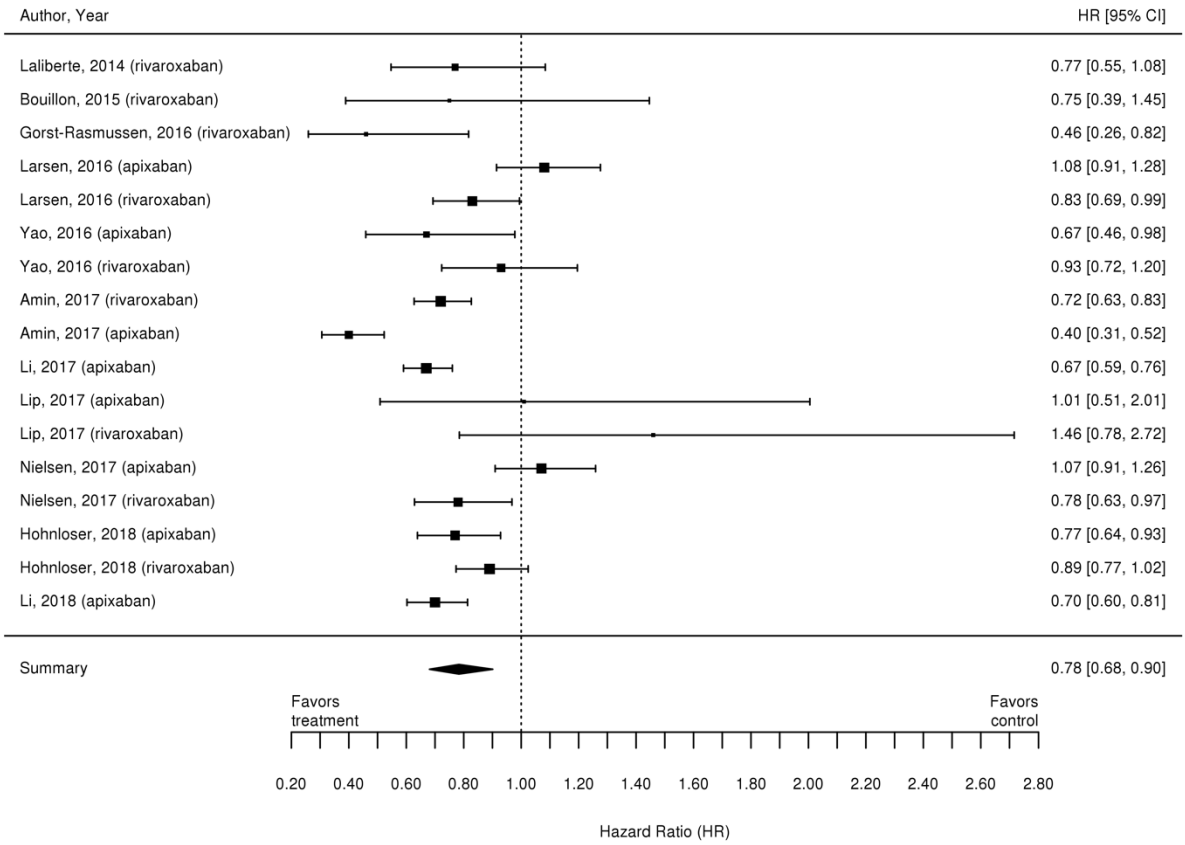
Table 55. Observational studies: stroke or systemic embolism—apixaban, rivaroxaban, or edoxaban versus warfarin

Database	Location	Direct Oral Anticoagulant	Risk Estimate (95% CI) DOAC vs. Warfarin
Analysis With Propensity-Matched Controls			
Danish national prescription registry, Danish national patient register, Danish civil registration system[299]	Europe	Apixaban 5mg bid	1.08 (0.91 to 1.27)
Danish national prescription registry, Danish national patient register, Danish civil registration system[299]	Europe	Rivaroxaban 20mg once daily	0.83 (0.69 to 0.99)
Danish national prescription registry, Danish national patient register, Danish civil registration system[329]	Europe	Apixaban 2.5mg	1.07 (0.91 to 1.26)
Danish national prescription registry, Danish national patient register, Danish civil registration system[329]	Europe	Rivaroxaban 15mg	0.78 (0.63 to 0.97)
Danish national prescription registry, Danish national patient register, Danish civil registration system[267]	Europe	Rivaroxaban (15mg: R15; or 20mg: R20)	R15 vs. warfarin: 0.46 (0.26 to 0.82) R20 vs. warfarin: 0.72 (0.51 to 1.01)
Observational cohort study of Danish citizens[311]	Europe	Apixaban 5mg bid	1.01 (0.51 to 2.01)
Observational cohort study of Danish citizens[311]	Europe	Rivaroxaban 20mg daily	1.46 (0.79 to 2.70)
Truven MarketScan® Commercial Claims and Encounter and Medicare Supplemental and	US	Apixaban	0.67 (0.59 to 0.76)

Database	Location	Direct Oral Anticoagulant	Risk Estimate (95% CI) DOAC vs. Warfarin
Coordination of Benefits Database ("MarketScan"), IMS PharMetrics Plus™ Database ("PharMetrics"), Optum Clinformatics™ Data Mart ("Optum"), and Humana Research Database ("Humana")[304]			
French national health-insurance database (Système National d'Information Inter-Régimes de l'Assurance Maladie [SNIIRAM][112]	Europe	Rivaroxaban 10mg-15mg Rivaroxaban 20mg	0.75 (0.39 to 1.45) Rivaroxaban 10mg-15mg: 1.41 (0.55 to 3.61) Rivaroxaban 20mg: 0.41 (0.15 to 1.12)
Symphony Health Solutions' (SHS) Patient Transactional Datasets[293]	US	Rivaroxaban	0.77 (0.55 to1.09)
OptumLabs Data Warehouse (OLDW)[370]	US	Apixaban	0.67 (0.46 to 0.98)
OptumLabs Data Warehouse (OLDW)[370]	US	Rivaroxaban	0.93 (0.72 to 1.19)
US Center for Medicare and Medicaid Services (CMS) data[395]	US	Rivaroxaban	0.72 (0.63 to 0.83) Reduced dose: 0.78 (0.63 to 0.96) Standard dose: 0.69 (0.58 to 0.83)
US Center for Medicare and Medicaid Services (CMS) data[395]	US	Apixaban	0.40 (0.31 to 0.53) Reduced dose: 0.60 (0.38 to 0.96) Standard dose: 0.34 (0.24 to 0.47)
German Applied Health Research Database[398]	Europe	Apixaban	0.77 (0.64 to 0.93)
German Applied Health Research Database[398]	Europe	Rivaroxaban	0.89 (0.77 to 1.02)
MarketScan, IMS PharMetrics Plus™ Database, Optum, Humana[400]	US	Apixaban	Standard dose: 0.70 (0.60 to 0.81) Reduced dose: 0.63 (0.49 to 0.81)
Analysis Without Propensity-Matched Controls			
Danish National Patient Registry[352]	Europe	Rivaroxaban	0.91 (0.74 to 1.12)
Danish National Patient Registry[352]	Europe	Apixaban	1.07 (0.87 to 1.31)

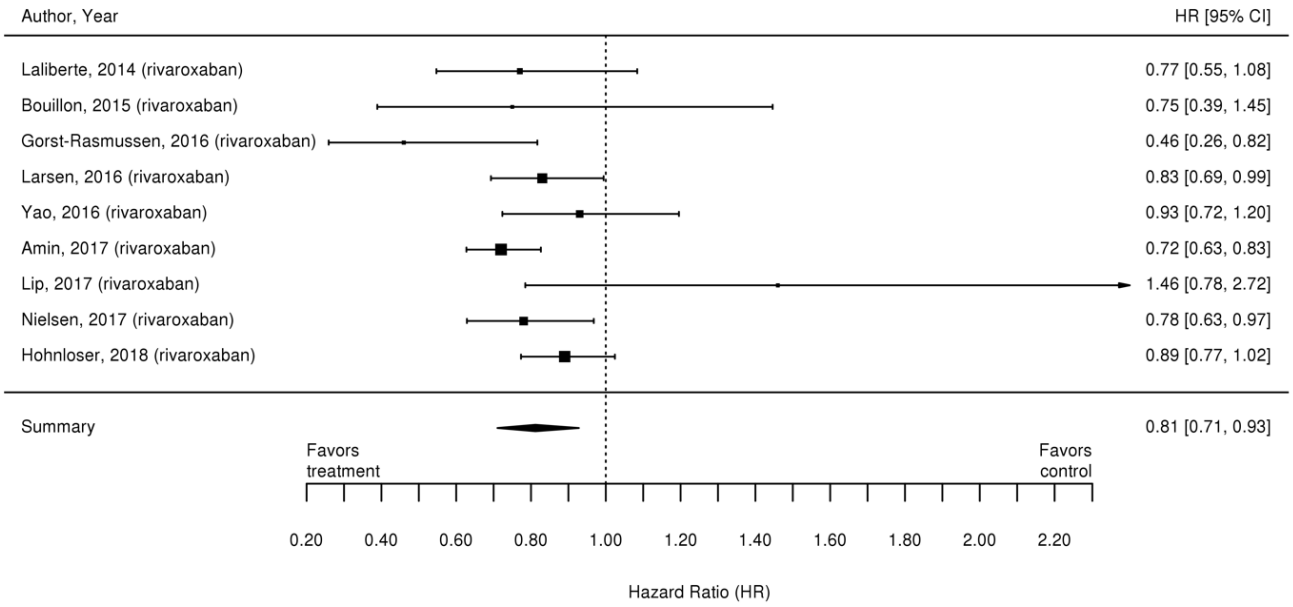
Abbreviations: CI=confidence interval; DOAC=direct oral anticoagulant

Figure 19. Forest plot for stroke or systemic embolism—apixaban, rivaroxaban, or edoxaban (treatment) versus warfarin (control) (observational)



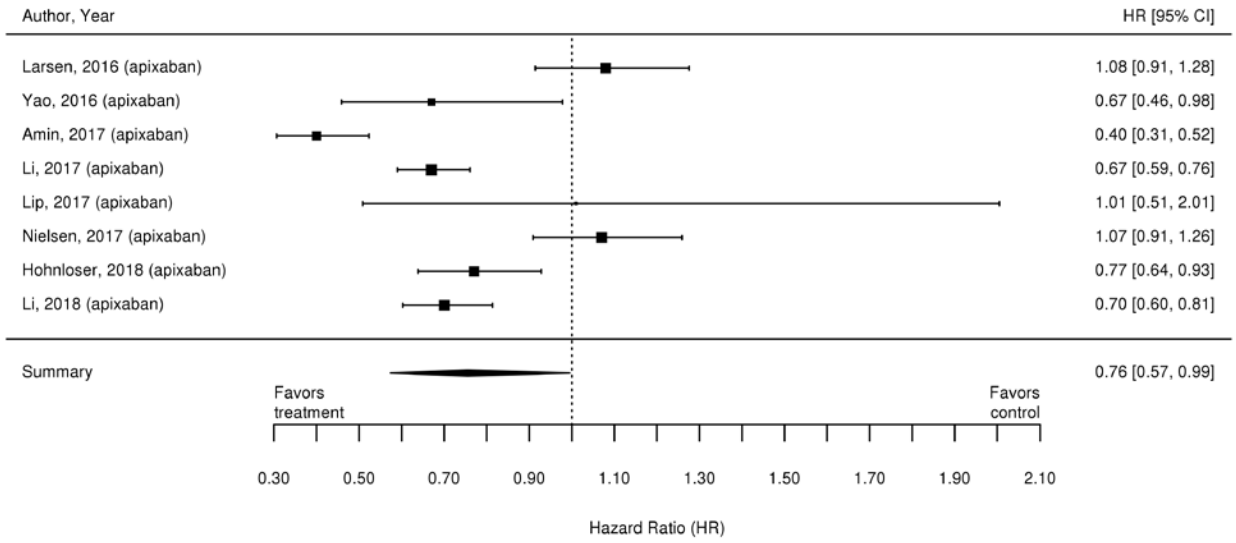
Abbreviation: CI=confidence interval

Figure 20. Forest plot for stroke or systemic embolism—rivaroxaban (treatment) versus warfarin (control) (observational)



Abbreviation: CI=confidence interval

Figure 21. Forest plot for stroke or systemic embolism—apixaban (treatment) versus warfarin (control) (observational)



Abbreviation: CI=confidence interval

Ischemic Stroke, Systemic Embolism, or Major Bleeding

The retrospective CARBOS study[287] used a German claims database to compare risk of stroke, systemic embolism or major bleeding between those initiated on apixaban, dabigatran or rivaroxaban versus VKA (phenprocoumon). In sensitivity analyses using propensity matching, the only group of patients in which there was a significant difference in risk of net clinical

combined outcome in those taking rivaroxaban versus phenprocoumon (HR 1.18; 95% CI 1.04 to 1.35; p=0.013).

Ischemic Stroke, TIA, Intracranial Hemorrhage, or Myocardial Infarction

An observational study[409] examined data from a German electronic medical record database to evaluate the risk of ischemic stroke, transient ischemic attack, intracerebral hemorrhage, other non-traumatic intracranial hemorrhage and myocardial infarction in patients treated with rivaroxaban versus warfarin. Following propensity score-matching, the study found a significantly decreased risk of the composite primary endpoint in patients treated with rivaroxaban (HR 0.54; 95% CI 0.31 to 0.92; p=0.025). While individual endpoints had numerically lower rates in the rivaroxaban group, none of these were statistically significant.

Intracranial Hemorrhage or Ischemic Stroke

A U.S. study using MarketScan data[229] found that, in analyses using propensity matching, rivaroxaban users had a significant decreased risk of intracranial hemorrhage or ischemic stroke when compared to warfarin (HR 0.61; 95% CI 0.45 to 0.82). They found a lower but nonsignificant difference when comparing apixaban to warfarin (HR 0.63; 95% CI 0.35 to 1.12).

Ischemic Stroke, Systemic Embolism, or Death

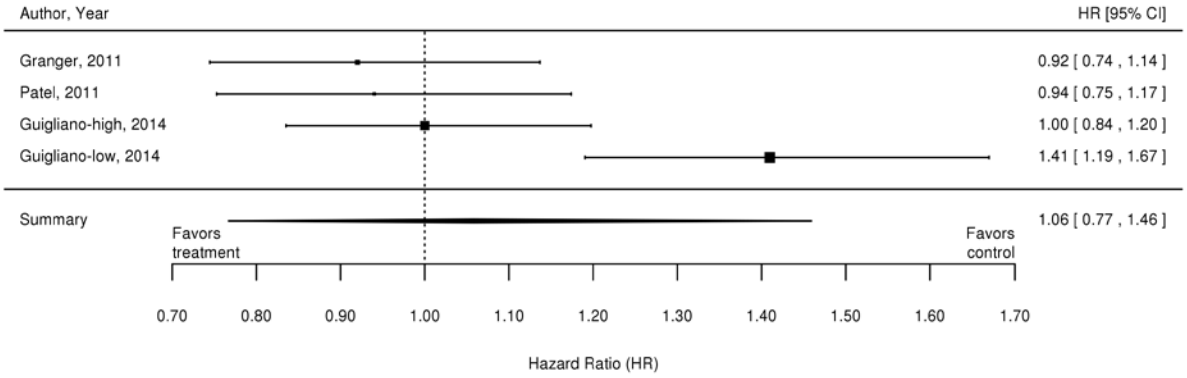
One study examined a sample of the Medicare database and compared the composite outcome of ischemic stroke, systemic embolism, or death in users of apixaban versus warfarin.[384] This study found a significantly lower risk of this composite outcome among apixaban users compared with warfarin with an adj HR (95% CI) of 0.86 (0.76 to 0.98). This same study also examined a sample of the Medicare database and compared the composite outcome of ischemic stroke, systemic embolism, or death in users of rivaroxaban versus warfarin. This study also found a significantly lower risk of this composite outcome among rivaroxaban users compared with warfarin with an adj HR (95% CI) of 0.82 (0.75 to 0.89).

Ischemic or Uncertain Stroke

One RCT[25] reported rates of ischemic or uncertain stroke that were not different between apixaban and warfarin (0.97% per year for apixaban vs. 1.05% per year for warfarin; HR 0.92; 95% CI 0.74 to 1.13; p=0.42) (high SOE). One other study reported this outcome in the on-treatment population for rivaroxaban compared to warfarin;[24] it showed no evidence of a difference in the rate of ischemic stroke between treatment groups. In this study, those on rivaroxaban had an event rate for ischemic stroke of 1.34/100 patient-years compared with 1.42/100 patient-years for those on warfarin (HR 0.94; 95% CI 0.75 to 1.17; p=0.581). Given the on-treatment analysis, the finding that there was no evidence of a difference between rivaroxaban and warfarin was rated to have moderate SOE.

In ENGAGE AF[26,265] there was no evidence of a difference in rates of ischemic stroke between warfarin and high dose edoxaban (1.25% per year for warfarin and 1.25% per year for edoxaban, HR1.00; 95% CI 0.83 to 1.19; p=0.97); however, there was a higher rate of ischemic stroke in those with low dose edoxaban as compared to warfarin (1.77% per year for edoxaban and 1.25% per year for warfarin, HR 1.41; 95% CI 1.19 to 1.67; p<0.001). There was moderate SOE that high dose edoxaban was no different from warfarin for ischemic or uncertain stroke but that low dose edoxaban increased this outcome. Figure 22 shows the forest plot for a meta-analysis of the combined Xa inhibitors compared with warfarin (HR 1.06, 95% CI 0.77 to 1.46, I^2 = 78.4%, Q = 13.9, p=0.003).

Figure 22. Forest plot for ischemic or uncertain stroke—Xa inhibitors (treatment) versus warfarin (control) (randomized controlled trials)



Abbreviation: CI=confidence interval

This outcome was also evaluated in 10 observational studies. Table 56 summarizes these findings, and in Figure 23 we synthesize those studies that included propensity-matched controls for all Xa inhibitors as compared to warfarin. Inconsistent with the RCT evidence, these findings demonstrate a reduction in ischemic or uncertain stroke with Xa inhibitors as compared to warfarin (HR 0.86; 95% CI 0.76 to 0.98, I^2 = 67.5%, Q = 40.1, p<0.001). Evaluating the findings for individual drugs the observational studies did not demonstrate a difference in risk for apixaban compared with warfarin (HR 0.90; 95% CI 0.72 to 1.14, I^2 = 81.3%, Q = 32.1, p<0.001) though did show a trend towards a reduction with rivaroxaban compared with warfarin (HR 0.85; 95% CI 0.72 to 0.99, I^2 = 23.4%, Q = 7.8, p=0.25).

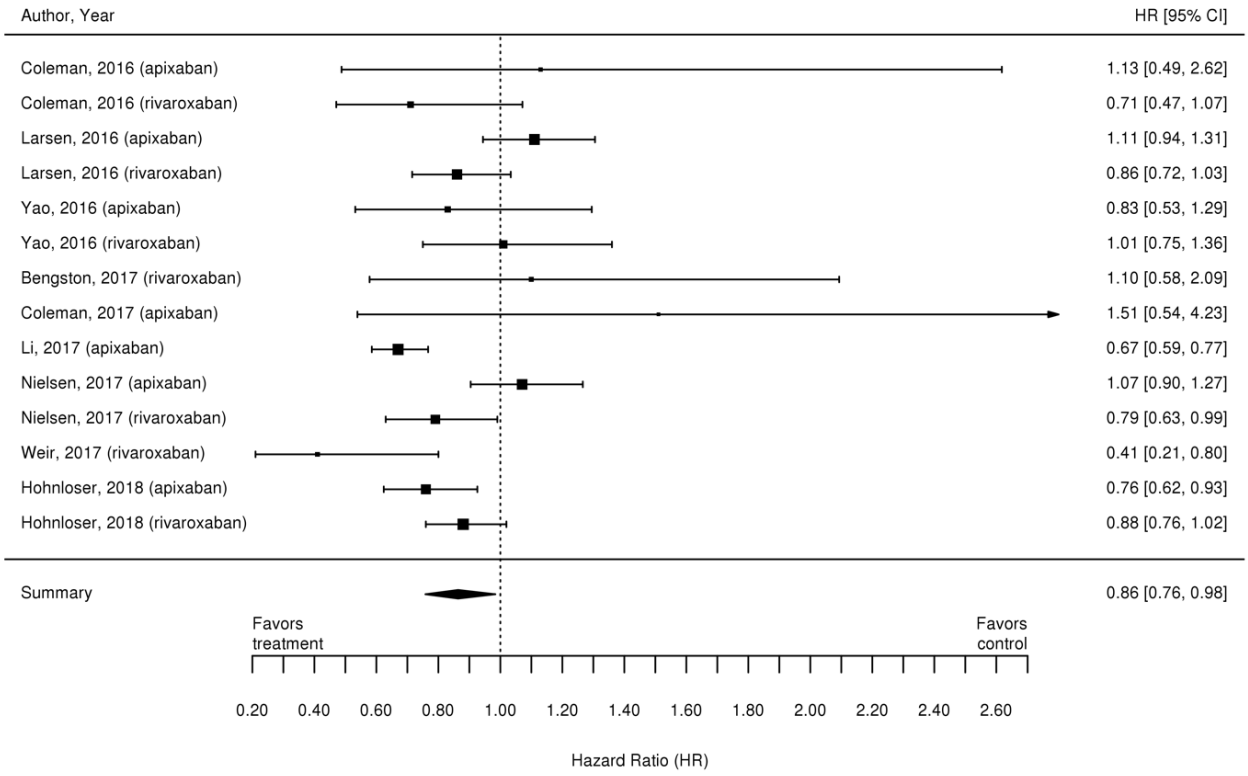
Table 56. Observational studies: ischemic or uncertain stroke—apixaban, rivaroxaban, or edoxaban versus warfarin

Database	Location	Direct Oral Anticoagulant	Risk Estimate (95% CI) DOAC vs. Warfarin
Analysis With Propensity-Matched Controls			
Danish national prescription registry, Danish national patient register, Danish civil registration system[299]	Europe	Apixaban 5mg bid	1.11 (0.94 to 1.30)
Danish national prescription registry, Danish national patient register, Danish civil registration system[299]	Europe	Rivaroxaban 20mg once daily	0.86 (0.72 to 1.04)
German Primary Care Physician panel of a longitudinal electronic medical record database (IMS Disease Analyzer)[230]	Europe	Apixaban	1.51 (0.54 to 4.24)
Danish national prescription registry, Danish national patient register, Danish civil registration system[329]	Europe	Apixaban 2.5mg	1.07 (0.90 to 1.26)
Danish national prescription registry, Danish national patient register, Danish civil registration system[329]	Europe	Rivaroxaban 15mg	0.79 (0.63 to 0.99)

Database	Location	Direct Oral Anticoagulant	Risk Estimate (95% CI) DOAC vs. Warfarin
Truven MarketScan® Commercial Claims and Encounter and Medicare Supplemental and Coordination of Benefits Database (“MarketScan”), IMS PharMetrics Plus™ Database (“PharMetrics”), Optum Clinformatics™ Data Mart (“Optum”), and Humana Research Database (“Humana”)[304]	US	Apixaban	0.67 (0.58 to 0.76)
Truven Health MarketScan1 Commercial Claims and Encounters Database and the Medicare Supplemental and Coordination of Benefits Database[218]	US	Rivaroxaban	1.10 (0.58 to 2.10)
OptumLabs Data Warehouse (OLDW)[370]	US	Apixaban	0.83 (0.53 to 1.29)
OptumLabs Data Warehouse (OLDW)[370]	US	Rivaroxaban	1.01 (0.75 to 1.36)
U.S. Truven MarketScan data[229]	US	Apixaban	1.13 (0.49 to 2.63)
U.S. Truven MarketScan data[229]	US	Rivaroxaban	0.71 (0.47 to 1.07)
Optum’s Integrated Claims–Clinical dataset[365]	US	Rivaroxaban	0.41 (0.21 to 0.80)
German Applied Health Research Database[398]	Europe	Apixaban	0.76 (0.62 to 0.92)
German Applied Health Research Database[398]	Europe	Rivaroxaban	0.88 (0.76 to 1.02)
Analysis Without Propensity-Matched Controls			
Danish National Patient Registry[352]	Europe	Rivaroxaban	0.89 (0.67 to 1.19)
Danish National Patient Registry[352]	Europe	Apixaban	0.98 (0.74 to 1.30)

Abbreviations: CI=confidence interval; DOAC=direct oral anticoagulant

Figure 23. Forest plot for ischemic or uncertain stroke—apixaban, rivaroxaban, or edoxaban (treatment) versus warfarin (control) (observational)



Abbreviation: CI=confidence interval

Ischemic Stroke

A U.S. study used MarketScan[392] to look at risk of ischemic stroke in patients with nonvalvular atrial fibrillation and a history of previous stroke or transient ischemic attack (REAFFIRM). In a propensity-matched analysis, rivaroxaban users had a significantly decreased risk of ischemic stroke when compared to warfarin (HR 0.48, 95% CI 0.29 to 0.79). There was no statistically significant difference when comparing apixaban to warfarin (HR 0.79, 95% CI 0.37 to 1.72). A U.S. propensity-matched analysis using CMS data found a lower risk of ischemic stroke comparing both rivaroxaban and apixaban to warfarin (rivaroxaban: HR 0.70, 95% CI 0.59 to 0.83); apixaban: HR 0.42, 95% CI 0.31 to 0.57).[395] Another U.S. propensity-matched study used data from Aetna, Humana, Optum and HealthCore to sequentially compare the outcome of ischemic stroke among rivaroxaban and warfarin initiators.[396] There was a significantly reduced risk of ischemic stroke among rivaroxaban initiators (adj HR 0.61, 95% CI 0.47 to 0.79).

A German propensity-matched study found no evidence of a difference in risk of ischemic stroke when comparing apixaban or rivaroxaban users to warfarin users (apixaban: adj HR 0.82, 95% CI 0.66 to 1.03; rivaroxaban: adj HR 0.91, 95% CI 0.77 to 1.07).[398]

A U.S. propensity-matched study using four major databases compared the effectiveness of standard and reduced dose apixaban compared to warfarin in preventing ischemic stroke.[400] At both the standard and reduced dose of apixaban, there was a reduced risk of ischemic stroke

compared to warfarin (standard dose: HR 0.70, 95% CI 0.60 to 0.82; reduced dose: HR 0.61, 95% CI 0.46 to 0.80).

A U.S. propensity-matched study compared rivaroxaban and apixaban to warfarin in patients with active cancer and nonvalvular atrial fibrillation.[402] The risk of ischemic stroke was nonsignificant between DOAC users versus warfarin users (rivaroxaban: adj HR 0.74, 95% CI 0.40 to 1.39; apixaban: adj HR 0.71, 95% CI 0.19 to 2.60).

Any Stroke or Transient Ischemic Attack

In one study,[366] any stroke or TIA were observed in 0.4, 0.8, 0.4, 1.1, and 1.6 percent of patients in the edoxaban 30mg daily, 30mg twice daily, 60mg daily, 60mg twice daily, and warfarin treatment groups, respectively. In a second study, ENGAGE AF,[26,265] there was no statistically significant difference in all stroke or TIA between high-dose edoxaban (2.00% of patients per year, HR 0.92; p=0.27) and warfarin or low-dose edoxaban (2.62% of patients per year, HR 1.21; 95% CI 0.97 to 1.31; p=0.005) and warfarin (2.17% patients per year).

A European cohort study using the Stockholm administrative health registry[258] examined risk of TIA/ischemic stroke/stroke unspecified and found no evidence of a difference in risk for those on apixaban compared to warfarin (HR 0.97, 95% CI 0.73 to 1.30) or for those on rivaroxaban compared to warfarin (HR 0.78, 95% CI 0.57 to 1.07).

Systemic Embolism

Six RCTs specifically reported the impact of therapy on systemic embolism separated out from stroke. In one study,[25] the rates of systemic embolism did not differ between groups (0.09% per year for apixaban vs. 0.10% per year for warfarin; HR 0.87; 95% CI 0.44 to 1.75; p=0.70.) Similar findings were seen in two other studies. In one, systemic embolism was observed in 0.4, 0.4, 0, 0, and 0 percent of patients in the edoxaban 30mg daily, 30mg twice daily, 60mg daily, 60mg twice daily, and warfarin treatment groups, respectively,[366] and in the second study there was no evidence of a difference in systemic embolic events in either the high dose edoxaban group (0.08% of patients per year, HR 0.65; 95% CI 0.34 to 1.24; p=0.19) or low dose edoxaban group (0.15% of patients per year, HR 1.24; 95% CI 0.72 to 2.15; p=0.43) as compared to warfarin (0.12% of patients per year).[26] In a prespecified additional analysis of ENGAGE AF,[263] there was no evidence of a difference in nonfatal systemic embolic or fatal events between high dose or low dose edoxaban compared with warfarin. Among those in the on-treatment population of the ROCKET trial,[24] there was a reduced rate of non-CNS systemic embolism for those on rivaroxaban compared with warfarin. Participants on rivaroxaban had an event rate for non-CNS systemic embolism of 0.04/100 patient-years compared with 0.19/100 patient-years for those on warfarin (HR 0.23; 95% CI 0.09 to 0.61; p=0.003). There was moderate SOE that there was no evidence of a difference between apixaban or edoxaban and warfarin arms. There was moderate SOE that rivaroxaban reduced risk. A secondary analysis[334] of the ROCKET trial[24] specifically examined noncentral nervous system systemic embolism in patients treated with once daily rivaroxaban versus warfarin. Overall, the rate of non-CNS systemic embolism was 0.183/100 patient-years of followup (95% CI 0.14 to 0.24). For 29 events, the embolism occurred in the lower extremities with 8 in mesenteric arteries, 6 in upper extremities, 2 in renal arteries, 1 in the splenic artery and 1 with unspecified location. A total of 11 patients with non-CNS systemic embolism died after the event at a range of within 30 days to >6 months after the event.

In an observational study within the US, apixaban was associated with a lower risk of systemic embolism compared to warfarin by propensity matching analyses adj HR (95% CI 0.46 0.26 to 0.82).[304]

A U.S. propensity-matched analysis using CMS data found a lower risk of systemic embolism with users of rivaroxaban compared to warfarin (HR 0.52, 95% CI 0.28 to 0.94), but a nonsignificant difference when comparing apixaban to warfarin (HR 0.43, 95% CI 0.11 to 1.65.[395]

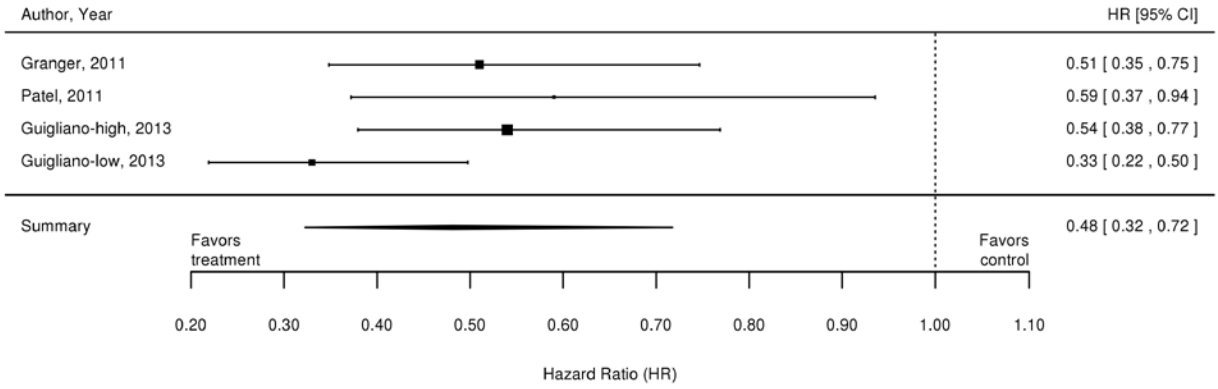
A U.S. propensity-matched study using four major databases compared the effectiveness of standard and reduced dose apixaban compared to warfarin in preventing systemic embolism.[400] At the standard dose of apixaban, there was a reduced risk of systemic embolism compared to warfarin users (HR 0.39, 95% CI 0.20 to 0.78). However, this effect was no longer statistically significant at the reduced dose of apixaban (HR 0.61, 95% CI 0.23 to 1.62).

Bleeding Outcomes

Hemorrhagic Stroke

Three RCTs evaluated rates of hemorrhagic stroke.[24-26] In one study,[25] apixaban was associated with lower rates of hemorrhagic stroke (0.24% per year for apixaban vs. 0.47% per year for warfarin; HR 0.51; 95% CI 0.35 to 0.75; p<0.001). In the ROCKET AF trial,[24] there was a reduced rate of hemorrhagic stroke for those on rivaroxaban compared to warfarin among those in the on-treatment population. The event rate for hemorrhagic stroke was 0.26/100 patient-years for those on rivaroxaban compared to 0.44/100 patient-years for those on warfarin (HR 0.59; 95% CI 0.37 to 0.93; p=0.024). Finally, in ENGAGE AF,[26,265] there was statistically significant lower rate of hemorrhagic stroke with high dose edoxaban (0.26% of patients per year, HR 0.54; 95% CI 0.38 to 0.77) and for lower dose edoxaban (0.16% of patients per year, HR 0.33; 95% CI 0.22 to 0.50) as compared to warfarin (0.47% patients per year). Based on these studies, there was evidence that either apixaban (high SOE) or edoxaban (moderate SOE) reduced risk of hemorrhagic stroke compared with warfarin. Given on-treatment (rather than intention-to-treat) and imprecise findings, there was low SOE of a benefit of rivaroxaban in reducing hemorrhagic stroke. Meta-analysis of the Xa inhibitors demonstrated this reduction in hemorrhagic stroke (HR 0.48, 95% CI 0.32 to 0.72, I^2 = 33.2%, Q = 4.5, p=0.21) (Figure 24).

Figure 24. Forest plot for hemorrhagic stroke—Xa inhibitors (treatment) versus warfarin (control) (randomized controlled trials)



Abbreviation: CI=confidence interval

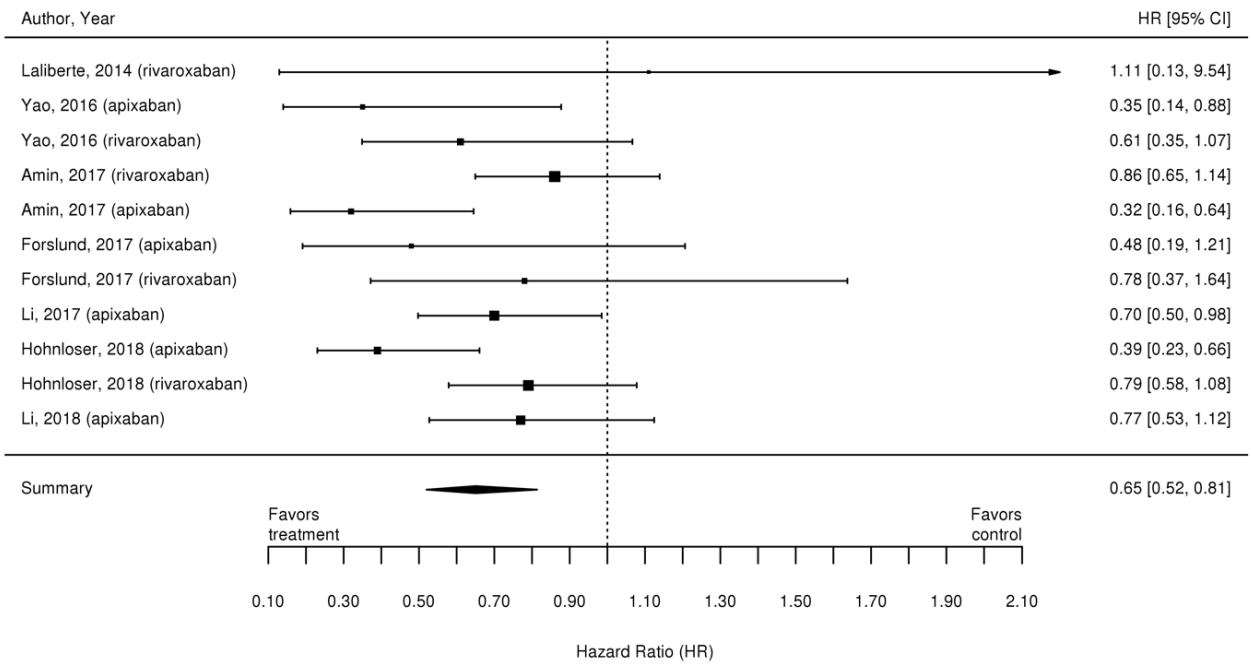
Hemorrhagic stroke was also evaluated in seven observational studies. Table 57 summarizes these findings and Figure 25 synthesizes the studies to demonstrate that Xa inhibitors reduce hemorrhagic stroke risk (HR 0.65, 95% CI 0.52 to 0.81, I^2 = 36.3%, Q = 15.7, p=0.11). This reduction was also found when the findings were evaluated for the individual drugs compared with warfarin (apixaban versus warfarin, HR 0.53, 95% CI 0.35 to 0.79, I^2 = 47.8%, Q = 9.6, p=0.088; rivaroxaban versus warfarin HR 0.80; 95% CI 0.69 to 0.93, I^2 = 0%, Q = 1.3, p=0.87).

Table 57. Observational studies: hemorrhagic stroke—apixaban, rivaroxaban, or edoxaban versus warfarin

Database	Location	Direct Oral Anticoagulants	Risk Estimate (95% CI) DOAC vs. Warfarin
Analysis With Propensity-Matched Controls			
Truven MarketScan® Commercial Claims and Encounter and Medicare Supplemental and Coordination of Benefits Database ("MarketScan"), IMS PharMetrics Plus™ Database ("PharMetrics"), Optum Clinformatics™ Data Mart ("Optum"), and Humana Research Database ("Humana")[304]	US	Apixaban	0.70 (050 to 0.99)
Health data register of the Stockholm Region (Va˚rdanalysdatabasen, VAL)[258]	Europe	Apixaban	0.48 (0.19 to 1.20)
Health data register of the Stockholm Region (Va˚rdanalysdatabasen, VAL)[258]	Europe	Rivaroxaban	0.78 (0.37 to 1.63)
Symphony Health Solutions' (SHS) Patient Transactional Datasets[293]	US	Rivaroxaban	1.11 (0.13 to 9.60)
OptumLabs Data Warehouse (OLDW)[370]	US	Apixaban	0.35 (0.14 to 0.88)
OptumLabs Data Warehouse (OLDW)[370]	US	Rivaroxaban	0.61 (0.35 to 1.07)
US Center for Medicare and Medicaid Services (CMS) data[395]	US	Rivaroxaban	0.86 (0.65 to 1.14)
US Center for Medicare and Medicaid Services (CMS) data[395]	US	Apixaban	0.32 (0.16 to 0.65)
German Applied Health Research Database[398]	Europe	Apixaban	0.39 (0.23 to 0.66)
German Applied Health Research Database[398]	Europe	Rivaroxaban	0.79 (0.58 to 1.08)
MarketScan, IMS PharMetrics Plus™ Database, Optum, Humana[400]	US	Apixaban	Standard dose: 0.77 (0.53 to 1.13) Reduced dose: 0.62 (0.32 to 1.20)

Abbreviations: CI=confidence interval; DOAC=direct oral anticoagulant

Figure 25. Forest plot for hemorrhagic stroke—apixaban, rivaroxaban, or edoxaban (treatment) versus warfarin (control) (observational)



Abbreviation: CI=confidence interval

Major Bleeding

Seven RCTs reported on the impact of Xa inhibitors versus warfarin on the outcome of major bleeding. Note that the definitions of major bleeding differed between the trials. Specifically the trials used the following definitions for major bleeding:

- ROCKET-AF
  - Clinically overt bleeding associated with any of the following: fatal outcome, involvement of a critical anatomic site, fall in Hb concentration > 2 g/dL, transfusion of > 2 units of whole blood or packed red blood cells, or permanent disability
- ARISTOTLE
  - International Society on Thrombosis and Haemostasis (ISTH): clinically overt bleeding accompanied by a decrease in the Hb level of > 2 g/dL over 24 hour or transfusion of > 2 units of packed red cells, occurring at a critical site, or resulting in death
- ENGAGE-AF
  - ISTH with minor modifications for Hb decrease and blood transfusion requirements. Clinically overt bleeding event that met > 1 of the following: fatal bleeding, symptomatic bleeding in a critical site, clinically overt bleeding event that causes a fall in Hb level of > 2 g/dL adjusted for transfusions.

In the ARISTOTLE trial,[25] which evaluated bleeding for events for all patients who received at least one dose of a study drug, apixaban was associated with lower rates of major bleeding when compared with warfarin (2.13% per year for apixaban vs. 3.09% per year for warfarin; HR

0.69; 95% CI 0.60 to 0.80; p<0.001). Two secondary analyses[280,291] of this ARISTOTLE study further examined the clinical consequences of major bleeds. These studies found that patients with major bleeds were older, had lower body weight, and were more likely to have prior myocardial infarction, prior bleeding episode, or prior stroke/TIA/systemic embolism. While almost half (49%) of patients had a change in anti-thrombotic therapy after a major bleed, there was no evidence of a difference between patients treated with apixaban versus warfarin. There was no evidence of a difference in resumption of anticoagulation with apixaban compared to warfarin; median time to resumption was 15 days. Additionally, in the analysis by Hylek, patients who received apixaban were significantly less likely to die within 30 days of a major hemorrhagic event (36 versus 71 events; HR 0.50; 95% CI 0.33 to 0.74; p<0.001). Patient baseline characteristics of increasing age, lower creatinine clearance or history of hemorrhage, prior stroke, TIA, or diabetes were independently associated with a first major hemorrhage.

In another study, in the safety, as-treated population,[24] there was also no evidence of a difference in rates of any major bleeding between the two groups (3.6% per year for rivaroxaban vs. 3.4% per year and warfarin; HR 1.04; 95% CI 0.90 to 1.20; p=0.58). Decreases in hemoglobin levels of 2 g/dL or more and transfusions were more common among patients in the rivaroxaban group, whereas fatal bleeding and bleeding at critical anatomical sites were less frequent. Major bleeding from a gastrointestinal site was more common in the rivaroxaban group (3.2% vs. 2.2%; p<0.001).

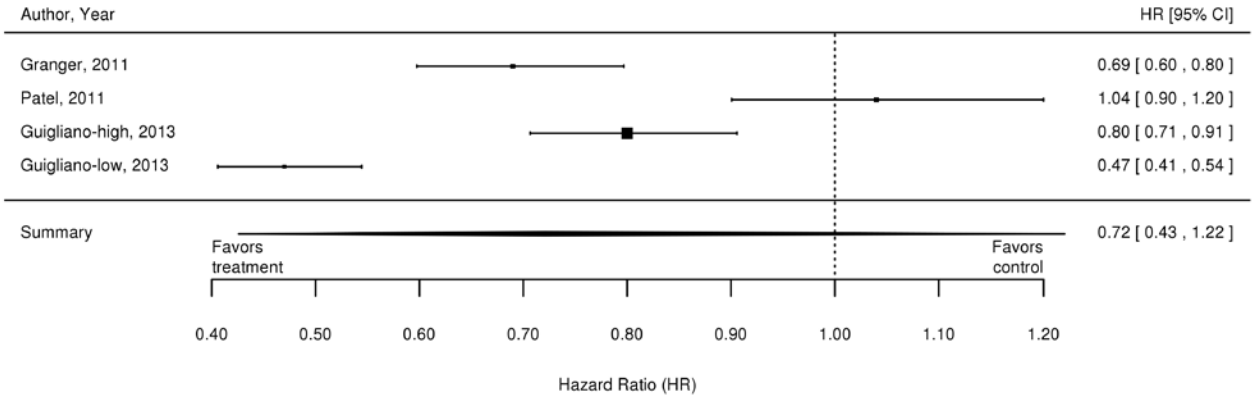
A substudy[187] of the ROCKET AF[24] study examined factors associated with major bleeding events in patients treated with once daily rivaroxaban versus warfarin. Multiple baseline independent predictors of major bleeding were found including increasing age (HR 1.17; 95% CI 1.12 to 1.23; p<0.0001), increasing diastolic blood pressure (HR 1.28; 95% CI 1.11 to 1.47; p=0.0005; for every 5 mmHg increase above 90 mmHg), history of COPD (HR 1.29; 95% CI 1.05 to 1.58; p=0.016), history of GI bleeding (HR 1.88; 95% CI 1.44 to 2.45; p<0.0001); prior aspirin use (HR1.42; 95% 1.23 to 1.64; p<0.0001) and anemia at baseline (HR 1.88; 95% CI 1.59 to 2.22; p<0.0001).

By contrast, in a fourth study,[366] major bleeding events were observed in 0, 2.0, 0.4, 3.3, and 0.4 percent of patients in the edoxaban 30mg daily, 30mg twice daily, 60mg daily, 60mg twice daily, and warfarin treatment groups, respectively. Compared with warfarin, the incidence of major bleeding was significantly higher with edoxaban doses of 30mg twice daily or 60mg twice daily. With the 30mg or 60mg daily edoxaban regimens, the incidence of major bleeding was similar to that in patients randomized to warfarin. Note that only doses of once daily are currently FDA-approved.

In ENGAGE AF,[26] there was statistically significantly lower rate of major bleeding with high dose edoxaban (2.75% of patients per year, HR 0.80; 95% CI 0.71 to 0.91; p<0.001) and for lower dose edoxaban (1.61% of patients per year, HR 0.47; 95% CI 0.41 to 0.55; p<0.001) as compared to warfarin (3.43% patients per year).

There was evidence that apixaban (high SOE) or edoxaban (moderate SOE) reduced risk of major bleeding compared with warfarin, and there was low SOE that there was no evidence of a difference between rivaroxaban and warfarin (Figure 26, HR = 0.72, 95% CI 0.43 to 1.22, I^2 = 95%, Q = 60.5, p<0.001).

Figure 26. Forest plot for major bleeding—Xa inhibitors (treatment) versus warfarin (control) (randomized controlled trials)



Abbreviation: CI=confidence interval

This outcome was also evaluated in 14 observational studies. These studies are summarized in Table 58 and Figures 27-29. Consistent with the RCT evidence, apixaban demonstrated a reduction in risk of major bleeding (HR 0.62, 95% CI 0.47 to 0.82, I^2 = 82.8%, Q = 52.2, p<0.001) while there a trend towards an increase in bleeding with rivaroxaban as compared to warfarin (HR 1.09, 95% CI 1.03 to 1.16, I^2 = 13.6%, Q = 9.3, p=0.32). This inconsistency in findings with the RCT evidence lowered the SOE rating to low. Across all Xa inhibitors there was a trend toward a reduction in risk (HR 0.82, 95% CI 0.68 to 0.99, I^2 = 95.1%, Q = 368.9, p<0.001).

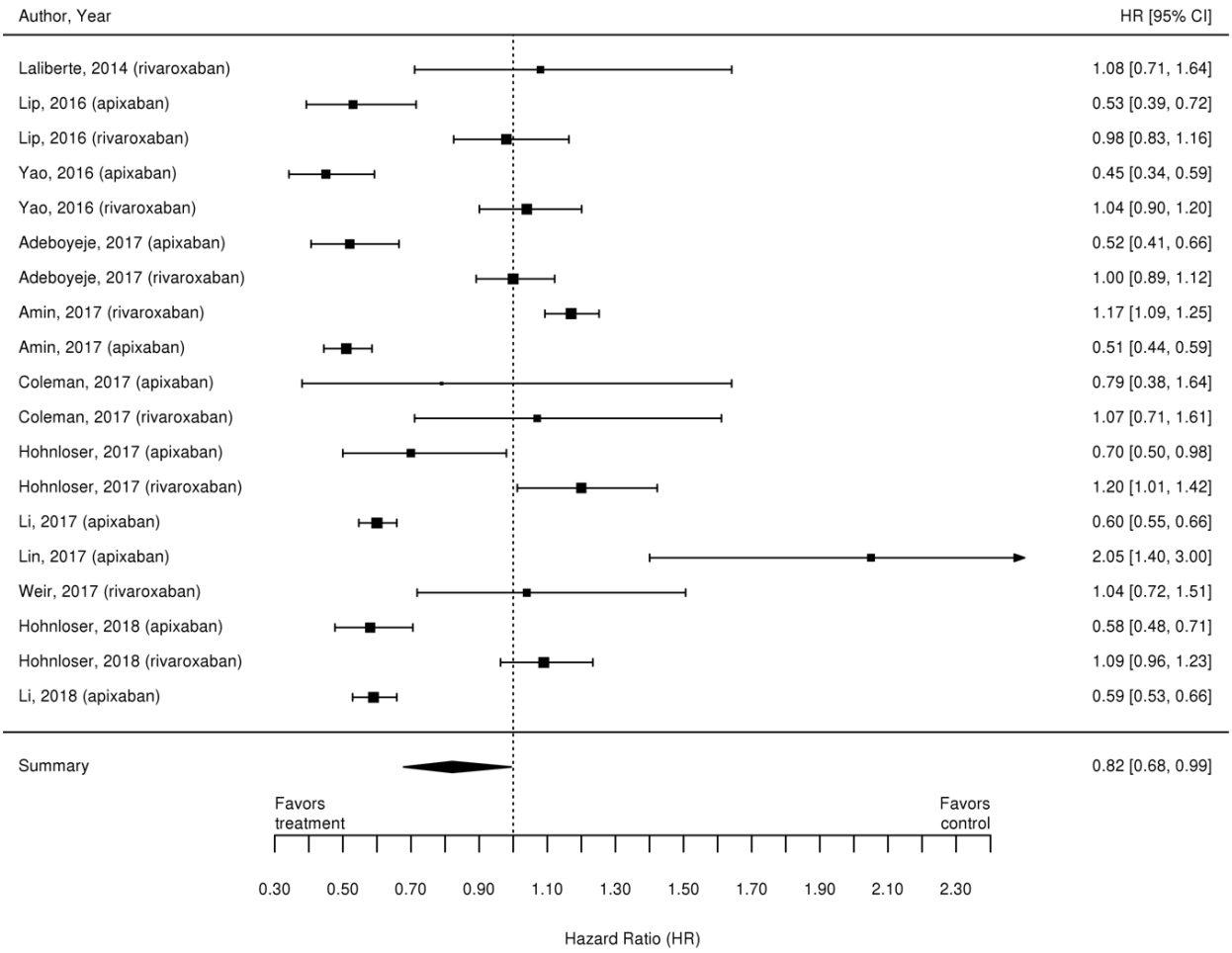
Table 58. Observational studies: major bleeding—apixaban, rivaroxaban, or edoxaban versus warfarin

Database	Location	Direct Oral Anticoagulant	Risk Estimate (95% CI) DOAC vs. Warfarin
Analysis With Propensity-Matched Controls			
Truven MarketScan® Commercial Claims and Encounter and Medicare Supplemental and Coordination of Benefits Databases[310]	US	Apixaban	0.53 (0.39 to 0.71)
Truven MarketScan® Commercial Claims and Encounter and Medicare Supplemental and Coordination of Benefits Databases[310]	US	Rivaroxaban	0.98 (0.83 to 1.17)
IMS Pharmetrics Plus database[305]	US	Apixaban	0.49 (0.33 to 0.71)
OptumLabs Data Warehouse (OLDW)[370]	US	Apixaban	0.45 (0.34 to 0.59)
OptumLabs Data Warehouse (OLDW)[370]	US	Rivaroxaban	1.04 (0.90 to 1.20)
Symphony Health Solutions' (SHS) Patient Transactional Datasets[293]	US	Rivaroxaban	1.08 (0.71 to 1.64)
Truven MarketScan® Commercial Claims and Encounter and Medicare Supplemental and Coordination of Benefits Database ("MarketScan"), IMS PharMetrics Plus™ Database ("PharMetrics"), Optum Clinformatics™ Data Mart ("Optum"), and Humana Research Database ("Humana")[304]	US	Apixaban	0.60 (0.54 to 0.65)
Optum's Integrated Claims–Clinical dataset[365]	US	Rivaroxaban	1.04 (0.72 to 1.51)
CARBOS study based on data from the Health Risk Institute (HRI)[287]	Europe	Apixaban	0.70 (0.50 to 0.98)
CARBOS study based on data from the Health Risk Institute (HRI)[287]	Europe	Rivaroxaban	1.20 (1.01 to 1.42)

Database	Location	Direct Oral Anticoagulant	Risk Estimate (95% CI) DOAC vs. Warfarin
Truven MarketScan® Commercial Claims and Encounter and Medicare Supplemental and Coordination of Benefits Database ("MarketScan")[392]; pts with prior stroke or TIA	US	Apixaban	0.79 (0.38 to 1.64)
US Center for Medicare and Medicaid Services (CMS) data[395]	US	Apixaban	0.51 (0.44 to 0.58) Reduced dose: 0.48 (0.38 to 0.60) Standard dose: 0.54 (0.46 to 0.64)
US Center for Medicare and Medicaid Services (CMS) data[395]	US	Rivaroxaban	1.17 (1.10 to 1.26) Reduced dose: 1.14 (1.03 to 1.27) Standard dose: 1.21 (1.11 to 1.33)
HealthCore Integrated Research Environment (HIRE)[387]	US	Apixaban	0.52 (0.41, 0.67)
HealthCore Integrated Research Environment (HIRE)[387]	US	Rivaroxaban	1.00 (0.89, 1.12)
German Applied Health Research Database[398]	Europe	Apixaban	0.58 (0.48 to 0.71)
German Applied Health Research Database[398]	Europe	Rivaroxaban	1.09 (0.96 to 1.23)
MarketScan, IMS PharMetrics Plus™ Database, Optum, Humana[400]	US	Apixaban	Standard dose: 0.59 (0.53 to 0.66) Reduced dose: 0.59 (0.49 to 0.71)
Analysis Without Propensity-Matched Controls			
Norwegian Patient Registry[273]	Europe	Apixaban	0.56 (0.40 to 0.76)
Norwegian Patient Registry[273]	Europe	Rivaroxaban	0.86 (0.68 to 1.10)
Truven MarketScan[309]	US	Apixaban	1.62 (1.20 to 2.18)

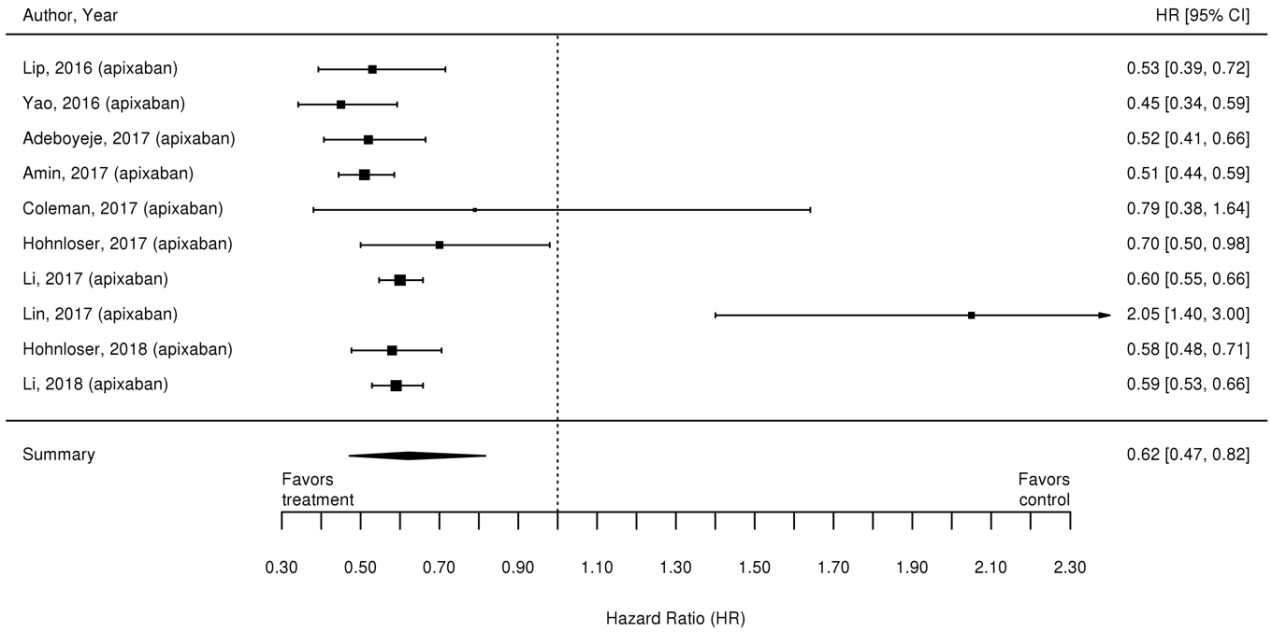
Abbreviations: CI=confidence interval; DOAC=direct oral anticoagulant

Figure 27. Forest plot for major bleeding—apixaban, rivaroxaban, or edoxaban (treatment) versus warfarin (control) (observational)



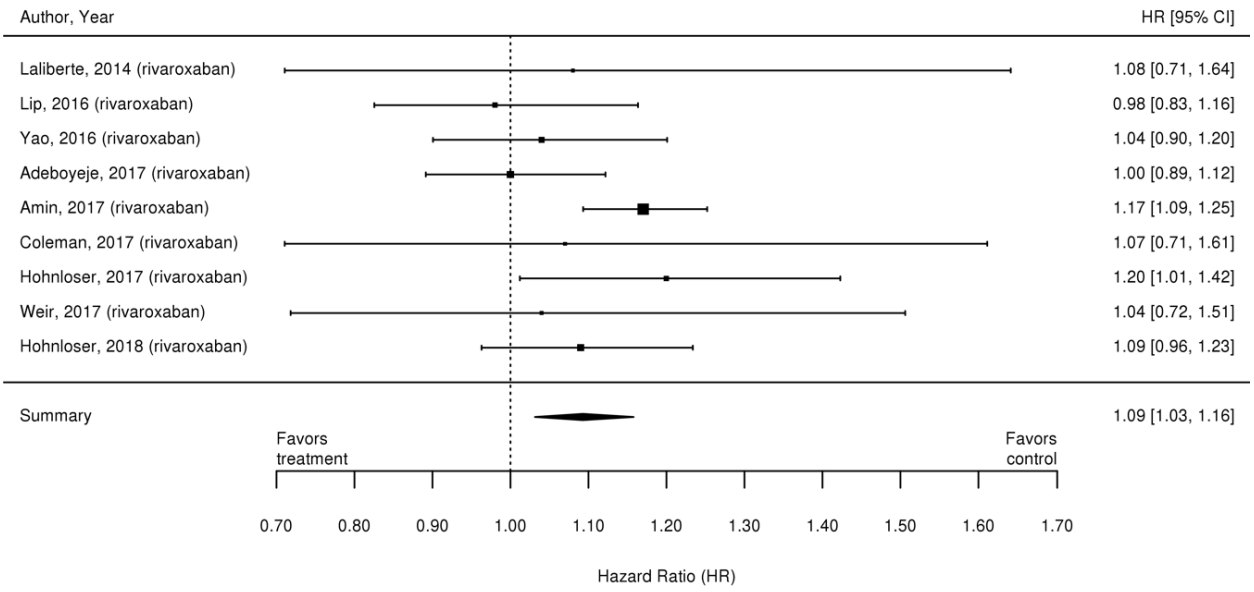
Abbreviation: CI=confidence interval

Figure 28. Forest plot for major bleeding—apixaban (treatment) versus warfarin (control) (observational)



Abbreviation: CI=confidence interval

Figure 29. Forest plot for major bleeding—rivaroxaban (treatment) versus warfarin (control) (observational)



Abbreviation: CI=confidence interval

Major, Non-Major Clinically Relevant, and Minor Bleeding

In the ENGAGE AF RCT,[26] there was statistically significantly lower rate of major or clinically relevant non-major bleeding with high dose edoxaban (11.1% of patients per year, HR

0.86; 95% CI 0.80 to 0.92; p<0.001) and for lower dose edoxaban (7.97% of patients per year, HR 0.62; 95% CI 0.57 to 0.67; p<0.001) as compared to warfarin (13.02% patients per year). Similarly, there was a lower risk of minor bleeding with high dose edoxaban (4.12% of patients per year, HR 0.84; 95% CI 0.76 to 0.94; p=0.002) and for low dose edoxaban (3.52% of patients per year, HR 0.72; 95% CI 0.65 to 0.81; p<0.001) as compared to warfarin (4.89% patients per year).

A secondary analysis[216] of the ARISTOTLE trial[25] evaluated the rates of non-major bleeding. Overall, non-major bleeding was three times more common than major bleeding. Patients treated with apixaban were less likely to experience non-major bleeding compared to treatment with warfarin (6.4 versus 9.4 per 100 patient years; HR 0.69; 95% CI 0.63 to 0.75). All sources of non-major bleeding were lower for those treated with apixaban with the exception of lower gastrointestinal bleeding.

This outcome was also evaluated in 7 observational studies. Table 59 summarizes these findings. Given the inconsistency among these studies in terms of the definition of outcomes, we did not combine this observational data quantitatively.

Table 59. Observational studies: major, non-major clinically relevant, and minor bleeding—apixaban, rivaroxaban, or edoxaban versus warfarin

Database	Location	Direct Oral Anticoagulant	Risk Estimate (95% CI) DOAC vs. Warfarin
Analysis With Propensity-Matched Controls			
Danish national prescription registry, Danish national patient register, Danish civil registration system[267]	Europe	Rivaroxaban (15mg: R15; or 20mg: R20)	R15 vs. warfarin: 0.90 (0.59 to 1.35) R20 vs. warfarin: 1.18 (0.90 to 1.55)
Observational cohort study of Danish citizens[311]	Europe	Apixaban 5mg bid	0.35 (0.17 to 0.72)
Observational cohort study of Danish citizens[311]	Europe	Rivaroxaban 20mg daily	0.84 (0.49 to1.44)
French national health-insurance database (Système National d'Information Inter-Régimes de l'Assurance Maladie [SNIIRAM][112]	Europe	Rivaroxaban 10mg-15mg Rivaroxaban 20mg	1.04 (0.68 to 1.58) Rivaroxaban 10mg-15mg: 0.90 (0.45 to 1.79) Rivaroxaban 20mg: 1.14 (0.68 to 1.93)
CARBOS study based on data from the Health Risk Institute (HRI)[287]	Europe	Apixaban	0.84 (0.71 to 0.99)
CARBOS study based on data from the Health Risk Institute (HRI)[287]	Europe	Rivaroxaban	1.26 (1.16 to 1.38)
Analysis Without Propensity-Matched Controls			
Norwegian Patient Registry[273]	Europe	Apixaban	0.70 (0.61 to 0.80)
Norwegian Patient Registry[273]	Europe	Rivaroxaban	1.05 (0.94 to 1.17)
Hernandez, 2017[384]	US	Apixaban	0.79 (0.70, 0.90)
Hernandez, 2017[384]	US	Rivaroxaban	1.15 (1.07, 1.24)
German Applied Health Research Database[398]	Europe	Apixaban	0.78 (0.71 to 0.86)
German Applied Health Research Database[398]	Europe	Rivaroxaban	1.12 (1.05 to 1.19)

Abbreviations: CI=confidence interval; DOAC=direct oral anticoagulant

Intracranial Bleeding

Six RCTs assessed intracranial bleeding, with three of these evaluating this outcome in a safety population. In two, the use of apixaban and rivaroxaban lowered such bleeding (apixaban: HR 0.42; 95% CI 0.30 to 0.58; p<0.001;[25] rivaroxaban: HR 0.67; 95% CI 0.47 to 0.93; p=0.02[24]).

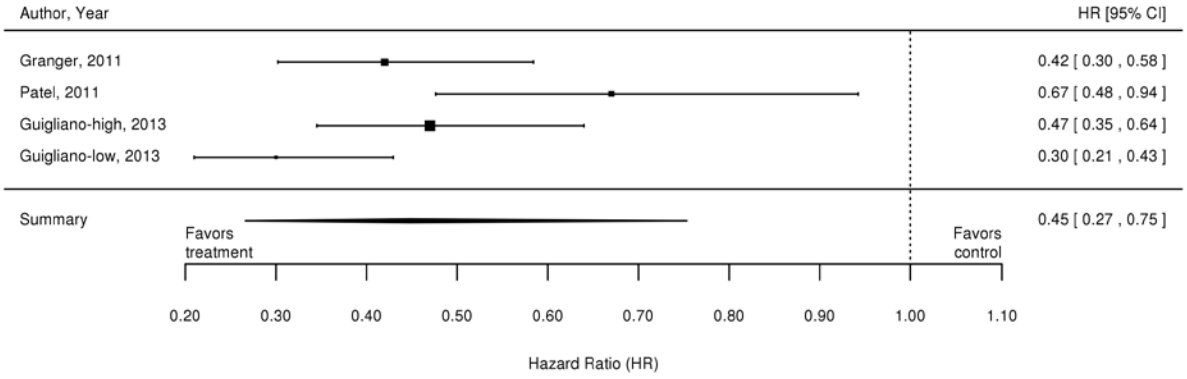
A secondary analysis[314] of the ARISTOTLE trial[25] also showed lower rates of intracranial, intracerebral and subdural intracranial hemorrhage in patients receiving apixaban (intracranial HR 0.42; 95% CI 0.30 to 0.58; p<0.0001; intracerebral HR 0.45; 95% CI 0.30 to 0.68; p<0.0001; subdural HR 0.33; 95% CI 0.17 to 0.65; p=0.0013) with a nonsignificant trend toward less subarachnoid hemorrhage (HR 0.54; 95% CI 0.18 to 1.6; p=0.28). Both groups of patients had similar rates of mortality after an intracranial bleed.

A secondary analysis[188] of the ROCKET AF trial[24] also examined intracranial bleeding. Overall, ICH during followup occurred at a rate of 0.67% per 100 patient-years. There was no evidence of a difference in site (intracerebral, hemorrhagic stroke, subdural hemorrhage, subarachnoid hemorrhage, extradural hemorrhage) of ICH in patients treated with rivaroxaban versus warfarin. The authors did identify several independent baseline predictors of increased risk for ICH including race (HR Asian 2.02; 95% CI 1.39 to 2.94; HR Black 3.25; 95% CI 1.43 to 7.41), age (HR 1.35; 95% CI 1.13 to 1.63 per 10-year increase), decreased serum albumin (HR 1.39; 95% CI 1.12 to 1.73 per 0.5 g/dL decrease), platelet count less than $210x10^9$/L (HR 1.08; 95% CI 1.02 to 1.13 per $10x10^9$/L decrease), previous stroke or TIA (HR 1.42; 95% CI 1.02 to 1.96) and increased diastolic blood pressure (HR 1.17; 95% CI 1.01 to 1.36 per 10 mmHg increase).

Finally, in ENGAGE AF,[26] there was statistically significantly lower rate of intracranial bleeding with high dose edoxaban (0.39% of patients per year, HR 0.47; 95% CI 0.34-0.63; p<0.001) and for lower dose edoxaban (0.26% of patients per year, HR 0.30; 95% CI 0.21-0.43; p<0.001) as compared to warfarin (0.85% patients per year).

There was evidence that apixaban (high SOE), edoxaban (moderate SOE), or rivaroxaban (high SOE) reduced risk of intracranial bleeding compared with warfarin. A meta-analysis of the three studies demonstrated a consistent reduction in intracranial bleeding (HR 0.45, 95% CI 0.27 to 0.75, I^2 = 71.1%, Q = 10.4, p=0.016) (Figure 30).

Figure 30. Forest plot for intracranial bleeding—Xa inhibitors (treatment) versus warfarin (control) (randomized controlled trials)



Abbreviation: CI=confidence interval

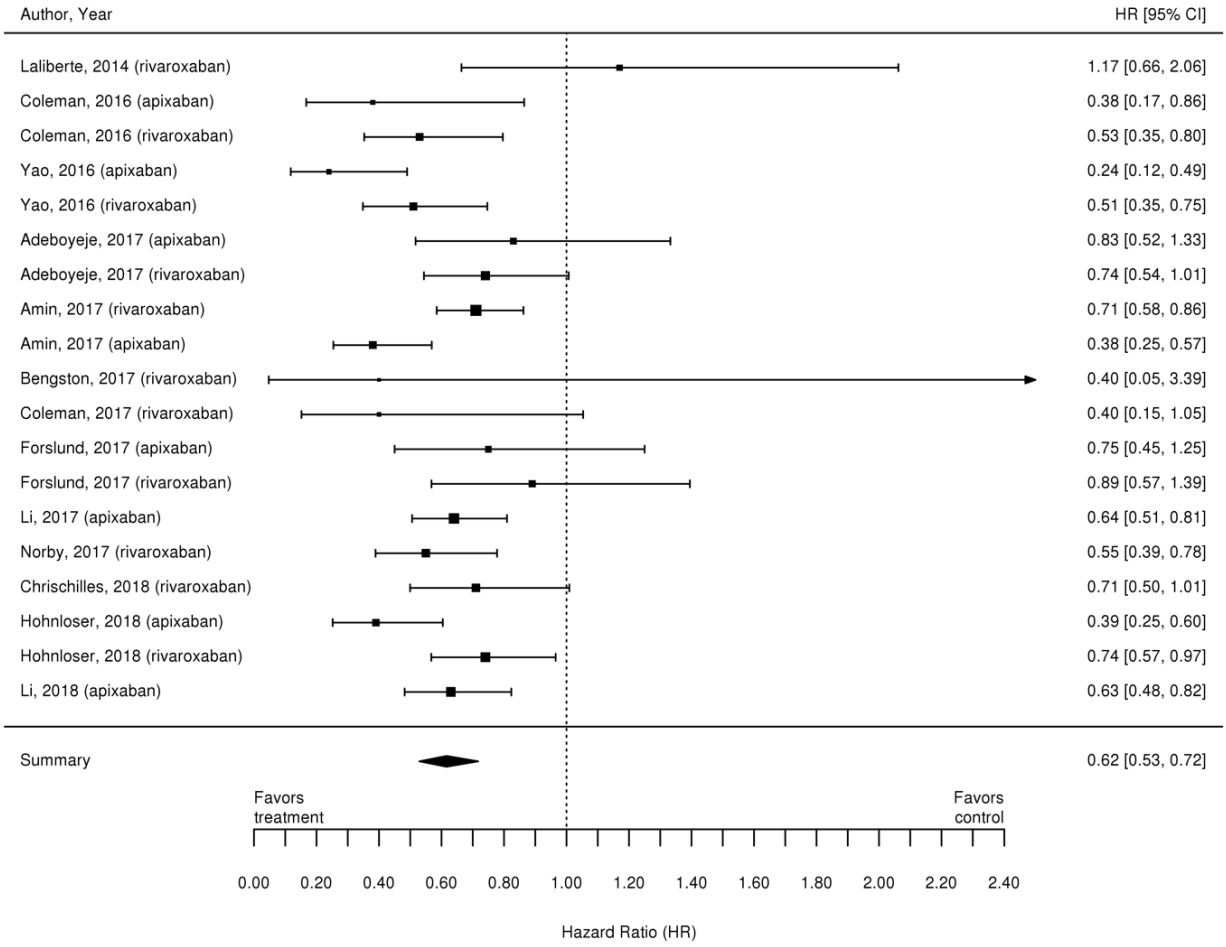
This outcome was also evaluated in 17 observational studies. Table 60 summarizes these findings. Consistent with the RCT evidence Figure 31 demonstrates that for Xa inhibitors there is a reduction in intracranial bleeding as compared to patients on warfarin (HR 0.62, 95% CI 0.53 to 0.72, I^2 = 49.3%, Q = 35.5, p=0.008). This finding was also confirmed for the individual Xa inhibitors (apixaban HR 0.53, 95% CI 0.38 to 0.73, I^2 = 61.8%, Q = 18.3, p=0.011, rivaroxaban HR 0.68, 95% 0.59 to 0.79, I^2 = 18.5%, Q = 12.3, p=0.27).

Table 60. Observational studies: intracranial bleeding—apixaban, rivaroxaban, or edoxaban versus warfarin

Database	Location	Direct Oral Anticoagulant	Risk Estimate (95% CI) DOAC vs. Warfarin
Analysis With Propensity-Matched Controls			
Truven MarketScan® Commercial Claims and Encounter and Medicare Supplemental and Coordination of Benefits Database ("MarketScan"), IMS PharMetrics Plus™ Database ("PharMetrics"), Optum Clinformatics™ Data Mart ("Optum"), and Humana Research Database ("Humana")[304]	US	Apixaban	0.64 (0.50 to 0.80)
OptumLabs Data Warehouse (OLDW)[370]	US	Apixaban	0.24 (0.12 to 0.50)
OptumLabs Data Warehouse (OLDW)[370]	US	Rivaroxaban	0.51 (0.35 to 0.75)
Truven MarketScan data[229]	US	Apixaban	0.38 (0.17 to 0.88)
Truven MarketScan data[229]	US	Rivaroxaban	0.53 (0.35 to 0.79)
Truven Health MarketScan1 Commercial Claims and Encounters Database and the Medicare Supplemental and Coordination of Benefits Database[218]	US	Rivaroxaban	0.40 (0.05 to 3.59)
Health data register of the Stockholm Region (Va˚rdanalysdatabasen, VAL)[258]	Europe	Apixaban	0.75 (0.45 to 1.25)
Health data register of the Stockholm Region (Va˚rdanalysdatabasen, VAL)[258]	Europe	Rivaroxaban	0.89 (0.57 to 1.40)
Symphony Health Solutions' (SHS) Patient Transactional Datasets[293]	US	Rivaroxaban	1.17 (0.66 to 2.05)
HealthCore Integrated Research Environment (HIRE)[387]	US	Apixaban	0.83 (0.52 to 1.34)
HealthCore Integrated Research Environment (HIRE)[387]	US	Rivaroxaban	0.74 (0.54 to 1.00)
Truven Health MarketScan® Commercial Claims and Encounters Database and the Medicare[382]	us	Rivaroxaban	adj HR (95% CI) of 0.55 (0.39 to 0.78)
Truven MarketScan® Commercial Claims and Encounter and Medicare Supplemental and Coordination of Benefits Database ("MarketScan")[392]	US	Rivaroxaban	0.40 (0.15 to 1.04)
US Center for Medicare and Medicaid Services (CMS) data[395]	US	Rivaroxaban	0.71 (0.59 to 0.87)
US Center for Medicare and Medicaid Services (CMS) data[395]	US	Apixaban	0.38 (0.25 to 0.56)
Aetna, Humana, Optum and HealthCore[396]	US	Rivaroxaban	0.71 (0.50 to 1.01)
German Applied Health Research Database[398]	Europe	Apixaban	0.39 (0.25 to 0.60)
German Applied Health Research Database[398]	Europe	Rivaroxaban	0.74 (0.57 to 0.97)
MarketScan, IMS PharMetrics Plus™ Database, Optum, Humana[400]	US	Apixaban	Standard dose: 0.63 (0.48 to 0.82) Reduced dose: 0.56 (0.36 to 0.88)
Analysis Without Propensity-Matched Controls			
VigiBase[324]	Europe	Rivaroxaban	1.65 (1.35 to 2.03)
Danish National Patient Registry[352]	Europe	Rivaroxaban	0.66 (0.45 to 0.98)
Danish National Patient Registry[352]	Europe	Apixaban	0.53 (0.34 to 0.83)
Norwegian Patient Registry[273]	Europe	Apixaban	0.56 (0.36 to 0.86)
Norwegian Patient Registry[273]	Europe	Rivaroxaban	0.93 (0.67 to 1.29)
Hernandez, 2017[384]	US	Apixaban	0.66 (0.39, 1.12)
Hernandez, 2017[384]	US	Rivaroxaban	0.49 (0.33, 0.72)

Abbreviations: CI=confidence interval; DOAC=direct oral anticoagulant

Figure 31. Forest plot for intracranial bleeding—apixaban, rivaroxaban, or edoxaban (treatment) versus warfarin (control) (observational)



Abbreviation: CI=confidence interval

Gastrointestinal Bleeding

One substudy[197] of the ROCKET AF RCT[24] evaluated gastrointestinal (GI) bleeding in patients randomized to treatment with daily rivaroxaban versus warfarin treatment. Overall, 684 patients (290, 42% warfarin; 394, 58% rivaroxaban) had a GI bleed during the time of followup. Patients with a GI bleed were younger (73 vs. 75) and more likely to have used a VKA previously (67% versus 62%). Patients treated with rivaroxaban were overall more likely to have GI bleed during followup (HR 1.42; 95% CI 1.22 to 1.66 p<0.0001). Those treated with rivaroxaban were also more likely to have major GI bleeding (HR 1.66; 95% CI 1.34 to 2.05; p<0.0001), a hemoglobin drop ≥ 2 g/dL (HR 1.69; 95% CI 1.35 to 2.12; p<0.0001) and to require transfusion (HR 1.56; 95% CI 1.20 to 2.02; p=0.0010).

Gastrointestinal bleeding was evaluated in 15 observational studies. Table 61 summarizes these findings. These studies did not demonstrate a difference in GI bleeding in patients on Xa inhibitors compared with warfarin (HR 0.94, 95% CI 0.78 to 1.12, I^2 = 94.2%, Q = 294.2, p<0.001 [Figure 32]). A reduction in GI bleeding was consistently shown for patients on apixapan (HR 0.67, 95% CI 0.56 to 0.79, I^2 = 59.4%, Q = 17.2, p=0.016 [Figure 33]). Consistent

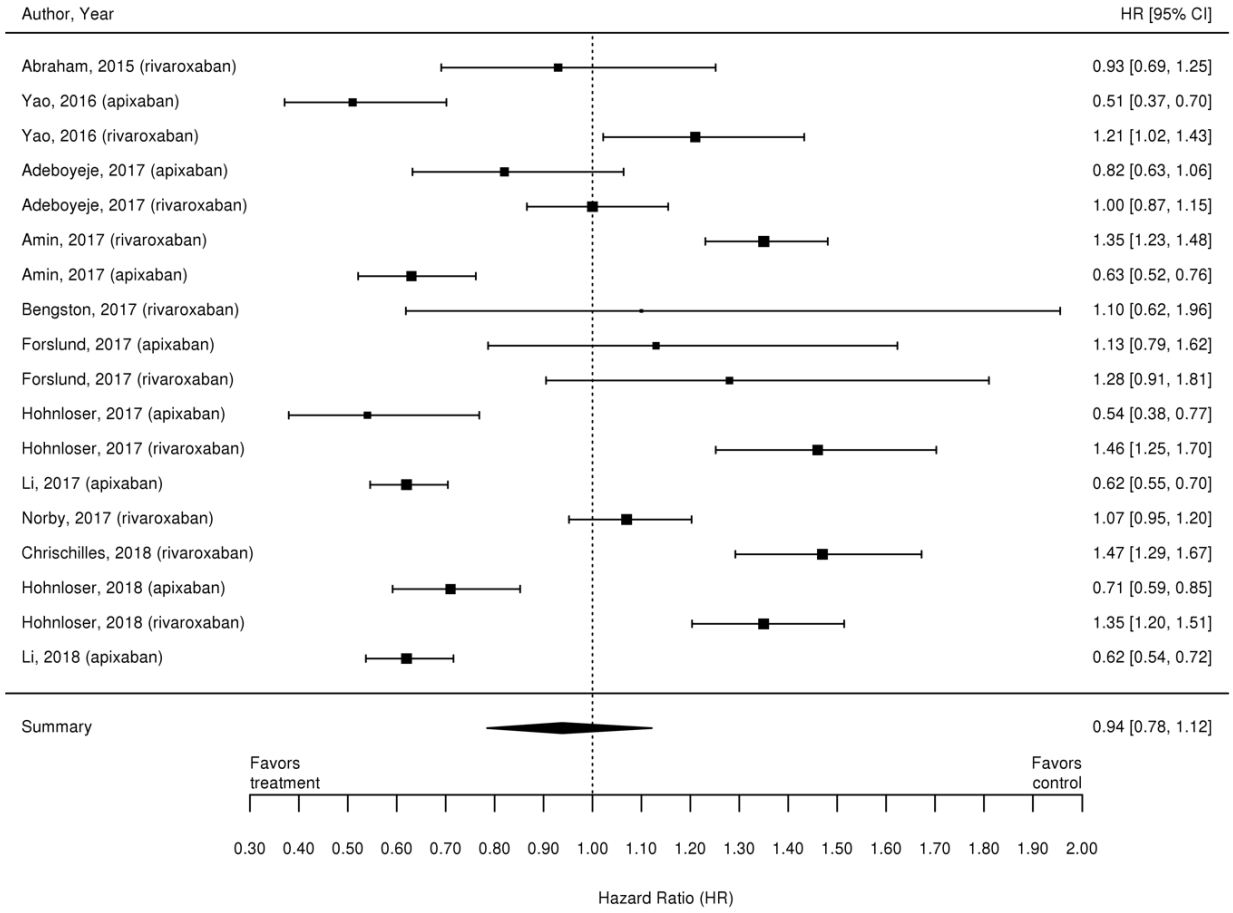
with RCT evidence, patients on rivaroxaban demonstrated an increase in GI bleeding (HR 1.23, 95% CI 1.10 to 1.38, I^2 = 73.9%, Q = 34.4, p<0.001 [Figure 34]).

Table 61. Observational studies: GI bleeding—apixaban, rivaroxaban, or edoxaban versus warfarin

Database	Location	Direct Oral Anticoagulant	Risk Estimate (95% CI) DOAC vs. Warfarin
Analysis With Propensity-Matched Controls			
Truven MarketScan® Commercial Claims and Encounter and Medicare Supplemental and Coordination of Benefits Database ("MarketScan"), IMS PharMetrics Plus™ Database ("PharMetrics"), Optum Clinformatics™ Data Mart ("Optum"), and Humana Research Database ("Humana")[304]	US	Apixaban	0.62 (0.55 to 0.71)
OptumLabs Data Warehouse (OLDW)[370]	US	Apixaban	0.51 (0.37 to 0.70)
OptumLabs Data Warehouse (OLDW)[370]	US	Rivaroxaban	1.21 (1.02 to 1.43)
Truven Health MarketScan1 Commercial Claims and Encounters Database and the Medicare Supplemental and Coordination of Benefits Database[218]	US	Rivaroxaban	1.10 (0.62 to 1.96)
Optum Labs Data Warehouse[207]	US	Rivaroxaban	0.93 (0.69 to 1.25)
Health data register of the Stockholm Region (Va˚rdanalysdatabasen, VAL)[258]	Europe	Apixaban	1.13 (0.79 to 1.63)
Health data register of the Stockholm Region (Va˚rdanalysdatabasen, VAL)[258]	Europe	Rivaroxaban	1.28 (0.90 to 1.80)
CARBOS study based on data from the Health Risk Institute (HRI)[287]	Europe	Apixaban	0.54 (0.38 to 0.77)
CARBOS study based on data from the Health Risk Institute (HRI)[287]	Europe	Rivaroxaban	1.46 (1.25 to 1.70)
US Center for Medicare and Medicaid Services (CMS) data[395]	US	Rivaroxaban	1.35 (1.23 to 1.48)
US Center for Medicare and Medicaid Services (CMS) data[395]	US	Apixaban	0.63 (0.52 to 0.76)
Aetna, Humana, Optum and HealthCore[396]	US	Rivaroxaban	1.47 (1.29 to 1.67)
German Applied Health Research Database[398]	Europe	Rivaroxaban	1.35 (1.20 to 1.51)
German Applied Health Research Database[398]	Europe	Apixaban	0.71 (0.59 to 0.85)
MarketScan, IMS PharMetrics Plus™ Database, Optum, Humana[400]	US	Apixaban	Standard dose: 0.62 (0.54 to 0.72) Reduced dose: 0.57 (0.44 to 0.75)
HealthCore Integrated Research Environment (HIRE)[387]	US	Apixaban	0.82 (0.63 to 1.06)
HealthCore Integrated Research Environment (HIRE)[387]	US	Rivaroxaban	1.00 (0.87 to 1.16)
Truven Health MarketScan® Commercial Claims and Encounters Database and the MedicareSupplemental and Coordination of Benefits Database[382]	US	Rivaroxaban	1.07 (0.95 to 1.20)
Analysis Without Propensity-Matched Controls			
VigiBase[324]	Europe	Rivaroxaban	1.38 (1.24 to 1.55)
VigiBase[324]	Europe	Apixaban	0.95 (0.65 to 1.39)
Norwegian Patient Registry[273]	Europe	Rivaroxaban	1.37 (1.12 to 1.69)
Norwegian Patient Registry[273]	Europe	Apixaban	0.77 (0.59 to 1.02)
Hernandez, 2017[384]	US	Apixaban	0.72 (0.57, 0.90)
Hernandez, 2017[384]	US	Rivaroxaban	1.35 (1.20, 1.52)

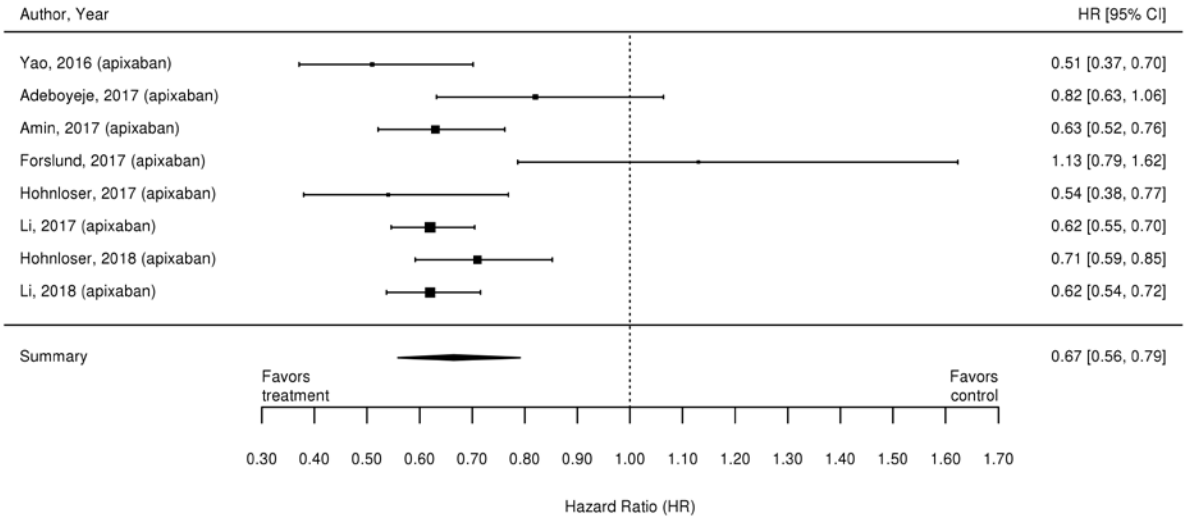
Abbreviations: CI=confidence interval; DOAC=direct oral anticoagulant

Figure 32. Forest plot for gastrointestinal bleeding—apixaban, rivaroxaban, or edoxaban (treatment) versus warfarin (control) (observational)



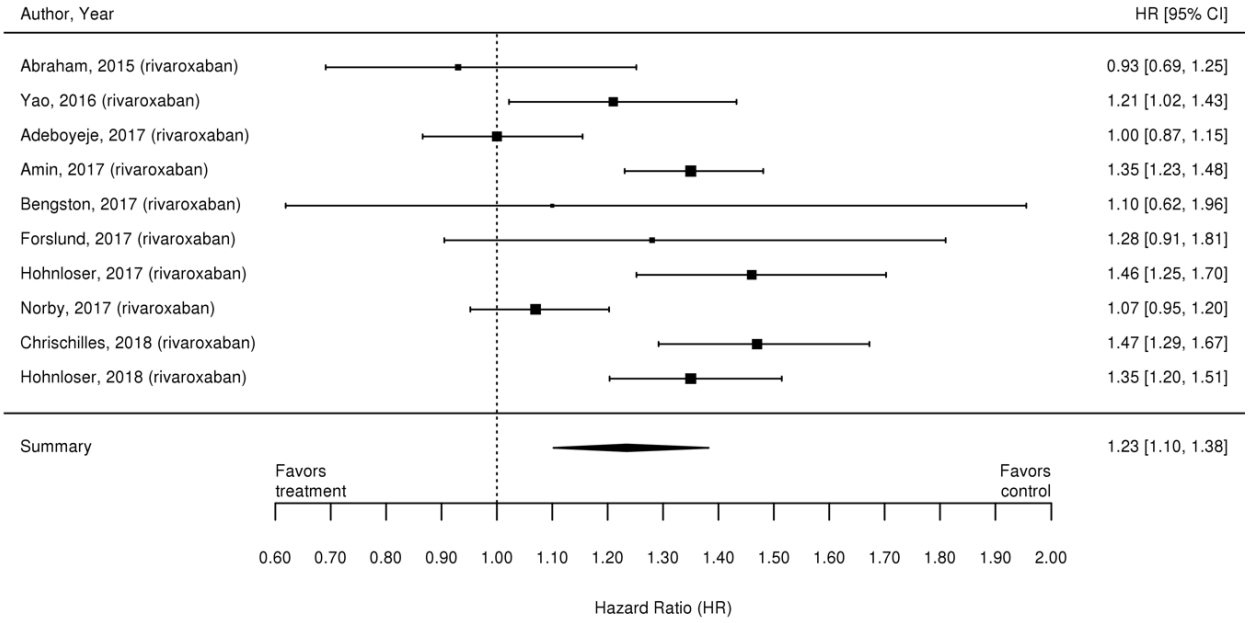
Abbreviation: CI=confidence interval

Figure 33. Forest plot for gastrointestinal bleeding—apixaban (treatment) versus warfarin (control) (observational)



Abbreviation: CI=confidence interval

Figure 34. Forest plot for gastrointestinal bleeding—rivaroxaban (treatment) versus warfarin (control) (observational)



Abbreviation: CI=confidence interval

Other Clinical Outcomes

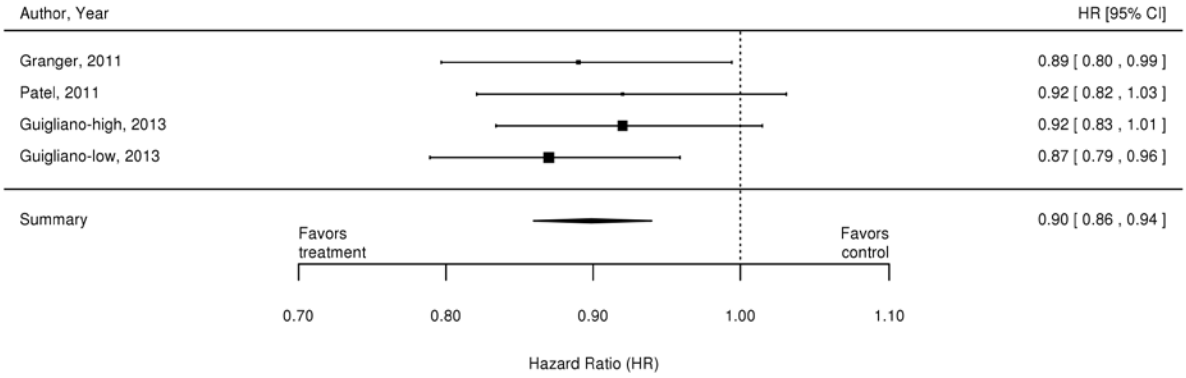
All-Cause Mortality

Four RCTs reported all-cause mortality. In one,[25] apixaban was associated with lower rates of death from any cause (3.52% per year for apixaban vs. 3.94% per year for warfarin; HR 0.89; 95% CI 0.80 to 0.998; p=0.047). In the other two studies, evaluating rivaroxaban and idraparinux, mortality rates were also similar between the Xa inhibitor and warfarin groups. Specifically, in one study,[24] in the ITT analysis, the rates of death from any cause were similar between groups and occurred in 4.5 percent and 4.9 percent per year in the rivaroxaban and warfarin groups, respectively (HR 0.92; 95% CI 0.82 to 1.03; p=0.15). This was similar to the prespecified per-protocol analysis (1.9% per year for rivaroxaban vs. 2.2% per year for warfarin; HR 0.85; 95% CI 0.70 to 1.02; p=0.07).

A subsequent substudy[338] of the ROCKET AF trial[24] evaluated predictors of all-cause mortality in patients treated with daily rivaroxaban versus warfarin. Compared to patients still alive at the end of followup, patients who died were older (76 vs. 72), more likely to have a history of heart failure (70.3% vs. 61.7%) or vascular disease (34.9% vs. 22.2%) and were more frequently male (661.% vs. 59.9%); p<0.0001 for all. There was no statistically significant difference in all-cause mortality between treatment groups (HR rivaroxaban 0.92; 95% CI 0.82 to 1.03; p=0.15).

There was low SOE that apixaban and low-dose edoxaban reduced risk of all-cause mortality, and moderate SOE that there was no evidence of a difference between rivaroxaban or high dose edoxaban and warfarin for this outcome. Across all Xa inhibitors there was a reduction in all-cause mortality as compared to warfarin (HR 0.90, 95% CI 0.86 to 0.94, I^2 = 0%, Q = 0.8, p=0.84) (Figure 35).

Figure 35. Forest plot for all-cause mortality—Xa inhibitors (treatment) versus warfarin (control) (randomized controlled trials)



Abbreviation: CI=confidence interval

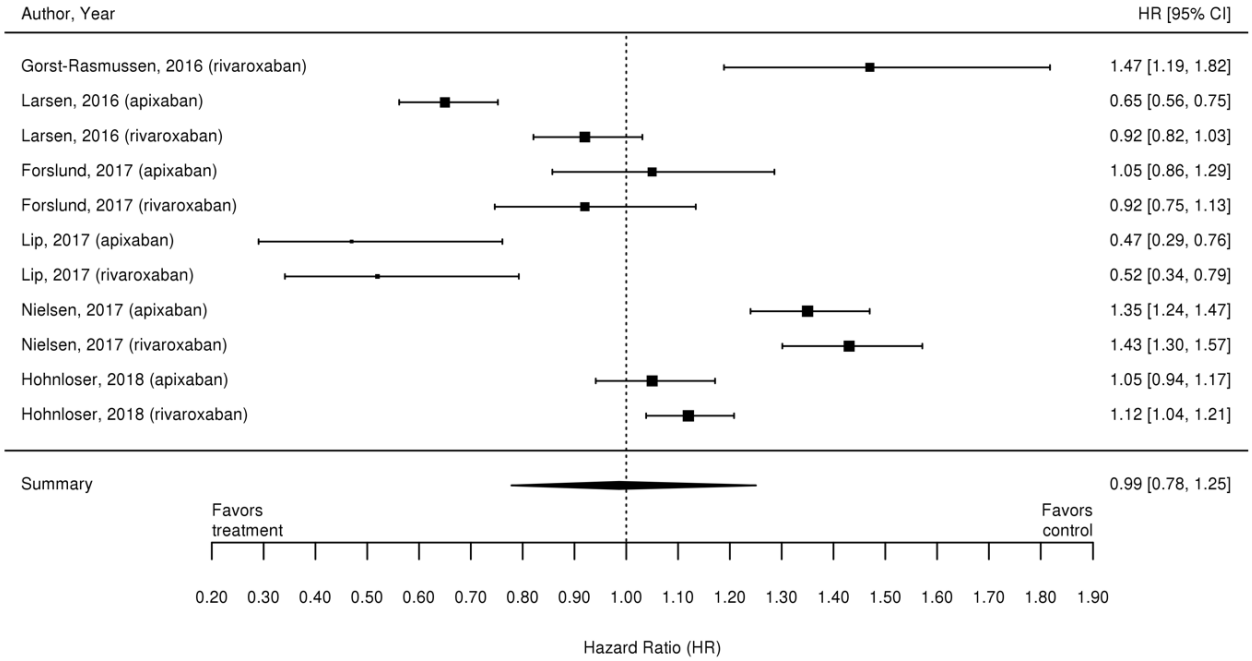
All-cause mortality was also evaluated in 6 observational studies. Table 62 summarizes these findings and Figure 36 shows the meta-analysis of these studies. Inconsistent with the RCT evidence, the observational studies did not show a reduction in all-cause mortality across Xa inhibitors (HR 0.99; 95% CI 0.78 to 1.25, I^2 = 93.1%, Q = 145.6, p<0.001), apixaban (HR 0.89; 95% CI 0.54 to 1.47, I^2 = 95.3%, Q = 84.6, p<0.001), or rivaroxaban (HR 1.06; 95% CI 0.74 to 1.51, I^2 = 91.5%, Q = 58.8, p<0.001). This inconsistent evidence lowered our SOE.

Table 62. Observational studies, all-cause mortality—apixaban, rivaroxaban, or edoxaban versus warfarin

Database	Location	Direct Oral Anticoagulant	Risk Estimate (95% CI) DOAC vs. Warfarin
Analysis With Propensity-Matched Controls			
Danish national prescription registry, Danish national patient register, Danish civil registration system[299]	Europe	Apixaban 5mg bid	0.65 (0.56 to 0.75)
Danish national prescription registry, Danish national patient register, Danish civil registration system[299]	Europe	Rivaroxaban 20mg once daily	0.92 (0.82 to 1.03)
Danish national prescription registry, Danish national patient register, Danish civil registration system[329]	Europe	Apixaban 2.5mg	1.35 (1.24 to 1.47)
Danish national prescription registry, Danish national patient register, Danish civil registration system[329]	Europe	Rivaroxaban 15mg	1.43 (1.30 to 1.57)
Danish national prescription registry, Danish national patient register, Danish civil registration system[267]	Europe	Rivaroxaban (15mg: R15; or 20mg: R20)	R15 vs. warfarin: 1.47 (1.19 to 1.82) R20 vs. warfarin 0.93 (0.75 to 1.16)
Observational cohort study of Danish citizens[311]	Europe	Apixaban 5mg bid	0.47 (0.29 to 0.76)
Observational cohort study of Danish citizens[311]	Europe	Rivaroxaban 20mg daily	0.52 (0.34 to 0.79)
Health data register of the Stockholm Region (Va˚rdanalysdatabasen, VAL)[258]	Europe	Apixaban	1.05 (0.86 to 1.29)
Health data register of the Stockholm Region (Va˚rdanalysdatabasen, VAL)[258]	Europe	Rivaroxaban	0.92 (0.75 to 1.14)
German Applied Health Research Database[398]	Europe	Apixaban	1.05 (0.94 to 1.17)
German Applied Health Research Database[398]	Europe	Rivaroxaban	1.12 (1.04 to 1.21)

Abbreviations: CI=confidence interval; DOAC=direct oral anticoagulant

Figure 36. Forest plot for all-cause mortality—apixaban, rivaroxaban, or edoxaban (treatment) versus warfarin (control) (observational)



Abbreviation: CI=confidence interval

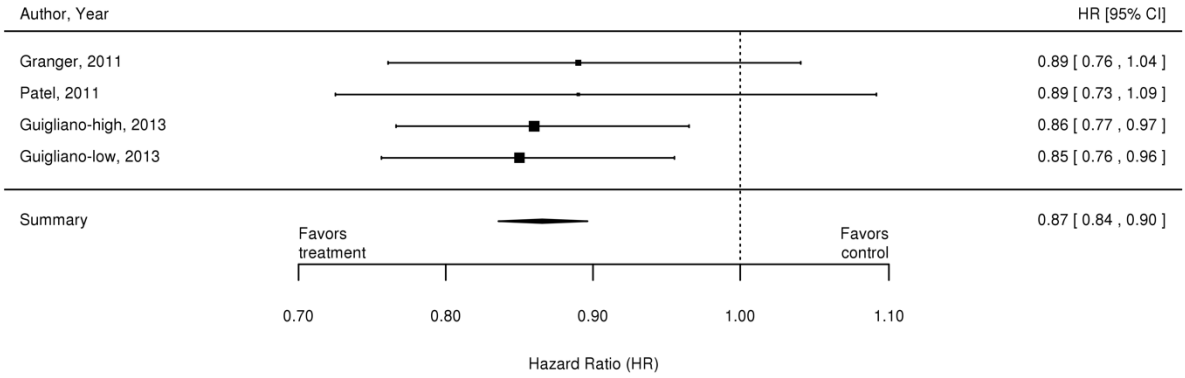
Death From Cardiovascular Causes

Four studies assessed death from cardiovascular causes.[24-26,366] Three studies showed similar rates of cardiovascular deaths across treatment arms (1.80% per year for apixaban vs. 2.02% per year for warfarin; HR 0.89; 95% CI 0.76 to 1.04;[25] and death from cardiovascular causes occurring in 0.9, 1.6, 0, 0, and 0.8 percent of patients in the edoxaban 30mg daily, 30mg twice daily, 60mg daily, 60mg twice daily, and warfarin treatment groups, respectively[366]). In the on-treatment population of the ROCKET trial, the event rate for vascular death was 1.53/100 patient-years among those on rivaroxaban compared with 1.71/100 patient-years for those on warfarin (HR 0.89; 95% CI 0.73 to 1.10; p=0.289). However, in the fourth study, ENGAGE AF,[26] there was a lower rate of death from cardiovascular causes in both the high dose edoxaban group (2.74 % patients per year, HR 0.86; 95% CI 0.77 to 0.97; p=0.013) and the low dose edoxaban group (2.71% patients per year, HR 0.85; 95% CI 0.76 to 0.96; p=0.008) than in the warfarin group (3.17% patients per year).

Finally, in ENGAGE AF,[26] there was no evidence of a difference in all-cause mortality with high-dose edoxaban (3.99% of patients per year, HR 0.92; 95% CI 0.83 to 1.01; p=0.08) as compared to warfarin (4.35% patients per year), but there was a lower rate in those who received low dose edoxaban (3.80% of patients per year, HR 0.87; 95% CI 0.79 to 0.96; p=0.006) as compared to warfarin.

There was moderate SOE of no evidence of a difference between treatment arms for apixaban and warfarin, and moderate SOE for of no evidence of a difference between treatment arms for rivaroxaban. There was also moderate SOE that there was a reduction in death from cardiovascular causes for edoxaban compared with warfarin (HR = 0.87, 95% CI 0.84 to 0.90, I^2 = 0%, Q = 0.3, p=0.96 Figure 37).

Figure 37. Forest plot for death from cardiovascular causes—Xa inhibitors (treatment) versus warfarin (control) (randomized controlled trials)



Abbreviation: CI=confidence interval

Myocardial Infarction

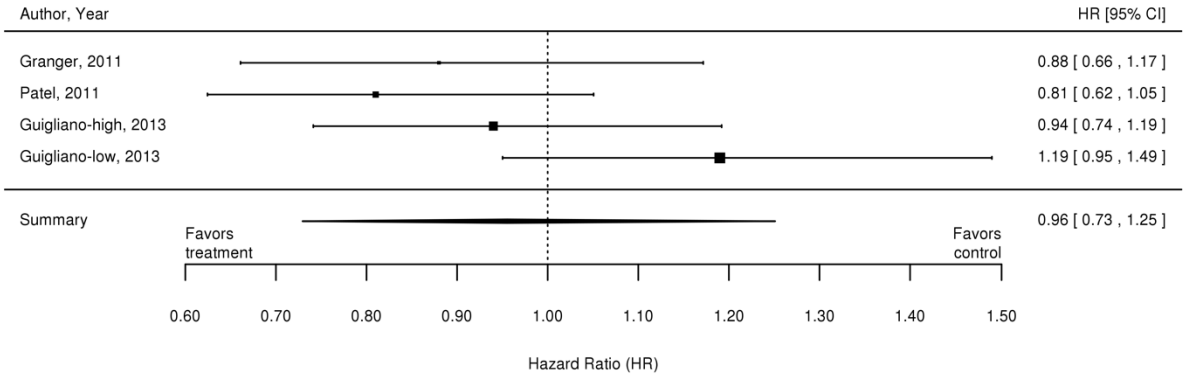
Five RCTs reported rates of MI across therapies. There were no statistically significant differences across treatment groups in any of the five studies. Specifically, in one study,[25] the rates of MI were lower in the apixaban group, but this difference was not statistically significant (0.53% per year for apixaban vs. 0.61% per year for warfarin; HR 0.88; 95% CI 0.66 to 1.17; p=0.37). In the second study,[366] MI occurred in 0.9, 0.4, 0.9, 0, and 0 percent of patients in the edoxaban 30mg daily, 30mg twice daily, 60mg daily, 60mg twice daily, and warfarin treatment groups, respectively. In the third study,[24] in the as-treated population, rates of MI were similar between groups (0.9% and 1.1% per year for rivaroxaban and warfarin, respectively; HR 0.81; 95% CI 0.63 to 1.06; p=0.12).

Next, a substudy[318] of the ROCKET AF RCT[24] evaluated ischemic cardiac outcomes in patients treated with daily rivaroxaban versus warfarin. Overall, 2468 (17.3%) of patients had a prior MI at baseline. While there was no statistically significant difference between groups in ischemic cardiovascular outcomes during followup, patients treated with rivaroxaban had trends toward lower rates of CV death/ MI/unstable angina (HR 0.86; 95% CI 0.73 to 1.00; p=0.051) and all-cause mortality (HR 0.85; 95% CI 0.70 to 1.02; p=0.074).

Finally, in ENGAGE AF,[26] there was no evidence of a difference with high dose edoxaban (0.70% of patients per year, HR 0.94; 95% CI 0.74 to 1.19; p=0.60) or low dose edoxaban (0.89% of patients per year, HR 1.19; 95% CI 0.95 to 1.49; p=0.13) as compared to warfarin (0.75% patients per year).

There was evidence that there was no evidence of a difference between apixaban (high SOE), edoxaban (moderate SOE), or rivaroxaban (high SOE) and warfarin in rates of MI. Across the Xa inhibitors there was no evidence of a difference in rates of MI as compared to warfarin (HR 0.96, 95% CI 0.73 to 1.25, I^2 = 45.6%, Q = 5.5, p=0.14 [Figure 38]).

Figure 38. Forest plot for myocardial infarction—Xa inhibitors (treatment) versus warfarin (control) (randomized controlled trials)



Abbreviation: CI=confidence interval

Myocardial infarction was also evaluated in 3 observational studies (Table 63). Given the heterogeneity between these findings they were not synthesized quantitatively although qualitatively they also support no evidence of a difference between Xa inhibitors and warfarin for the outcome of MI.

Table 63. Observational studies: myocardial infarction—apixaban, rivaroxaban, or edoxaban versus warfarin

Database	Location	Direct Oral Anticoagulant	Risk Estimate (95% CI) DOAC vs. Warfarin
Analysis With Propensity-Matched Controls			
Truven Health MarketScan1 Commercial Claims and Encounters Database and the Medicare Supplemental and Coordination of Benefits Database[218]	US	Rivaroxaban	1.44 (0.70 to 2.96)
German Primary Care Physician panel of a longitudinal electronic medical record database (IMS Disease Analyzer)[230]	Europe	Apixaban	0.33 (0.11 to 1.03)
French national health-insurance database (Système National d'Information Inter-Régimes de l'Assurance Maladie [SNIIRAM][112]	Europe	Rivaroxaban 10mg-15mg Rivaroxaban 20mg	0.76 (0.41 to 1.39) Rivaroxaban 10mg-15mg: 1.24 (0.41 to 3.75) Rivaroxaban 20mg: 0.62 (0.29 to 1.30)

Abbreviations: CI=confidence interval; DOAC=direct oral anticoagulant

Hospitalization/Health Care Utilization

One RCT[366] assessed hospitalization rates and found these to be similar between treatment arms: 0.9, 0.8, 3.0, 0, and 0.4 percent of patients in the edoxaban 30mg daily, 30mg twice daily, 60mg daily, 60mg twice daily, and warfarin treatment groups, respectively**.**

A secondary analysis[236] of the ARISTOTLE RCT[25] evaluated hospitalization in patients treated with 5mg twice daily of apixaban compared with warfarin. There was no statistically significant difference in number of admissions between the apixaban and warfarin treatment arms (26.6% versus 28.1%; p=0.31).

A substudy[240] of the ROCKET AF[24] RCT evaluated hospitalizations in patients randomized to treatment with daily rivaroxaban versus warfarin. During followup, 1925 (14%) of patients had at least one hospitalization. The comorbidities of chronic lung disease (HR 1.46; 95% CI

1.29 to 1.66), diabetes (HR 1.22; 95% CI 1.11 to 1.34), prior myocardial infarction (HR 1.27; CI 1.13 to 1.42) and impaired renal function (HR 1.07 per 5 unit decrease in CrCl below 65 mL/min; 95% CI 1.04 to 1.10) were independently associated with increased risk of hospitalization. There was no statistically significant difference between treatment groups with regard to rates of hospitalization during followup (p=0.45).

One observational study of the Humana database compared measures of healthcare utilization for users of rivaroxaban and warfarin.[294] This study, using propensity-matching, found that, compared to warfarin, users of rivaroxaban tended to have lower healthcare utilization measures. Over the observation period of approximately 4 months, compared to warfarin, users of rivaroxaban had significantly fewer all-cause hospitalization days, difference (95% CI) of -1.16 (-2.15 to -0.08); and fewer hospitalization days related to AF -0.91 (-1.72 to -0.13).[294] Additionally, compared to warfarin, users of rivaroxaban had significantly fewer all-cause outpatient visits, -10.53 (-13.59 to -7.25); p<0.001; and significantly fewer hospitalizations related to AF -0.17 (-0.34 to -0.03); p=0.022, and significantly fewer outpatient visits related to AF -3.59 (-5.15 to -1.98); p<0.001.[294] However, compared to warfarin, users of rivaroxaban had significantly more ED visits related to AF +0.23 (0.05 to 0.43); but no statistically significant difference with regard to all-cause ED visits +0.19 (-0.04 to 0.45); p=0.114; or all-cause hospitalizations -0.18 (-0.40 to 0.03); p=0.084.[294]

A propensity-matched observational study using a U.S. claims database[305] showed a higher risk for all-cause hospitalization for those treated with warfarin vs. apixaban (HR 2.22, 95% CI 1.9 to 2.5, P<0.001). Hospital length of stay was significantly less for those treated with apixaban (mean (SD) 0.2 (1.6) days per patient per month vs. 0.5 (2.9) days per patient per month; p<0.05). Apixaban treatment was also associated with lower mean number of outpatient claims for all causes compared to warfarin (mean (SD) 2.5 (2.7) vs. 3.8 (3.7) per patient per month; p<0.05).

Another study of the Humana database compared measures of healthcare utilization for users of apixaban and warfarin.[379]This study demonstrated statistically significant lower healthcare utilization and costs during the followup period for users of apixaban compared with warfarin. Compared to warfarin, users of apixaban had lower inpatient hospitalizations, smaller inpatient lengths of stay, and lower total inpatient costs.

An analysis of the OptumInsight Research Database of Medicare beneficiaries evaluated rates of all-cause hospitalization for patients with NVAF taking warfarin versusapixaban; and, compared to apixaban, found a statistically significant higher risk of hospitalization with warfarin, adj HR (95% CI) 1.30 (1.21 to 1.40), p<0.001.[380] Additionally this study found a higher risk of hospitalization due to stroke/systemic embolism in users of warfarin, adj HR (95% CI) 1.60 (1.23 to 2.07); as well as higher risk of hospitalization for major bleeding for those taking warfarin with an adj HR (95% CI) 1.95 (1.60 to 2.39). There were no statistically significant differences in costs related to stroke/systemic embolism between the 2 groups; but there was a statistically significant lower cost associated with major bleeding for those taking apixaban compared to warfarin, p=0.002.

Adverse Events

Studies evaluating apixaban, edoxaban, and rivaroxaban specifically looked at adverse events.[25,366] In one,[25] adverse events occurred in almost equal proportions of patients in the apixaban group and the warfarin group (81.5% and 83.1%, respectively). The rates of abnormalities on liver function testing and liver-related serious adverse events were also similar

in the two groups. In another study,[366] there were 11.1, 13.5, 11.5, 22.2, and 18.4 percent drug-related treatment-emergent adverse events in the edoxaban 30mg daily, 30mg twice daily, 60mg daily, 60mg twice daily, and warfarin treatment groups, respectively. Of these, the percentage of subjects with serious treatment-emergent adverse events was similar in the edoxaban (5.9%) and warfarin (4.4%) treatment groups. There were no evidence of differences in the incidence of abnormal hepatic function tests across treatment groups. There was moderate SOE that there was no evidence of a difference between apixaban and warfarin for adverse events.

Medication Adherence

Eight observational studies evaluated medication persistence or discontinuation (Table 64). These studies consistently demonstrated better adherence with rivaroxaban as compared to warfarin (HR 0.63; 95% CI 0.59 to 0.67, I^2 = 0%, Q = 1.5, p=0.47).

Table 64. Observational studies: medication non-persistence—apixaban, rivaroxaban, or edoxaban versus warfarin

Database	Location	Direct Oral Anticoagulant	Risk Estimate (95% CI) DOAC vs. Warfarin
Analysis With Propensity-Matched Controls			
Truven Health MarketScan Research Databases: the Commercial Claims and Encounters (Commercial) Database and the Medicare Supplemental and Coordination of Benefits (Medicare) Database[327]	US	Rivaroxaban	0.63 (0.59 to 0.68)
Truven Health MarketScan databases: the Commercial Claims and Encounters and the Medicare Supplemental and Coordination of Benefits databases[228]	US	Rivaroxaban	0.62 (0.59 to 0.64)
Symphony Health Solutions' (SHS) Patient Transactional Datasets[293]	US	Rivaroxaban	0.66 (0.60 to 0.72)
Analysis Without Propensity-Matched Controls			
Beyer-Westendorf 2016[220]	Europe	Rivaroxaban	Higher medication persistence at both 180 and 360 days
Danish National Patient Registry[295]	Europe	Apixaban	1.22 (1.12 to 1.33)
Clinical Practice Research Datalink[292]	Europe	Apixaban	0.92 (0.68 to 1.23)
Stockholm Health Claims Database[257]	Europe	Apixaban	0.88 (0.62 to 1.25)
Stockholm Health Claims Database[257]	Europe	Rivaroxaban	1.50 (1.24 to 1.81)
French primary care data (IMS Longitudinal Patient Database)[397]	Europe	Rivaroxaban	1.28 (1.13 to 1.45)
French primary care data (IMS Longitudinal Patient Database)[397]	Europe	Apixaban	1.12 (0.96 to 1.32)

Abbreviations: CI=confidence interval; DOAC=direct oral anticoagulant

Strength of Evidence

Table 65 summarizes the SOE for outcomes of interest for these comparisons.

Table 65. Strength of evidence—factor Xa inhibitors versus warfarin

Outcome	Number of Studies (Subjects)	Risk of Bias	Consistency	Directness	Precision	Reporting Bias	SOE and Effect (95% CI)
Xa Inhibitor (Apixaban) vs. Warfarin							
Stroke or systemic embolism	1 RCT[25] (18,201) 9 Obs[299,304,311,329,352,370,395,398,400] (652,156)	Low	Consistent	Direct	Precise	None	**SOE=High** Apixaban reduced risk (HR 0.79; 95% CI 0.66 to 0.95)
Ischemic/ Uncertain stroke	1 RCT[25] (18,201) 8 Obs[230,299,304,311,329,352,370,398] (407,778)	Low	Consistent	Direct	Precise	None	**SOE=High** No evidence of a difference (HR 0.92; 95% CI 0.74 to 1.13)
Hemorrhagic stroke	1 RCT[25] (18,201) 6 Obs[258,304,370,395,398,400] (499,683)	Low	Consistent	Direct	Precise	None	**SOE=High** Apixaban reduced risk (HR 0.51; 95% CI 0.35 to 0.75)
Systemic embolism	1 RCT[25] (18,201) 1 Obs[304] (76,940)	Low	Consistent	Direct	Imprecise	None	**SOE= Moderate** No evidence of a difference (HR 0.87; 95% CI 0.44 to 1.75)

Outcome	Number of Studies (Subjects)	Risk of Bias	Consistency	Directness	Precision	Reporting Bias	SOE and Effect (95% CI)
Major bleeding	1 RCT[25] (18,201) 13 Obs[273,287,304,305,309,310,370,387,392,395,398,400,402] (713,345)	Low	Consistent	Direct	Precise	None	**SOE=High** Apixaban reduced risk (HR 0.69; 95% CI 0.60 to 0.80)
Intracranial bleeding	1 RCT[25] (18,201) 11 Obs[229,258,273,304,352,370,384,387,396,398,400] (636,093)	Low	Consistent	Direct	Precise	None	**SOE=High** Apixaban reduced risk (HR 0.42; 95% CI 0.30 to 0.58)
GI bleeding	11 Obs[258,273,287,304,324,370,384,387,395,398,400] (686,396)	Low	Consistent	Direct	Precise	None	**SOE=Low** Reduction in GI bleeding with apixaban (HR 0.67, 95% CI 0.56 to 0.79)
All-cause mortality	1 RCT[25] (18,201) 5 Obs[258,299,311,329,398] (214,745)	Low	Inconsistent	Direct	Precise	None	**SOE=Low** Apixaban reduced risk (HR 0.89; 95% CI 0.80 to 0.998), SOE was reduced given inconsistency with findings from observational studies
Death from cardiovascular causes	1 RCT[25] (18,201)	Low	NA	Direct	Precise	None	**SOE=Moderate** No evidence of a difference (HR 0.89; 95% CI 0.76 to 1.04)
Myocardial infarction	1 RCT[25] (18,201) 1 Obs[230] (1,670)	Low	Consistent	Direct	Precise	None	**SOE=High** No evidence of a difference (HR 0.88; 95% CI 0.66 to 1.17)

Outcome	Number of Studies (Subjects)	Risk of Bias	Consistency	Directness	Precision	Reporting Bias	SOE and Effect (95% CI)
Adverse events	1 RCT[25] (18,201)	Low	NA	Direct	Imprecise	None	**SOE= Moderate** Adverse events occurred in almost equal proportions of patients in the apixaban and the warfarin therapy arms
Xa Inhibitor (Rivaroxaban) vs. Warfarin							
Stroke or systemic embolism	1 RCT[24] (14,264) 10 Obs[112,267,293,299,311,329,352,370,395,398] (556,370)	Low	Inconsistent	Direct	Precise	None	**SOE= Low** No evidence of a difference (HR 0.88; 95% CI 0.74 to 1.03)
Ischemic/ Uncertain stroke	1 RCT[24] (14,264) 8 Obs[218,229,299,329,352,365,370,398] (484,891)	Low	Consistent	Direct	Precise	None	**SOE= Moderate** No evidence of a difference in on-treatment analyses (HR 0.94; 95% CI 0.75 to 1.17), SOE was reduced since analysis was on-treatment rather than ITT

Outcome	Number of Studies (Subjects)	Risk of Bias	Consistency	Directness	Precision	Reporting Bias	SOE and Effect (95% CI)
Hemorrhagic stroke	1 RCT[24] (14,264) 5 Obs[258,293,370,395,398] (364,159)	Low	Inconsistent	Direct	Imprecise	None	**SOE=Low** In on-treatment analyses, one large RCT demonstrated benefit of rivaroxaban (HR 0.59; 95% CI 0.37 to 0.93); a smaller study showed a trend toward no difference (HR 0.73; 95% CI 0.16 to 3.25)
Systemic embolism	1 RCT[24] (14,264) 1 Obs[395] (186,132)	Low	NA	Direct	Precise	None	**SOE= Moderate** Rivaroxaban reduced risk in on-treatment analyses (HR 0.23; 95% CI 0.09 to 0.61). SOE was reduced since on treatment analysis rather than ITT
Major bleeding	1 RCT[24] (14,264) 11 Obs[273,287,293,310,365,370,387,392,395,398,402] (529,053)	Low	Inconsistent	Direct	Precise	None	**SOE= Low** No evidence of a difference in RCT (HR 1.04, 95% CI 0.90 to 1.20). Observational studies support a trend towards a small increase (HR 1.09, 95% CI 1.03 to 1.16)

Outcome	Number of Studies (Subjects)	Risk of Bias	Consistency	Directness	Precision	Reporting Bias	SOE and Effect (95% CI)
Intracranial bleeding	1 RCT[24] (14,264) 15 Obs[218,229,258,273,293,324,352,370,382,384,387,392,395,396,398] (897,011)	Low	Consistent	Direct	Precise	None	**SOE= High** Rivaroxaban reduced risk in on-treatment analyses (HR 0.67; 95% CI 0.47 to 0.93)
GI bleeding	1 RCT[24] (14,264) 14 Obs[207,218,258,273,287,304,324,370,382,384,387,395,396,398] (1,145,385)	Low	Inconsistent	Direct	Imprecise	None	**SOE=Low** Increased GI bleeding with rivaroxaban compared with warfarin (HR 1.42; 95% CI 1.22 to 1.66)
All-cause mortality	1 RCT[24] (14,264) 6 Obs[258,267,299,311,329,398] (237,103)	Low	Consistent	Direct	Precise	None	**SOE= Moderate** No evidence of a difference (HR 0.92; 95% CI 0.82 to 1.03)
Death from cardiovascular causes	1 RCT[24] (14,264)	Low	NA	Direct	Precise	None	**SOE= Moderate** No evidence of a difference in on-treatment analyses (HR 0.89; 95% CI 0.73 to 1.10)
Myocardial infarction	1 RCT[24] (14,264) 2 Obs[112,218] (169,377)	Low	Consistent	Direct	Precise	None	**SOE=High** No evidence of a difference in on-treatment analyses (HR 0.81; 95% CI 0.63 to 1.06)
Medication adherence	3 Obs[228,293,327] (65,422)	Low	Consistent	Direct	Precise	None	**SOE=Moderate** Better adherence with rivaroxaban compared with warfarin (HR 0.63; 95% CI 0.59 to 0.67)

Outcome	Number of Studies (Subjects)	Risk of Bias	Consistency	Directness	Precision	Reporting Bias	SOE and Effect (95% CI)
Xa Inhibitor (Edoxaban) vs. Warfarin							
Stroke or systemic embolism	1 RCT[26] (21,105)	Low	NA	Direct	Precise	None	**SOE= Moderate** No evidence of a difference for either dose (low dose HR 1.13, 95% CI 0.96 to 1.34; high dose HR 0.87 95% CI 0.73 to 1.04)
Ischemic stroke	1 RCT[26] (21,105)	Low	NA	Direct	Precise	None	**SOE= Moderate** No evidence of a difference for high dose, increase for low dose (low dose HR 1.41, 95% CI 1.19 to 1.67; high dose HR 1.00 95% CI 0.83 to 1.19)
Hemorrhagic stroke	1 RCT[26] (21,105)	Low	NA	Direct	Precise	None	**SOE=Moderate** Reduction in risk with either dose (low dose HR 0.33, 95% CI 0.22 to 0.50; high dose HR 0.54 95% CI 0.38 to 0.77)
Systemic embolism	1 RCT[26] (21,105)	Low	NA	Direct	Imprecise	None	**SOE= Moderate** No evidence of a difference either dose

Outcome	Number of Studies (Subjects)	Risk of Bias	Consistency	Directness	Precision	Reporting Bias	SOE and Effect (95% CI)
Major bleeding	1 RCT[26] (21,105)	Low	NA	Direct	Precise	None	**SOE=Moderate** Lower bleeding on either dose (low dose HR 0.47, 95% CI 0.41 to 0.55; high dose HR 0.80 95% CI 0.71 to 0.91)
Intracranial bleeding	1 RCT[26] (21,105)	Low	NA	Direct	Precise	None	**SOE=Moderate** Lower intracranial bleeding with either dose (low dose HR 0.30, 95% CI 0.21 to 0.43; high dose HR 0.47 95% CI 0.34 to 0.63)
All-cause mortality	1 RCT[26] (21,105)	Low	NA	Direct	Precise	None	**SOE=Low** Reduction in risk for low dose (HR 0.87, 95% CI 0.79 to 0.96) **SOE= Moderate** No evidence of a difference in risk for high dose (HR 0.92, 95% CI 0.83 to 1.01)
Death from cardiovascular causes	1 RCT[26] (21,105)	Low	NA	Direct	Precise	None	**SOE=Moderate** Reduction in risk for either dose (low dose HR 0.85, 95% CI 0.76 to 0.96; high dose HR 0.86 95% CI 0.77 to 0.97)

Outcome	Number of Studies (Subjects)	Risk of Bias	Consistency	Directness	Precision	Reporting Bias	SOE and Effect (95% CI)
Myocardial infarction	1 RCT[26] (21,105)	Low	NA	Direct	Precise	None	**SOE=Moderate** No evidence of a difference in risk for either dose (low dose HR 1.19, 95% CI 0.95 to 1.49; high dose HR 0.94 95% CI 0.74 to 1.19)

Abbreviations: CI=confidence interval; HR=hazard ratio; NA=not applicable; Obs=observational; RCT=randomized controlled trial; SOE=strength of evidence

12. Factor Xa Inhibitors (Idraparinux) Versus Warfarin

One good-quality RCT (AMADAEUS) involving 4,576 patients comparing idraparinux with warfarin[113] Note that this agent is not currently approved by the FDA for use within the US.

Although each of these RCTs compared an Xa inhibitor with warfarin, they differed in significant ways. Specifically, the ROCKET AF, ENGAGE AF, and ARISTOTLE studies were Phase III trials of oral anticoagulants. In the AMADAEUS trial, treatment was given subcutaneously and once a week, having a very different pharmacokinetics and pharmacodynamics profile from the other direct oral anticoagulants previously discussed.

In this study, idraparinux was noninferior to warfarin in preventing stroke and systemic embolism (0.9% and 1.3% in the idraparinux and warfarin groups, respectively; HR 0.71; 95% CI 0.39 to 1.30; p=0.007 for noninferiority in the ITT population). Idraparinux was also noninferior to warfarin in the per-protocol analysis (HR 0.74; 95% CI 0.38 to 1.43; p=0.018 for noninferiority). Hemorrhagic stroke occurred in 0.2 percent of patients in both the idraparinux and warfarin groups.

Rates of major bleeding in the ITT population were significantly higher in the idraparinux group when compared with warfarin (3.9% vs. 1.4%). Fatal bleeding was also more frequent with idraparinux (0.7% vs. <0.1%). Major bleeding other than intracranial hemorrhage occurred in 2.8 percent of patient-years in the idraparinux group and in 0.9 percent patient-years in the warfarin group. A separate post hoc analysis of this study showed that patients receiving combination antithrombotic therapy had a 2.5 fold increase risk of major bleeding events compared with those receiving anticoagulation therapy only.[296] There was no evidence of a difference in mortality between treatment groups in the ITT population (3.2% per year in the idraparinux group vs. 2.9% per year in the warfarin group; p=0.49). The rates of MI were similar between groups (0.8% for idraparinux vs. 0.6% for warfarin).

13. Factor Xa Inhibitors (Apixaban, Rivaroxaban, or Edoxaban) Versus Dabigatran

Twenty-three observational studies evaluated Xa inhibitors compared with dabigatran.[208,220,226,228,239,257,267,269,292,295,305,309,310,330,382-387,389,402,406]

Thromboembolic Outcomes

Stroke or Systemic Embolism

A propensity-matched cohort study using a U.S. claims database[330] compared dabigatran to rivaroxaban and apixaban and found no evidence of a difference in the risk of stroke or systemic embolism (HR 1.00; 95% CI 0.75 to 1.32; p=0.99 for rivaroxaban vs. dabigatran; HR 0.82; 95% CI 0.51 to 1.31; p=0.41 for apixaban vs. dabigatran).

A propensity-matched cohort using the Danish Patient Registry examined the composite outcome of ischemic stroke/systemic embolism/transient ischemic attack (stroke/SE/TIA) of low dose rivaroxaban 15mg daily versus low dose dabigatran 110mg daily as well as full dose rivaroxaban 20mg daily versus full dose dabigatran 150mg daily.[267] For both comparisons, there was no statistically significant difference in outcome. For low-dose rivaroxaban 15mg daily versus low dose dabigatran 110mg daily, the adj HR (95% CI) of stroke/SE/TIA was 0.78 (0.51 to 1.19); for full dose rivaroxaban 20mg daily versus full dose dabigatran 150mg daily, the adj HR (95% CI) was 0.84 (0.59 to 1.20).[267]

A study of the Danish Patient Registry which did not use propensity matching evaluated risk of stroke/thromboembolism between apixaban versus dabigatran and rivaroxaban versus dabigatran at full doses and reduced doses.[385] This study found no statistically significant difference in risk for either comparison at full or reduced doses.

Ischemic Stroke, Systemic Embolism, or Death

One study (without propensity matching) examined a sample of the Medicare database and compared the composite outcome of ischemic stroke, systemic embolism, or death in users of apixaban versus dabigatran.[384] This study found no statistically significant difference in risk of this composite outcome among apixaban users compared with dabigatran with an adj HR (95% CI) of 1.18 (0.97 to 1.43). This same study also examined a sample of the Medicare database and compared the composite outcome of ischemic stroke, systemic embolism, or death in users of dabigatran versus rivaroxaban. This study also found no statistically significant difference in risk of this composite outcome among dabigatran users compared with rivaroxaban with an adj HR (95% CI) of 0.90 (0.76 to 1).[384]

Thromboembolic Stroke

One prospective cohort study using Medicare claims data for adults ≥65 years of age and using dabigatran versus rivaroxaban for nonvalvular AF.[269] Compared to dabigatran, rivaroxaban was associated with a trend towards a lower risk of thromboembolic stroke (adj HR 0.81; 95% CI 0.65 to 1.01; p=0.070).

Ischemic Stroke

A propensity-matched cohort study using a U.S. claims database[330] compared dabigatran to rivaroxaban and apixaban and found no evidence of a difference in the risk of ischemic stroke (HR 0.91; 95% CI 0.66 to 1.27; p=0.58 for rivaroxaban vs. dabigatran; HR 0.93; 95% CI 0.55 to 1.57; p=0.79 for apixaban vs. dabigatran).

A study of the Truven Health MarketScan® Commercial Claims and Encounters Database and the Medicare compared risk of ischemic stroke among new users of rivaroxaban versus dabigatran using propensity matching.[382] After a mean followup of 12 months, compared to

dabigatran, users of rivaroxaban had a lower risk of ischemic stroke which was not statistically significant with an adj HR (95% CI) 0.77 (0.58, 1.03), p=0.08.

A study of the Danish Patient Registry (without propensity matching) evaluated risk of ischemic stroke between apixaban versus dabigatran and rivaroxaban versus dabigatran at full doses and reduced doses.[385] This study found no statistically significant difference in risk for either comparison at full or reduced doses.

A U.S. propensity-matched study using MarketScan examined risk of ischemic stroke between dabigatran and rivaroxaban in patients with nonvalvular AF and active cancer.[402] An increased risk of ischemic stroke was seen with dabigatran compared to rivaroxaban (adj HR 7.61, 95% CI 1.52 to 38.12).

Myocardial Infarction

A study of the Truven Health MarketScan® Commercial Claims and Encounters Database and the Medicare compared risk of myocardial infarction (MI) among new users of rivaroxaban versus dabigatran using propensity matching.[382] After a mean followup of 12 months, there was no statistically significant difference in risk of MI; rivaroxaban versus dabigatran adj HR (95% CI) 1.11 (0.87 to 1.41).

Bleeding Outcomes

Hemorrhagic Stroke

A propensity-matched cohort study using a U.S. claims database[330] compared dabigatran to rivaroxaban and apixaban and found no statistically significant difference in risk of hemorrhagic stroke (HR1.70; 95% CI 0.84 to 3.43; p=0.14 for rivaroxaban vs. dabigatran; HR 0.72; 95% CI 0.18 to 2.86; p=0.64 for apixaban vs. dabigatran).

Intracranial Hemorrhage

Intracranial hemorrhage was evaluated in 5 observational studies. Table 66 summarizes these findings and Figure 39 shows the meta-analysis of the studies which used propensity-matched controls. The observational studies demonstrated an increased risk of intracranial hemorrhage with Xa inhibitors as compared to dabigatran (HR 1.63, 95% CI 1.14 to 2.34, I^2 = 8.3%, Q = 4.4, p=0.36). This finding was also found in the three studies which targeted rivaroxaban versus dabigatran (HR 1.75, 95% CI 1.34 to 2.28, I^2 = 0%, Q = 0.4, p=0.82) (SOE low).

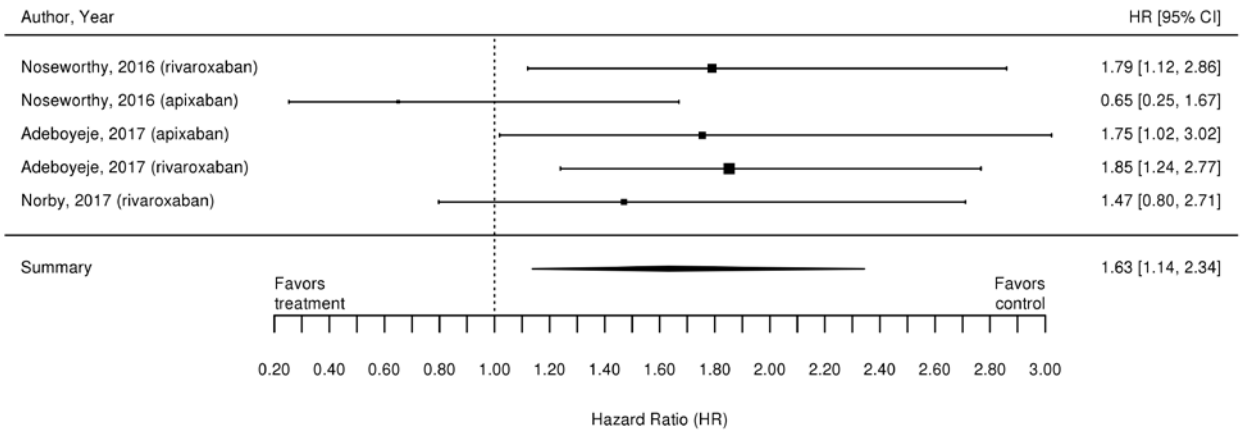
Table 66. Observational studies: intracranial hemorrhage—apixaban, rivaroxaban, or edoxaban versus dabigatran

Database	Intervention	Comparator	Risk Estimate (95% CI) DOAC vs. Dabigatran
Analysis With Propensity-Matched Controls			
Optum Labs Data Warehouse[330]	Rivaroxaban	Dabigatran	1.79; (1.12 to 2.86)
Optum Labs Data Warehouse[330]	Apixaban	Dabigatran	0.65; (0.25 to 1.65)
Truven Health MarketScan® Commercial Claims and Encounters Database and the Medicare[382]	Rivaroxaban	Dabigatran	1.47 (0.80, 2.72)
HealthCore Integrated Research Environment (HIRE)[387]	Apixaban	Dabigatran	1.75 (1.02 to 3.03)
HealthCore Integrated Research Environment (HIRE)[387]	Rivaroxaban	Dabigatran	1.85 (1.04 to 2.32)
Analysis Without Propensity-Matched Controls			

Database	Intervention	Comparator	Risk Estimate (95% CI) DOAC vs. Dabigatran
Danish Patient Registry[385]	Rivaroxaban	Dabigatran	0.23% (0.06% to 0.41%) (absolute risk difference)
Danish Patient Registry[385]	Apixaban	Dabigatran	0.18% (0.01% to 0.34%) (absolute risk difference)
Medicare database[384]	Apixaban	Dabigatran	1.42 (0.60 to 3.35)
Medicare database[384]	Rivaroxaban	Dabigatran	0.95 (0.43, 2.07)

Abbreviations: CI=confidence interval; DOAC=direct oral anticoagulant

Figure 39. Forest plot for intracranial hemorrhage—apixaban, rivaroxaban, or edoxaban (treatment) versus dabigatran (control) (observational)



Abbreviation: CI=confidence interval

Major Bleeding

Seven observational studies evaluated major bleeding for Xa inhibitors as compared to dabigatran. These studies are summarized in Table 67 and Figure 40. These studies did not demonstrate a difference in major bleeding (HR 0.91, 95% CI 0.66 to 1.24, I^2 = 87.2%, Q = 54.6, p<0.001) across all Xa inhibitors as compared to dabigatran. They did however demonstrate a reduction in major bleeding for apixaban (HR 0.67, 95% CI 0.47 to 0.94, I^2 = 30.2%, Q = 4.3, p=0.23) as compared to dabigatran (Figure 41), while demonstrating an increase in major bleeding risk with rivaroxaban compared with dabigatran (HR 1.32, 95% CI 1.02 to 1.70, I^2 = 37.7%, Q = 4.8, p=0.19) (Figure 42) (SOE low for all comparisons).

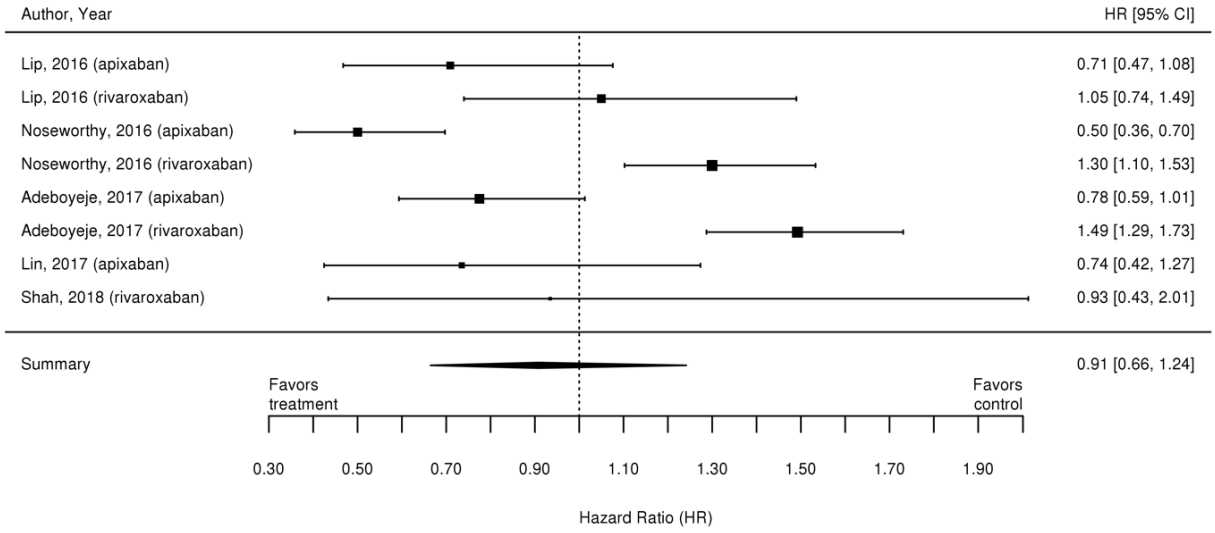
One study of the Truven MarketScan database which did not use propensity matched controls examined different risks of major bleeding in patients initiating dabigatran and apixaban.[309] For both risk of major bleeding requiring hospitalization and risk of major critical site bleeding (inpatient or outpatient settings), there was a statistically non-significant higher risk with dabigatran compared with apixaban. Compared with apixaban, the adj HR (95% CI) of major bleeding requiring hospitalization with dabigatran was 1.71 (0.94 to 3.1). Compared with apixaban, the adj HR (95% CI) of major critical site bleeding (inpatient or outpatient settings) with dabigatran was 1.28 (0.92 to 1.78). An analysis of this cohort specifying a comparison in risk of major bleeding requiring hospitalization for patients taking dabigatran 150mg twice daily with apixaban 5mg twice daily had similar results. Compared to those taking apixaban 5mg twice daily, those taking dabigatran 150mg twice daily had an adj HR (95% CI) of major bleeding requiring hospitalization of 1.50 (0.79 to 3.04).[309]

Table 67. Observational studies: major bleeding— apixaban, rivaroxaban, or edoxaban versus dabigatran

Database	Intervention	Comparator	Risk Estimate (95% CI) DOAC vs. Dabigatran
Analysis With Propensity-Matched Controls			
Truven MarketScan® Commercial Claims and Encounter and Medicare Supplemental and Coordination of Benefits Databases[310]	Apixaban	Dabigatran	0.71 (0.47 to 1.08)
Truven MarketScan® Commercial Claims and Encounter and Medicare Supplemental and Coordination of Benefits Databases[310]	Rivaroxaban	Dabigatran	1.05 (0.74 to 1.49)
Optum Labs Data Warehouse[330]	Apixaban	Dabigatran	0.50 (0.36 to 0.70)
Optum Labs Data Warehouse[330]	Rivaroxaban	Dabigatran	1.30 (1.10 to 1.53)
IMS Pharmetrics Plus database[305]	Apixaban	Dabigatran	0.73 (0.42 to 1.25)
HealthCore Integrated Research Environment (HIRE)[387]	Apixaban	Dabigatran	0.77 (0.59 to 1.01)
HealthCore Integrated Research Environment (HIRE)[387]	Rivaroxaban	Dabigatran	1.49 (1.28 to 1.72)
MarketScan[402]	Rivaroxaban	Dabigatran	0.93 (0.43 to 2)
Analysis Without Propensity-Matched Controls			
Danish Patient Registry[385]	Rivaroxaban	Dabigatran	Full doses 0.93% (0.38%, 1.45%) (absolute risk difference) Reduced doses 1.08% (0.03%, 2.09%) (absolute risk difference)
Truven MarketScan[309]	Dabigatran	Apixaban	1.71 (0.94 to 3.1) Full doses 1.50 (0.79 to 3.04)

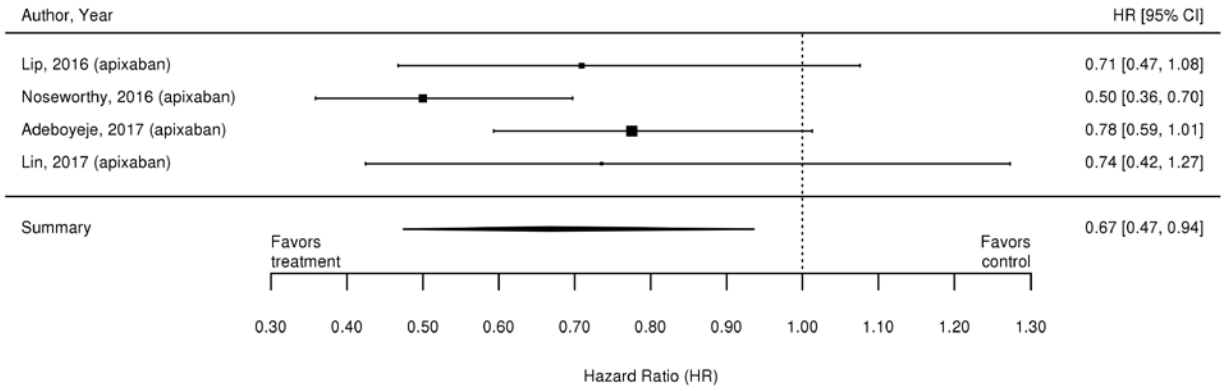
Abbreviations: CI=confidence interval; DOAC=direct oral anticoagulant

Figure 40. Forest plot for major bleeding —apixaban, rivaroxaban, or edoxaban (treatment) versus dabigatran (control) (observational)



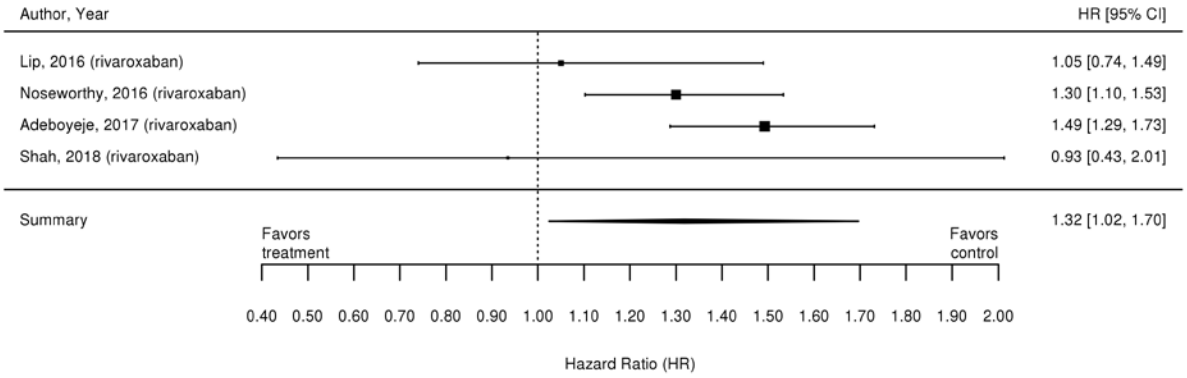
Abbreviation: CI=confidence interval

Figure 41. Forest plot for major bleeding—apixaban (treatment) versus dabigatran (control) (observational)



Abbreviation: CI=confidence interval

Figure 42. Forest plot for major bleeding—rivaroxaban (treatment) versus dabigatran (control) (observational)



Abbreviation: CI=confidence interval

Any Bleeding

One study examined a sample of the Medicare database and compared the outcome of any bleeding in users of apixaban versus dabigatran.[384] This study found a lower risk of any bleeding among apixaban users compared with dabigatran which was not statistically significant with an adj HR (95% CI) of 0.87 (0.73 to 1.04) . This same study also examined a sample of the Medicare database and compared the outcome of any bleeding in users of dabigatran versus rivaroxaban. This study found a significantly lower risk of any bleeding among dabigatran users compared with rivaroxaban with an adj HR (95% CI) of 0.79 (0.69 to 0.92).

A propensity-matched cohort using the Danish Patient Registry examined the outcome of any bleeding (including intracranial bleeding, GI bleeding, and major bleeding events) of low dose rivaroxaban 15mg daily versus low dose dabigatran 110mg daily as well as full dose rivaroxaban 20mg daily versus full dose dabigatran 150mg daily.[267] For low doses, there was no statistically significant difference in outcome. For low-dose rivaroxaban 15mg daily versus low dose dabigatran 110mg daily, the adj HR(95% CI) of any bleeding was 1.29 (0.87 to 1.90). However, for full dose rivaroxaban 20mg daily versus full dose dabigatran 150mg daily, there was a statistically significant increase in risk of any bleeding with rivaroxaban compared to dabigatran with an adj HR (95% CI) of 1.73 (1.24 to 2.42).[267]

Gastrointestinal Bleeding

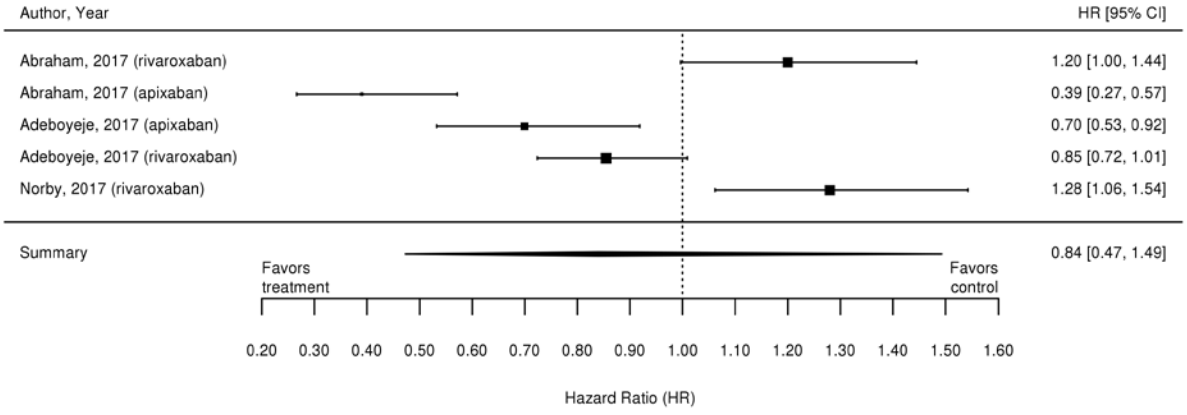
Five observational studies evaluated GI bleeding for Xa inhibitors as compared to dabigatran. These studies are summarized in Table 68 and Figure 43. These studies did not demonstrate a difference in GI bleeding (HR 0.84, 95% CI 0.47 to 1.49, I^2 = 90.7%, Q = 43.1, p<0.001) across all Xa inhibitors as compared to dabigatran, nor for the three studies which focused on the comparison of rivaroxaban versus dabigatran (HR 1.09, 95% CI 0.63 to 1.88, I^2 = 83.4%, Q = 12, p=0.002) (SOE low).

Table 68. Observational studies: GI bleeding—apixaban or edoxaban versus dabigatran

Database	Intervention	Comparator	Risk Estimate (95% CI) DOAC vs. Dabigatran
Analysis With Propensity-Matched Controls			
OptumLabs Data Warehouse[208]	Rivaroxaban	Dabigatran	1.20 (1.00 to 1.45)
OptumLabs Data Warehouse[208]	Apixaban	Dabigatran	0.39 (0.27 to 0.58)
Truven Health MarketScan® Commercial Claims and Encounters Database and the Medicare[382]	Rivaroxaban	Dabigatran	1.28 (1.06 to 1.54)
HealthCore Integrated Research Environment (HIRE)[387]	Apixaban	Dabigatran	0.70 (0.53 to 0.92)
HealthCore Integrated Research Environment (HIRE)[387]	Rivaroxaban	Dabigatran	0.85 (0.72 to 1.01)
Analysis Without Propensity-Matched Controls			
Danish Patient Registry[385]	Rivaroxaban	Dabigatran	Full dose 0.15% (-0.24% to 0.51%) absolute risk difference Reduced dose 0.20% (-0.55% to 0.96%)
Danish Patient Registry[385]	Apixaban	Dabigatran	Full dose -0.05% (-0.42% to 0.29%) absolute risk difference Reduced dose -0.68% (-1.35% to -0.02%)
Hernandez, 2017[384]	Apixaban	Dabigatran	0.76 (0.56 to 1.03)
Hernandez, 2017[384]	Dabigatran	Rivaroxaban	0.70 (0.55 to 0.89)

Abbreviations: CI=confidence interval; DOAC=direct oral anticoagulant

Figure 43. Forest plot for gastrointestinal bleeding—apixaban, rivaroxaban, or edoxaban (treatment) versus dabigatran (control) (observational)



Abbreviation: CI=confidence interval

Other Clinical Outcomes

Composite of Ischemic Stroke or Intracranial Bleeding

A propensity-matched cohort using the Danish Patient Registry examined a composite outcome of ischemic stroke or intracranial bleeding of low dose rivaroxaban 15mg daily versus low dose dabigatran 110mg daily as well as full dose rivaroxaban 20mg daily versus full dose dabigatran 150mg daily.[267] For both doses, there was no statistically significant difference in outcome. For low-dose rivaroxaban 15mg daily versus low dose dabigatran 110mg daily, the adj HR (95% CI) of the composite outcome was 0.77 (0.45 to 1.30). Also, for full dose rivaroxaban 20mg daily versus full dose dabigatran 150mg daily, there was no statistically significant difference in risk with adj HR (95% CI) of 1.02 (0.68 to 1.51).[267]

Composite of Ischemic Stroke or Intracranial Bleeding or Death

A propensity-matched cohort using the Danish Patient Registry examined a composite outcome of ischemic stroke or intracranial bleeding or death of low dose rivaroxaban 15mg daily versus low dose dabigatran 110mg daily as well as full dose rivaroxaban 20mg daily versus full dose dabigatran 150mg daily.[267] There was a statistically significant higher risk of this composite with low-dose rivaroxaban 15mg daily versus low dose dabigatran 110mg daily with an adj HR (95% CI) of the composite outcome of 1.24 (1.00 to 1.55). However, for full dose rivaroxaban 20mg daily versus full dose dabigatran 150mg daily, there was no statistically significant difference in risk of this composite outcome with adj HR (95% CI) of 1.24 (0.94 to 1.63).[267]

Mortality

One prospective cohort study using Medicare claims data for adults ≥65 years of age and using dabigatran versus rivaroxaban for nonvalvular AF.[269] Compared to dabigatran, rivaroxaban was associated with a trend towards a higher risk of mortality (adj HR 1.15; 95% CI 1.00 to 1.32; p=0.051.

A propensity-matched cohort using the Danish Patient Registry examined the outcome of all cause death comparing low dose rivaroxaban 15mg daily with low dose dabigatran 110mg daily as well as full dose rivaroxaban 20mg daily compared with full dose dabigatran 150mg daily.[267] For both doses, there was a statistically significantly higher risk of all-cause death with rivaroxaban compared with dabigatran. For low-dose rivaroxaban 15mg daily versus low dose dabigatran 110mg daily, the adj HR(95% CI) of all cause death was 1.47 (1.21 to 1.79). For full dose rivaroxaban 20mg daily versus full dose dabigatran 150mg daily, the adj HR (95% CI) of all-cause death was 1.40 (1.03 to 1.91).[267]

Acute Myocardial Infarction

One prospective cohort study using Medicare claims data for adults ≥65 years of age and using dabigatran versus rivaroxaban for nonvalvular AF.[269] Compared to dabigatran, rivaroxaban was not associated with significantly different risk of acute MI (adj HR 0.88; 95% CI 0.72 to 1.06; p=0.18.

Hospitalization

Hospitalization rates were evaluated by three observational studies. A propensity-matched study using a U.S. claims database showed a higher risk for all-cause hospitalization for those treated with dabigatran versus apixaban (HR 1.98, 95% CI 1.6 to 2.4, P<0.001).[305]

A retrospective study using Premier and Cemer databases found a nonsignificant difference in all cause hospital readmission in those taking dabigatran compared to apixaban (Premier: OR 1.1; 95% CI 1.0 to 1.2; p=0.21; Cerner: OR 1.02; 95% CI 0.9 to 1.2; p=0.80).[239]

A third study of the OptumInsight Research Database with Medicare recipients analyzed the risk of hospitalization for all-causes, stroke/systemic embolism, and major bleeding in patients on dabigatran versus apixaban.[380] Compared with apixaban, dabigatran was associated with a higher risk of hospitalization for all-causes, adj HR (95% CI) 1.11 (0.99 to 1.25), p=0.083 which was not statistically significant. Risk of hospitalization for stroke/systemic embolism was not statistically significant between the 2 groups; dabigatran versus apixaban adj HR (95% CI) 1.25 (0.78 to 2.00), p=0.365. However, compared to apixaban, dabigatran was associated with a higher risk of hospitalization for major bleeding, adj HR (95% CI) 1.46 (1.02 to 2.10), p=0.039.[380] Costs tended to be lower with apixaban, but there were no statistically significant differences in costs related to stroke/systemic embolism or major bleeding.

Medication Adherence

Medication adherence was explore by 11 observational studies. These studies varied in the Xa inhibitor assessed and the specific definitions of adherence used.

Nine studies demonstrated greater adherence with Xa inhibitors as compared to dabigatran. Specifically, a retrospective propensity-matched cohort analysis of U.S. MarketScan claims[228] examined medication persistence and discontinuation rates. Medication persistence was defined as absence of refill gap >60 days and discontinuation was defined as no additional refill for >90 days and through to end of followup. Use of rivaroxaban was associated with significantly lower levels of non-persistence compared with dabigatran (HR 0.64; 95% CI 0.62 to 0.67) and significantly lower rate of discontinuation than with dabigatran (HR 0.61; 95% CI 0.58 to 0.64).

This was similarly examined in another propensity-matched retrospective study using two different MarketScan databases (both commercial and Medicare databases).[406] Patients receiving rivaroxaban were less likely to be non-persistent (adj HR 0.89, 95% CI 0.84 to 0.95). Older age, higher $CHADS_2$ score and being treated with more medications were associated with reduced risk of non-persistence. Rivaroxaban users also had significantly lower discontinuation rates compared to dabigatran (20.9% vs. 41.5%, p< 0.001), adj HR 0.71, 95% CI 0.66 to 0.77).

An observational cohort study using MarketScan[226] found a lower rate of medication adherence, as measured by proportion of days covered with therapy ≥0.80, at 3, 6 and 9 months when comparing dabigatran to either rivaroxaban or apixaban (dabigatran vs. rivaroxaban: 3 months OR 0.60; 95% CI 0.53 to 0.70; 6 months OR 0.66; 95% CI 0.57 to 0.77; 9 months OR 0.72; 95% CI 0.60 to 0.87) (dabigatran vs. apixaban: 3 months OR 0.73; 95% CI 0.69 to 0.79; 6 months OR 0.75; 95% CI 0.69 to 0.83; 9 months OR 0.70; 95% CI 0.57 to 0.87).

A cohort study using a UK clinical practice database[292] found a higher rate of medication non-persistence with dabigatran compared to apixaban (HR 1.67; 95% CI 1.20 to 2.32). This held true both during the first 2 months of followup (HR 1.56; 95% CI 1.20 to 2.03; p<0.001) as well as after the first 2 months of followup (HR 2.32; 95% CI 1.63 to 3.31; p<0.001).

A German retrospective study examined medication adherence and persistence.[220] At 180 days, persistence with rivaroxaban was significantly higher compared with dabigatran (66.0 vs. 60.3%; p=0.008). At 360 days, rivaroxaban persistence was not statistically different from dabigatran (53.1 vs. 47.3%; p=0.100). In terms of adherence, high adherence (MPR ≥0.80%) was observed in 61.4% of rivaroxaban users and in 49.5% of dabigatran users (chi-squared test:

p<0.001) after 180 days. At 360 days, high adherence was observed in 62.6% of rivaroxaban users compared to 47.6% of dabigatran users (chi-squared test p<0.001).

An observational study in Sweden explored treatment persistence at 12 months in patients with non valvular atrial fibrillation and demonstrated apixaban having higher odds for persistence than initiations on dabigatran (apixaban vs. dabigatran OR 2.07, 95% CI 1.45 to 2.94, rivaroxaban versus dabigatran OR 1.21, 95% CI 1.00 to 1.46).[257]

A study of a Scottish national database compared outcomes related to medication adherence for patients with non valvular atrial fibrillation prescribed one of 4 new direct oral anticoagulants (DOACs)—dabigatran, apixaban, rivaroxaban, and edoxaban.[389] Compared to those taking rivaroxaban, those taking dabigatran had a shorter time to discontinuation of the medication: Median time to discontinuation for dabigatran was 206 days, 95% CI (185 to 247), while median time to discontinuation for rivaroxaban was 414 days, 95% CI (382 to 462). Additionally, compared to apixaban and rivaroxaban dabigatran had evidence of lower medication refill adherence rates, compliance rates, but statistical testing was not demonstrated in these comparisons.

A study of the Truven Health Analytics MarketScan database also compared medication adherence for the DOACs dabigatran, rivaroxaban, apixaban.[386] This study found that at 3, 6, and 9 months, medication persistence, defined as proportion of days covered (PDC), was lowest with dabigatran. Adherence with a PDC >80% was achieved by 71.0%, 71.2%, and 60.5% for rivaroxaban, apixaban, and dabigatran at 3 months respectively, p<0.001; 59.5%, 60.0%, and 47.8% for rivaroxaban, apixaban, and dabigatran at 6 months respectively, p<0.001; and 47.1%, 47.9%, and 37.1% for rivaroxaban, apixaban, and dabigatran at 9 months respectively, p<0.001. Similar patterns, with lower persistence with dabigatran, were noted among patients with different risk based on CHA_2DS_2-VASc score.

A retrospective cohort study using the VA Healthcare system examined medication adherence among those initiated on dabigatran, rivaroxaban or apixaban over a 5 year period with a CHA_2DS_2-VASc ≥ 2.[383] Adherence was calculated in the first year of therapy as proportion of days covered (PDC). Adherence was defined as PDC> 80%. Mean PDC was 0.84 ±0.20 for dabigatran, 0.86 ± 0.18 for rivaroxaban and 0.89 ± 0.14 for apixaban (p<0.01). Factors associated with greater adherence were age (OR 0.98, p<0.01), hypertension (OR 0.69, p=0.04), diabetes (OR 0.57, p<0.01) and stroke (OR 0.36, p<0.01). Nonadherence at 6 months to dabigatran was associated with increased risk of death or stroke (HR 1.54; 95% CI 1.20 to 1.97; p < 0.01). There was a similar trend for rivaroxaban but it was not statistically significant (HR 1.74; 95% CI 0.77 to 3.94; p = 0.18).

Two studies however demonstrated an decrease in adherence outcomes with Xa inhibitors compared with dabigatran or did not find a difference. Specifically, a Danish nationwide cohort study found an increased risk of medication nonpersistence (defined as >30 day gap in treatment) when comparing apixaban to dabigatran (HR 1.45; 95% CI 1.33 to 1.59).[295]

A study of the VA Healthcare System compared medication adherence for patients on DOACs (dabigatran, rivaroxaban, apixaban).[383] Adherence was measured as proportion of days covered (PDC), with adherence defined as a PDC >80%. Based on an outcome of nonadherence with a PDC <80%, there was no statistically significant difference in medication non-adherence between patients on dabigatran, rivaroxaban, or apixaban.

14. Factor Xa Inhibitors (Apixaban, Rivaroxaban, or Edoxaban) Versus Another Xa Inhibitor

Eighteen observational studies compared one Xa inhibitor with another Xa inhibitor.[208,226,239,257,292,295,305,309,310,330,380,382,384,385,387,389,405,407]

Thromboembolic Outcomes

Stroke or Systemic Embolism

A propensity-matched cohort study using a U.S. claims database compared apixaban vs. rivaroxaban and found no evidence of a difference in the risk of stroke or systemic embolism (HR 1.05; 95% CI 0.64 to 1.72; p=0.85).[330]A second study evaluating the Danish Patient Registry also found no statistically significant difference in stroke/thromboembolism between rivaroxaban and apixaban for full or reduced doses.[385]

Ischemic Stroke

A propensity-matched cohort study using a U.S. claims database compared apixaban vs. rivaroxaban and found no evidence of a difference in the risk of ischemic stroke (HR 1.27; 95% CI 0.73 to 2.23; p=0.39).[330]

A study of the Danish Patient Registry also found no statistically significant difference in ischemic stroke between rivaroxaban and apixaban for full or reduced doses.[385]

A study of the Truven Health MarketScan® Commercial Claims and Encounters Database and the Medicare compared risk of ischemic stroke among new users of rivaroxaban versus warfarin using propensity matching.[382] After a mean followup of 12 months, compared to warfarin users of rivaroxaban had a significantly lower risk of ischemic stroke with an adj HR (95% CI) of 0.75 (0.62 to 0.91)

Ischemic Stroke, Systemic Embolism, Death

One study examined a sample of the Medicare database and compared the composite outcome of ischemic stroke, systemic embolism, or death in users of apixaban versus rivaroxaban.[384] This study found no statistically significant difference in risk of this composite outcome among apixaban users compared with rivaroxaban with an adj HR (95% CI) of 1.05 (0.92 to 1.21).

Myocardial Infarction

A study of the Truven Health MarketScan® Commercial Claims and Encounters Database and the Medicare compared risk of myocardial infarction (MI) among new users of rivaroxaban versus warfarin.[382] After a mean followup of 12 months, there was no statistically significant difference in risk of MI between groups, adj HR (95% CI) 0.88 (0.75 to 1.03), p=0.11.

Bleeding Outcomes

Hemorrhagic Stroke

A propensity-matched cohort study using a U.S. claims database compared apixaban vs. rivaroxaban and found no evidence of a difference in the risk of hemorrhagic stroke (HR 0.66, 95% CI 0.16 to 2.78; p=0.57).[330]

Major Bleeding

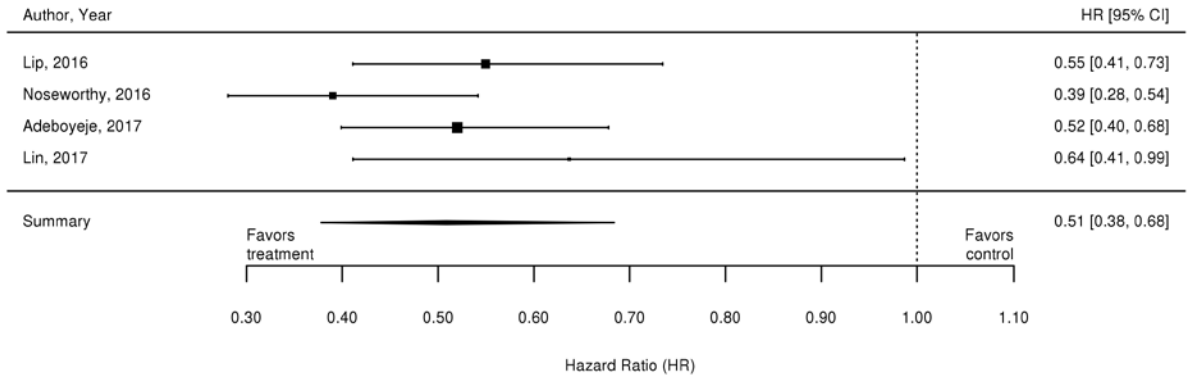
In a propensity-matched study using MarketScan,[310] there was a significantly higher risk of bleeding with rivaroxaban 20mg daily compared to apixaban 5mg bid. A propensity-matched cohort study using a U.S. claims database similarly found rivaroxaban to have a higher risk of bleeding.[330] This was again seen in another propensity-matched study using a U.S. claims database,[305] and a fourth study using HealthCore Integrated Research Environment (HIRE)[387] (Table 69). Meta analysis of the studies with propensity-matched controls demonstrated a reduction in major bleeding with apixaban as compared to rivaroxaban (HR 0.51, 95% CI 0.38 to 0.68, I^2 = 21.6%, Q = 3.8, p=0.28) (Figure 44) (SOE low).

Table 69. Observational studies: major bleeding—apixaban, rivaroxaban, or edoxaban versus another Xa inhibitor

Database	Intervention	Comparator	Risk Estimate (95% CI) Apixaban vs. Rivaroxaban
Analysis With Propensity-Matched Controls			
Truven MarketScan® Commercial Claims and Encounter and Medicare Supplemental and Coordination of Benefits Databases[310]	Apixaban	Rivaroxaban	0.55 (0.41 to 0.73)
Optum Labs Data Warehouse[330]	Apixaban	Rivaroxaban	0.39 (0.28 to 0.54)
IMS Pharmetrics Plus database[305]	Apixaban	Rivaroxaban	0.64 (0.41 to 0.99)
HealthCore Integrated Research Environment (HIRE)[387]	Apixaban	Rivaroxaban	0.52 (0.40 to 0.68)
Analysis Without Propensity-Matched Controls			
Danish Patient Registry[385]	Apixaban	Rivaroxaban	Full doses: -0.54% (-0.99% to -0.05%) (absolute risk difference) Reduced doses: -1.27% (-2.19% to -0.22%) (absolute risk difference)

Abbreviation: CI=confidence interval

Figure 44. Forest plot for major bleeding—apixaban (treatment) versus rivaroxaban (control) (observational)



Abbreviation: CI=confidence interval

Any Bleeding

One study examined a sample of the Medicare database and compared the outcome of any bleeding in users of apixaban versus rivaroxaban.[384] This study found a significantly lower risk

of any bleeding among apixaban users compared with rivaroxaban with an adj HR (95% CI) of 0.69 (0.60 to 0.79).

Gastrointestinal Bleeding

Four observational studies explored the outcome of GI bleeding in patients on apixaban as compared to rivaroxaban (Table 70). These studies consistently demonstrated a lower risk of GI bleeding with apixaban (low SOE).

Table 70. Observational studies: GI bleeding—rivaroxaban or edoxaban versus another Xa inhibitor

Database	Intervention	Comparator	Risk Estimate (95% CI) Apixaban vs. Rivaroxaban
Analysis With Propensity-Matched Controls			
OptumLabs Data Warehouse[208]	Apixaban	Rivaroxaban	0.33 (0.22 to 0.49)
HealthCore Integrated Research Environment (HIRE)[387]	Apixaban	Rivaroxaban	0.53 (0.42 to 0.68)
Analysis Without Propensity-Matched Controls			
Danish Patient Registry[385]	Apixaban	Rivaroxaban	Full dose: -0.20% (-0.50% to 0.10%) absolute risk difference Reduced dose: -0.87% (-1.58% to -0.15%) absolute risk difference
Hernandez, 2017[384]	apixaban	rivaroxaban	0.53 (0.42 to 0.68)

Abbreviation: CI=confidence interval

Intracranial Bleeding

Four observational studies evaluated intracranial bleeding for patients on apixaban as compared to rivaroxaban (Table 71). No evidence of a difference was seen for this outcome across the studies (low SOE).

Table 71. Observational studies: intracranial bleeding—apixaban, rivaroxaban, or edoxaban versus another Xa inhibitor

Database	Intervention	Comparator	Risk Estimate (95% CI) Apixaban vs. Rivaroxaban
Analysis With Propensity-Matched Controls			
Optum Labs Data Warehouse[330]	Apixaban	rivaroxaban	0.56 (0.21 to 1.45)
HealthCore Integrated Research Environment (HIRE)[387]	Apixaban	rivaroxaban	1.13 (0.66 to 1.93)
Analysis Without Propensity-Matched Controls			
Danish Patient Registry[385]	Apixaban	rivaroxaban	Full doses: -0.05% (-0.24% to 0.12%) absolute risk difference Reduced doses: -0.13% (-0.55% to 0.28%) absolute risk difference
Hernandez, 2017[384]	Apixaban	rivaroxaban	1.34 (0.72 to 2.50)

Abbreviation: CI=confidence interval

Other Clinical Outcomes

Hospitalization

A propensity-matched study using a U.S. claims database showed a higher risk for all-cause hospitalization for those treated with rivaroxaban vs. apixaban (HR 1.44; 95% CI 1.2 to 1.7; p<0.001).[305] Apixaban was also associated with lower mean number of outpatient claims for all causes compared to rivaroxaban (2.4 vs. 2.6 per patient per month; p=0.003).

In a retrospective study using Premier and Cerner databases, Premier found that rivaroxaban had a significantly higher risk of all-cause hospitalization, however Cerner did not (Premier: OR 1.2; 95% CI 1.1 to 1.3; p<0.001; Cerner: OR 1.05; 95% CI 0.9 to 1.2; p=0.58).[239]

A study of the OptumInsight Research Database with Medicare beneficiaries analyzed the risk of hospitalization for all-causes, stroke/systemic embolism, and major bleeding in patients on rivaroxaban versus apixaban.[380] Compared with apixaban, rivaroxaban was associated with a higher risk of all-cause hospitalization, adj HR (95% CI) 1.15 (1.07 to 1.24); and higher risk of hospitalization for major bleeding, adj HR (95% CI) 1.71 (1.39 to 2.10). There was no statistically significant difference in risk of hospitalization for stroke/systemic embolism; compared with apixaban, for rivaroxaban, the adj HR (95% CI) was 1.18 (0.89 to 1.57). Additionally, compared to rivaroxaban, use of apixaban was associated with significantly lower costs related to major bleeding, but not for stroke/systemic embolism.

Medication Adherence

Seven observational studies explored medication persistence. The findings of these studies were inconsistent and heterogeneous in terms of definitions of adherence or persistence used.

Three studies did not demonstrate a difference between medication persistence with apixaban or rivaroxaban. Specifically, a Danish nationwide cohort study found no evidence of a difference in medication persistence between apixaban and rivaroxaban (HR 1.07; 95% CI 0.96 to 1.20).[295] An observational cohort study using MarketScan[226] found no evidence of a difference in medication adherence, as measured by proportion of days covered (PDC) with therapy ≥0.80, at 3, 6 and 9 months when comparing apixaban to rivaroxaban (3 months OR 0.82; 95% CI 0.67 to 1.01; 6 months OR 0.88; 95% CI 0.69 to 1.12; 9 months OR 1.03; 95% CI 0.69 to1.53). A Scottish National database compared medication adherence of rivaroxaban and apixaban and showed no evidence of a difference in medication refill adherence or compliance rates.[389]

Two studies demonstrated better persistence outcomes with rivaroxaban. Specifically an observational matched cohort study using MarketScan evaluated both medication persistence and gaps in care in newly initiated apixaban and rivaroxaban users.[407] At both 90 days and 180 days, rivaroxaban users had significantly higher PDC ≥ 0.80 than apixaban users (90 days: 85.3% vs. 79.9%, p<0.001; 180 days: 75.8% vs. 72.2%, p=0.003). The medication possession ratio was also higher in the rivaroxaban cohort compared to apixaban cohort (0.92 vs. 0.89, p<0.001). Rivaroxaban users also have significantly fewer gaps in care, less proportion of gaps more than 5 days and proportion of gaps more than 10 days, compared to apixaban users (gaps > 5 days 54.2% vs. 62.4%, p<0.001; gaps > 10 days 40.0% vs. 49.2%, p<0.001).

A cohort study using a UK clinical practice database[292] found medication non-persistence higher with rivaroxaban compared to apixaban after 2 months of followup (HR 1.69; 95% CI 1.19 to 2.39; p=0.003). During the first 2 months of followup, no evidence of a difference in non-persistence was seen (HR 1.17; 95% CI 0.91 to 1.50; p=0.224).

Finally, two studies favored apixaban in terms of persistence outcomes. An observational study in Sweden explored treatment persistence at 12 months in patients with non valvular atrial fibrillation and demonstrated apixaban having higher odds for persistence than rivaroxaban (apixaban vs. rivaroxaban OR 1.71, 95% CI 1.18 to 2.47).[257]

A propensity-matched U.S. study using two commercial insurance claims databases (IMS and MarketScan) examined medication adherence by measuring PDC.[405] There was similar findings in both databases. Apixaban users had significantly better adherence (defined as % of patients with PDC ≥0.8) at 6 months post-index date compared to rivaroxaban users (IMS: 56.6% vs. 54.4%, p<0.05; MarketScan 57.9% vs. 62.2%, p<0.05). This effect was not longer seen when examining patients with only ≥ 2 dispensings of medication. When examining only chronic users of medication (defined as ≥2 dispensings, ≥6 months apart and with >60 days supply), rivaroxaban users had greater adherence (IMS: 79.6% vs. 74.6%, p<0.05; MarketScan: 82.4% vs. 77.9%, p<0.05). Given the inconsistent findings and observational study designs of the included studies, the SOE was rated as insufficient.

15. Factor Xa Inhibitor (Apixaban) Versus Aspirin

One good-quality RCT involving 5,599 patients compared the efficacy and safety of the direct Xa inhibitor apixaban with aspirin in AF patients in whom warfarin therapy was unsuitable.[115] This study demonstrated that in the ITT population, apixaban reduced the risk of stroke or systemic embolism without significantly increasing the risk of major bleeding or intracranial hemorrhage.

Stroke or Systemic Embolism

Apixaban was superior to aspirin in reducing the incidence of stroke or systemic embolism (1.6% per year vs. 3.7% per year; HR 0.45; 95% CI 0.32 to 0.62; p<0.001). Systemic embolism was more frequent in the aspirin group (0.1% per year for apixaban vs. 0.4% per year for aspirin; HR 0.16; 95% CI 0.03 to 0.68; p=0.01) (moderate SOE).

Ischemic Stroke

The rates of ischemic stroke were lower in the apixaban group (1.1% per year for apixaban vs. 3.0% per year for aspirin; HR 0.37; 95% CI 0.25 to 0.55; p<0.001) (moderate SOE).

Hemorrhagic Stroke

There was a trend toward a benefit of apixaban reducing hemorrhagic stroke (0.2% per year for apixaban vs. 0.3% per year for aspirin; HR 0.67; 95% CI 0.24 to 1.88; p=0.45) (moderate SOE).

Major Bleeding

There were no statistically significant differences in major bleeding rates between the groups (1.4% per year for apixaban vs. 1.2% per year for aspirin; HR 1.13; 95% CI 0.74 to 1.75; p=0.57) (moderate SOE).

Minor Bleeding

There was an increased risk of minor bleeding in patients on apixaban (6.3% per year for apixaban vs. 5.0% per year for aspirin; HR 1.24; 95% CI 1.00 to 1.53; p=0.05) (moderate SOE).

Intracranial Bleeding

There was a trend toward a reduction in risk of intracranial bleeding for patients on apixaban **(**HR 0.85; 95% CI 0.38 to 1.90; p=0.69) (low SOE). A subgroup analysis was done to explore the effect of apixaban, compared with aspirin, on clinical and covert brain infarction and on microbleeds in patients with atrial fibrillation.[331] Brain MRI were performed (T1, T2, fluid-attenuated inversion recovery, and T2* gradient echo sequences) in 1,180 at baseline and in 931 participants at followup. Baseline MRI scans revealed brain infarct(s) in 26.2 percent and microbleed(s) in 10.5 percent. The rate of the primary outcomes was 2.0% in the apixaban group and 3.3% in the aspirin group (HR 0.55; 95% CI 0.27 to 1.14) from baseline to followup MRI scan (mean duration of followup, 1 year). In those who completed baseline and followup MRI scans, the rate of new infarction detected on MRI was 2.5 percent in the apixaban group and 2.2 percent in the aspirin group (HR 1.09; 95% CI 0.47 to 2.52), but new infarcts were smaller in the apixaban group (p=.03). There was no evidence of a difference in proportion with new microbleeds on followup MRI (HR 0.92; 95% CI 0.53 to 1.60) between treatment groups.

All-Cause Mortality

Although not reaching statistical significance, there was a trend toward a reduction in all-cause mortality for patients on apixaban (3.5% per year for apixaban vs. 4.4% per year for aspirin; HR 0.79; 95% CI 0.62 to 1.02; p=0.07) (low SOE).

Death From Vascular Causes

Death from vascular causes was similar between groups (2.7% per year for apixaban vs. 3.1% per year for aspirin; HR 0.87; 95% CI 0.66 to 1.17; p=0.37) (moderate SOE).

Myocardial Infarction

There were no statistically significant differences in MI rates (0.8% per year for apixaban vs. 0.9% per year for aspirin; HR 0.86; 95% CI 0.50 to 1.48; p=0.59) (moderate SOE).

Hospitalization

Hospitalization for cardiovascular cause was lower in the apixaban group (12.6% per year for apixaban vs. 15.9% per year for aspirin; HR 0.79; 95% CI 0.69 to 0.91; p <0.001) (moderate SOE).

Adverse Events

No evidence of differences in liver function or other adverse events were seen between the groups (moderate SOE).

Strength of Evidence

Table 72 summarizes the SOE for outcomes of interest for this comparison.

Table 72. Strength of evidence domains for preventing thromboembolic events—Xa inhibitor (apixaban) versus aspirin

Outcome	Number of Studies (Subjects)	Risk of Bias	Consistency	Directness	Precision	Reporting Bias	SOE and Effect (95% CI)
Stroke or systemic embolism	1[115] (5,599)	RCT/ Low	NA	Direct	Precise	None	**SOE=Moderate** Apixaban reduced risk; HR 0.45 (0.32 to 0.62)
Ischemic stroke	1[115] (5,599)	RCT/ Low	NA	Direct	Precise	None	**SOE=Moderate** Apixaban reduced risk; HR 0.37 (0.25 to 0.55)
Hemorrhagic stroke	1[115] (5,599)	RCT/ Low	NA	Direct	Imprecise	None	**SOE=Moderate** Trend toward a reduction in risk with apixaban; HR 0.67 (0.24 to 1.88)
Major bleeding	1[115] (5,599)	RCT/ Low	NA	Direct	Precise	None	**SOE=Moderate** No evidence of a difference; HR 1.13 (0.74 to 1.75)
Minor bleeding	1[115] (5,599)	RCT/ Low	NA	Direct	Precise	None	**SOE=Moderate** Apixaban increased risk; HR 1.20 (1.00 to 1.53)
Intracranial bleeding	1[115] (5,599)	RCT/ Low	NA	Direct	Imprecise	None	**SOE=Low** Trend toward a reduction in risk with apixaban; HR 0.85 (0.38 to 1.90); SOE is reduced since effect did not reach statistical significance
All-cause mortality	1[115] (5,599)	RCT/ Low	NA	Direct	Imprecise	None	**SOE=Low** Trend toward a reduction in risk with apixaban; HR 0.79 (0.62 to 1.02); SOE is reduced given the closeness of the HR to 1
Death from vascular causes	1[115] (5,599)	RCT/ Low	NA	Direct	Imprecise	None	**SOE=Moderate** No evidence of a difference; HR 0.87 (0.66 to 1.17)
Myocardial infarction	1[115] (5,599)	RCT/ Low	NA	Direct	Imprecise	None	**SOE=Moderate** No evidence of a difference; HR 0.86 (0.50 to 1.48)
Hospitalization	1[115] (5,599)	RCT/ Low	NA	Direct	Precise	None	**SOE=Moderate** Apixaban reduced risk; HR 0.79 (0.69 to 0.91)

Outcome	Number of Studies (Subjects)	Risk of Bias	Consistency	Directness	Precision	Reporting Bias	SOE and Effect (95% CI)
Adverse events	1[115] (5,599)	RCT/ Low	NA	Direct	Imprecise	None	**SOE=Moderate** No evidence of differences in liver function or other adverse events between therapies

Abbreviations: CI=confidence interval; HR=hazard ratio; NA=not applicable; RCT=randomized controlled trial; SOE=strength of evidence

16. Unspecified Direct Oral Anticoagulants Versus Vitamin K Antagonists

Seven studies evaluated DOACs compared with VKAs for nonvalvular AF but did not specify which specific DOAC was used.[258,303,321,322,381,391,394]

Thromboembolic Outcomes

Stroke (All-Cause, Ischemic, Hemorrhagic, Unspecified)

One U.S. study of patients at a single academic medical center compared the outcomes of patients with nonvalvular AF prescribed warfarin to those prescribed DOACs including dabigatran, rivaroxaban, and apixaban.[303] Using propensity-matching, this study found that compared to warfarin, patients on DOACs had no statistically significantly different risk of all-cause stroke (adj HR 1.04; 95% CI 0.6 to 1.8; p=0.9).

A Swedish study (merging 4 national databases) examined outcomes of all-cause stroke in users of DOACs (dabigatran, rivaroxaban, apixaban) versus warfarin using propensity matching. There was no statistically significant difference in risk; compared with warfarin, users of DOACs had an adj HR (95% CI) of all-cause stroke of 0.89 (0.68 to 1.17), p=0.41.[391]

Stroke (All-Cause, Ischemic, Hemorrhagic, Unspecified) and Systemic Embolism

A Swedish study (merging 4 national databases) examined outcomes of all-cause stroke and systemic embolism in users of DOACs (dabigatran, rivaroxaban, apixaban) versus warfarin using propensity matching.[391] There was no statistically significant difference in risk; compared with warfarin, users of DOACs had an adj HR (95% CI) of all-cause stroke or systemic embolism of 0.89 (0.69 to 1.15), p=0.36.

Ischemic Stroke

One Italian study using a claims database examined the outcome of ischemic stroke in patients taking DOACs (dabigatran, rivaroxaban, or apixaban) compared with warfarin.[381] This study found no statistically significant difference in risk of ischemic stroke between the 2 groups; compared to warfarin, users of DOACs had an adj HR (95% CI) of ischemic stroke of 1.05(0.61 to 1.81).

A Swedish study (merging 4 national databases) examined outcomes of ischemic stroke in users of DOACs (dabigatran, rivaroxaban, apixaban) versus warfarin using propensity matching.[391] There was no statistically significant difference in risk; compared with warfarin, users of DOACs had an adj HR (95% CI) of ischemic stroke of 1.04 (0.75 to 1.43), p=0.83.

Unspecified TIA or Stroke/Bleeding/Death

A European study[258] used the Stockholm administrative health registry to examine stroke and bleeding characteristics between warfarin and DOACs (dabigatran, rivaroxaban, and apixaban). DOAC versus warfarin treatment was associated with similar risks for TIA/ischaemic or unspecified/death (HR 0.94; 95% CI 0.85 to 1.05) and severe bleeds (HR 1.02; 95% CI 0.88 to 1.19); lower risks of intracranial bleeds (HR 0.72; 95% CI 0.53 to 0.97) or hemorrhagic stroke (HR 0.56; 95% CI 0.34 to 0.93), but a higher risk for gastrointestinal bleeds (HR 1.28; 95% CI 1.04 to 1.59).

A subgroup analysis of those below 80 years and above 80 years revealed no statistically significant differences between DOAC and warfarin treated patients aged 80 and above for TIA/ischemic stroke or unspecified stroke/death (HR 1.01; 95% CI 0.87 to 1.16) or any severe bleed (HR 1.08; 95% CI 0.85 to 1.36). There was a dose reduction in 72 percent of DOAC patients above the age of 80. After adjustments, for those aged ≥80, dose reduction of DOAC treatment was associated with a marked risk reduction for hemorrhagic stroke (HR 0.27; 95% CI 0.08 to 0.89).

Hemorrhagic Stroke

A Swedish study (merging 4 national databases) examined outcomes of hemorrhagic stroke in users of DOACs (dabigatran, rivaroxaban, apixaban) versus warfarin using propensity matching. Compared with warfarin, users of DOACs had a significantly lower risk of hemorrhagic stroke with an adj HR (95% CI) of 0.49 (0.28 to 0.86), p=0.01.[391]

Major Bleeding

A Swedish study (merging 4 national databases) examined outcomes of major bleeding in users of DOACs (dabigatran, rivaroxaban, apixaban) versus warfarin using propensity matching. Compared with warfarin, users of DOACs had a significantly lower risk of major bleeding with an adj HR (95% CI) of 0.78 (0.67 to 0.92), p=0.003.[391]

Unspecified TIA or Stroke/Bleeding/Death

A European study[258] used the Stockholm administrative health registry to examine stroke and bleeding characteristics between warfarin and DOACs (dabigatran, rivaroxaban, and apixaban). DOAC versus warfarin treatment was associated with similar risks for TIA/ischaemic or unspecified/death (HR 0.94; 95% CI 0.85 to 1.05] and severe bleeds (HR 1.02; 95% CI 0.88 to 1.19); lower risks of intracranial bleeds (HR 0.72; 95% CI 0.53 to 0.97) or hemorrhagic stroke (HR 0.56; 95% CI 0.34 to 0.93), but a higher risk for gastrointestinal bleeds (HR 1.28; 95% CI 1.04 to 1.59).

A subgroup analysis of those below 80 years and above 80 years revealed no statistically significant differences between DOAC and warfarin treated patients aged 80 and above for TIA/ischemic stroke or unspecified stroke/death (HR 1.01; 95% CI 0.87 to 1.16) or any severe bleed (HR 1.08; 95% CI 0.85 to 1.36). There was a dose reduction in 72 percent of DOAC patients above the age of 80. After adjustments, for those aged ≥80, dose reduction of DOAC treatment was associated with a marked risk reduction for hemorrhagic stroke (HR 0.27; 95% CI 0.08 to 0.89).

All Bleeding

One Italian study using a claims database examined the outcome of all bleeding in patients taking DOACs (dabigatran, rivaroxaban, or apixaban) compared with warfarin.[381] This study

found no statistically significant difference in risk of all bleeding between the 2 groups; compared to warfarin, users of DOACs had an adj HR (95% CI) of all bleeding of 0.89 (0.65 to 1.23).

Intracranial Bleeding

One Italian study using a claims database examined the outcome of intracranial bleeding in patients taking DOACs (dabigatran, rivaroxaban, or apixaban) compared with warfarin.[381] Compared to warfarin, users of DOACs had a lower risk of intracranial bleeding with an adj HR (95% CI) of 0.52 (0.30 to 0.90).

A Swedish study (merging 4 national databases) examined outcomes of intracranial bleeding in users of DOACs (dabigatran, rivaroxaban, apixaban) versus warfarin using propensity matching.[391] Compared with warfarin, users of DOACs had a significantly lower risk of intracranial bleeding with an adj HR (95% CI) of 0.59 (0.40 to 0.87), p=0.008.

GI Bleeding

A Swedish study (merging 4 national databases) examined outcomes of GI bleeding in users of DOACs (dabigatran, rivaroxaban, apixaban) versus warfarin using propensity matching.[391]There was no statistically significant difference in risk of GI bleeding between these groups; compared with warfarin, users of DOACs had an an adj HR (95% CI) of GI bleeding 1.14 (0.88 to 1.46), p=0.32.

Other Clinical Outcomes

Mortality

One U.S. study of patients at a single academic medical center compared the outcomes of patients with nonvalvular AF prescribed warfarin to those prescribed DOACs including dabigatran, rivaroxaban, and apixaban.[303] Using propensity matching, this study found that compared to warfarin, patients on DOACs had a significantly reduced risk of death (adj HR 0.51; 95% CI 0.28 to 0.93; p=0.03).

One Italian study using a claims database examined the outcome of death in patients taking DOACs (dabigatran, rivaroxaban, or apixaban) compared with warfarin.[381] Compared to warfarin, users of DOACs had a lower risk of death with an adj HR (95% CI) of 0.84 (0.73 to 0.97).

A Swedish study (merging 4 national databases) examined outcomes of all-cause mortality in users of DOACs (dabigatran, rivaroxaban, apixaban) versus warfarin using propensity matching.[391] There was no statistically significant difference in risk; compared with warfarin, users of DOACs had an adj HR (95% CI) of all-cause mortality of 0.94 (0.82 to 1.07), p=0.33.

Myocardial Infarction

One Italian study using a claims database examined the outcome of myocardial infarction (MI) in patients taking DOACs (dabigatran, rivaroxaban, or apixaban) compared with warfarin.[381] This study found no statistically significant difference in risk of risk of MI between the 2 groups; compared to warfarin, users of DOACs had an adj HR (95% CI) of MI of 0.77 (0.41 to 1.45).

A Swedish study (merging 4 national databases) examined outcomes of MI in users of DOACs (dabigatran, rivaroxaban, apixaban) versus warfarin using propensity matching.[391] There

was no statistically significant difference in risk; compared with warfarin, users of DOACs had an adj HR (95% CI) of MI of 0.95 (0.72 to 1.24), p=0.68.

Medication Adherence

One UK study using the CPRD database compared the persistence of use of 2 classes of anticoagulants: VKAs which included acenocoumarol, phenindione, or warfarin versus non-VKA oral anticoagulants (DOACs), which for this study included apixaban, dabigatran or rivaroxaban.[322] Rate of persistence was assessed for each group up to 1 year. At each time point, compared to VKAs, persistence was significantly higher for use of DOACs. DOACs had a higher percentage persistence at 90 days of 94.7 percent compared to warfarin 87.2 percent ($p<0.0001$); at 180 days, 85.9 percent versus 76.5 percent ($p<0.0001$); at 270 days, 82.4 percent versus 69.3 percent ($p<0.0001$); and at 365 days, 79.2 percent versus 63.3 percent ($p<0.0001$).[322] Among those with CHA2DS2VASc < 2, DOACs had higher rate of persistence only at 90 days; there was no statistically significant difference between DOACs and VKAs for persistence at other time-points up to 1 year. However, for those with CHA2DS2VASc ≥ 2, DOACs had significantly higher persistence compared to warfarin at all time points up to 1 year.[322]
A Canadian study used the Canadian Province of Quebec's health insurance database to examine treatment persistence of patients on NOACs compared to vitamin K antagonists.[394] After 3 years, medication persistence was 54% with DOACs versus 24% with VKAs. Discontinuation of anticoagulation was less likely for patients > 80 years old (HR 0.47, 95% CI 0.40 to 0.55} or with CHA_2DS_2-VASc greater than or equal to 2 (HR 0.64, 95% CI 0.57 to 0.70).

Health-Related Quality of Life

A European cross-sectional multicenter study (ALADIN) compared the satisfaction of patients receiving VKA versus DOACs (dabigatran, rivaroxaban, and apixaban) to determine the impact on quality of life.[321] Outpatients were asked to complete the ACTS (Anti-Clot Treatment Scale), SAT-Q (Satisfaction Questionnaire) and eQ-5D-3L (EuroQol 5 dimensions questionnaire, level 3 version). The ACTS is a patient-reported measure of satisfaction with anticoagulation treatment, which includes 12 items that assess burden and 3 items that assess benefits. The ACTS Burden score ranges from 12-60 with higher scores indicating less burden. The ACTS Benefits score ranges from 3 to 15 with higher score indicating higher benefit. The ACTS Burdens score and ACTS Benefits score were significantly higher with DOACs than with VKAs (54.83 ± 6.11 vs. 49.50 ± 9.15; $p<0.001$ and 12.36 ± 2.34 vs. 11.48 ± 2.46; $p<0.001$ respectively). There was no statistically significant difference seen between dabigatran, rivaroxaban and apixaban on ACTS Burden or Benefits scores (ACTS Burdens: Dabigatran 55.54 ± 5.33, Rivaroxaban 54.58 ± 6.24, Apixaban 54.36 ± 6.82; p=0.299, ACTS Benefits: Dabigatran 12.26 ± 2.48, Rivaroxaban 12.42 ± 2.13, Apixaban 12.33 ± 2.53; p=0.918).

The SAT-Q analyzes patient satisfaction with healthcare and medication. The score ranges from 0 to 100 with higher score representing higher satisfaction. Factors associated with satisfaction were DOAC use, higher ACTS benefits score and higher ACTS burdens score (DOAC OR 1.07; 95% CI 1.003 to 1.15; p=0.042; ACTS Benefits OR 1.64; 95% CI 1.46 to 1.84; $p<0.001$; ACTS Burdens OR 1.11; 95% CI 1.07 to 1.15; $p<0.001$). There was no statistically significant difference seen between dabigatran, rivaroxaban and apixaban SAT-Q scores (Dabigatran 69.7 ± 15.63, Rivaroxaban 70.62± 13.69, Apixaban 69.62 ± 15.91; p=0.879). The EQ-5D-3L measures health-related quality of life and of health outcomes. The score ranges from 0 to 100, with 100 representing best imaginable health. Healthcare quality of life was not

statistically different between those taking DOACs versus VKAs (76.26 ± 20.63 vs. 75.05 ± 21.07; p=0.297); and there was no statistically significant difference in EQ-5D-3L score by type of DOAC (Dabigatran 74.75 ± 19.86, Rivaroxaban 78.33 ± 20.79, Apixaban 75.06 ± 21.04; p=0.065).

17. Left Atrial Appendage Closure Devices

Five studies evaluated left atrial appendage closure devices compared with other devices. This included one multicenter prospective observational study which compared Watchman versus Lariat left atrial appendage occlusion devices.[337] Two studies examined patients who underwent LAA closure with the Amplatzer Cardiac plug (ACP) versus Watchman device.[227,253] Both of these were European studies, one an Italian retrospective study[253] and the other a German prospective nonrandomized study.[227] A Swedish prospective study compared those who underwent LAA closure with non-dedicated devices (such as those that close ASDs, PFOs, VSDs) versus ACP.[345] Finally, an observational study of a Swedish retrospective analysis of prospectively collected data (n=100) comparing first (ACP) versus second generation (Amulet) Amplatzer occluders.[266]

Thromboembolic Outcomes

Two studies examined risk of thromboembolism.[227,345] All showed no statistically significant difference in thromboembolism between devices. One study[227] compared the Watchman to ACP LAA occlusion device; and there were no thromboembolic events in either group over a median followup period of approximately 1 year. The other study[345] compared nondedicated devices atrial and ventricular septal occluders (NDAs) to the dedicated device of an ACP occlusion device and showed no evidence of a difference in thromboembolism (3% vs. 0%; p=0.31). over a mean followup of 7.2 ± 2.7 months.

TIA or Stroke

There was no evidence of a difference in risk of TIA or stroke between devices compared in these studies. A U.S. study showed no evidence of a difference in risk of TIA or stroke following LAA closure with Watchman versus Lariat devices (1.3% vs. 1.1%; p=0.99).[337] The study comparing Watchman to ACP had 0 patients in the Watchman group and 1 patient in the ACP group with TIA (p=0.385); neither group had any ischemic strokes.[253] The study comparing NDA to ACP showed no occurrence of ischemic stroke over their respective followup periods.[345] In a Swedish study comparing ACP versus Amulet, there was no evidence of a difference in neurologic events over the followup period (0% vs. 4%; p=0.49).[266]

Bleeding Outcomes

Hemorrhagic Stroke

A European study showed no evidence of a difference in risk of hemorrhagic stroke following LAA closure with Watchman versus ACP devices (1.5% vs. 0%; p=0.395).[253]

Bleeding

A Swedish study evaluated risk of bleeding between ACP versus Amulet devices. There was no evidence of a difference in either major bleeding (2% vs. 4%; p=0.30) or any bleeding (2% vs. 6%; p=0.62).[266]

Other Clinical Outcomes

Periprocedural Complications

None of the included studies showed any statistically significant different in pericardial effusions between devices.[227,253,337,345] An Italian study showed a numerically higher, but nonsignificant, incidence of pericardial effusions with the Watchman device versus ACP (4.5% vs. 1.0%; p=0.1.0).[253] There was additionally no evidence of a difference in cases of pericardial tamponade (1.5% vs. 0%; p=1.0). This was similarly seen in a German study comparing these devices, with 1 case of delayed tamponade in each of the Watchman and ACP device groups, p=1.00.[227]

A U.S. study comparing Watchman to Lariat LAA occlusion devices showed no statistically significant difference in pericardial effusions (1% vs. 0%) or cardiac tamponade (0% vs. 1.5%) between the groups, however noted that after switching needles for pericardial access midway through the study no tamponade or effusions occurred.[337]

A Swedish study showed a numerically higher, but nonsignificant, number of pericardial effusions in NDA group versus ACP group (6% vs. 3%; p=0.55) with more of those in the NDA group requiring pericardiocentesis (6% vs. 0%; p=0.15).[345] Another Swedish study found an increased, but nonsignificant number of periprocedural adverse events with the ACP device compared to the Amulet (24% vs. 14%; p=0.31).[266] There were an increased number of pericardial effusions that did not require drainage (14% vs. 4%; p=0.08) and injury of the great or coronary arteries (4% vs. 0%; p=0.15).

Mortality and Morbidity

There was no evidence of a difference in mortality between devices compared. An Italian retrospective study,[253] over a mean followup of 448 days, showed nonsignificant difference in overall mortality, cardiovascular mortality and major bleeding in those who received the Watchman versus ACP device (mortality overall: 0% vs. 5.4%; p=0.157; cardiovascular mortality: 0% vs. 2.0%; p=0.519; major bleeding: 1.5% vs. 1.1%; p=1.0). This was similarly seen in the German study comparing these devices.[227] Over a median of 364 days, there was no statistically significant difference in overall mortality between the Watchman group and the ACP device (2.6% vs. 5%; p=1.0). The Swedish study comparing NDAs and ACP devices[345] had 0 "device-related" deaths after a median followup of 7.2 months; however, after longer-term followup, there were 5 deaths described in the NDA arm and 0 deaths in the ACP device arm. The U.S. study comparing Watchman and Lariat devices had no cases of death attributed to the respective devices.[337] There was no evidence of a difference in death when comparing ACP versus Amulet devices (2% vs. 8%; p=0.36).[266]

Device Embolization

A Swedish study showed significantly more device embolization and reduced overall procedural success when comparing NDAs versus ACP device (device embolization: 16% vs. 0%; p=0.02; procedural success: 84% vs. 100%; p=0.02).[345]Device embolism was also examined in the U.S. study comparing Watchman to Lariat devices.[337] There was no occurrence of device embolization in the Lariat group (n=259) and only one occurrence in the Watchman group (n=219).

18. Percutaneous Left Atrial Appendage Closure Versus Warfarin

One good-quality RCT (PROTECT AF) involving 707 patients compared the safety and efficacy of percutaneous left atrial appendage (LAA) closure to warfarin in patients with nonvalvular AF.[288]

There were also three observational studies which one multicenter prospective observational study compared Watchman versus Lariat left atrial appendage occlusion devices.[337] Two studies examined patients who underwent LAA closure with the Amplatzer Cardiac plug (ACP) versus Watchman device.[227,253] Both of these were European studies, one an Italian retrospective study[253] and the other a German prospective nonrandomized study.[227]

Thromboembolic Outcomes

Composite of Stroke, Cardiovascular Death, and Systemic Embolism

The primary outcome in the RCT[288] was a composite of stroke, cardiovascular death, and systemic embolism in the ITT population. This composite outcome was lower in the LAA group (3 per 100 patient-years vs. 4.9 per 100 patient-years; rate ratio 0.62; 95% CI 0.35 to 1.25), which reached the noninferiority criteria. At 2 years of followup, the cumulative composite event rate for the LAA group was 5.9 percent compared with 8.3 percent within the warfarin group. The efficacy results were consistent across all subgroups except for sex with men having a lower HR than women (p=0.03).

Ischemic Stroke

After the periprocedural timeframe, in the RCT[288] 9 patients in the LAA group (1.3 events per 100 patient-years) and 6 patients in the warfarin group had ischemic stroke (1.6 events per 100 patient-years). There was low SOE that there was no evidence of a difference between treatment arms.

Hemorrhagic Stroke

A European observational study showed no evidence of a difference in risk of hemorrhagic stroke following LAA closure with Watchman versus ACP devices (1.5% vs. 0%; p=0.395).[253]

All Stroke

The rate of all strokes was lower in the LAA group in the RCT,[288] although the difference did not reach statistical significance (RR 0.71; 95% CI 0.35 to 1.64).

In the observational studies, there was no evidence of a difference in risk of TIA or stroke between devices compared in these studies. A U.S. study showed no evidence of a difference in risk of TIA or stroke following LAA closure with Watchman versus Lariat devices (1.3% vs. 1.1%; p=0.99).[337] A study comparing Watchman to ACP had 0 patients in the Watchman group and 1 patient in the ACP group with TIA; p=0.385; neither group had any ischemic strokes.[253] Low SOE for no evidence of a difference in stroke risk.

Bleeding Outcomes

Major Bleeding

In the RCT,[288] major bleeding was less frequent in the LAA group than in the warfarin group (3.5% vs. 4.1%) (low SOE).

Other Clinical Outcomes

All-Cause Mortality

In the RCT,[288] the cumulative mortality rates were similar between the groups in the first year (3% in the LAA group and 3.1% in the warfarin group) and lower in the LAA group at 2 years (9.1% vs. 5.9%; RR 0.62; 95% CI 0.34 to 1.24).

There was no evidence of a difference in mortality between devices compared in the observational studies. An Italian retrospective study[253] over a mean followup of 448 days, showed nonsignificant difference in overall mortality, cardiovascular mortality and major bleeding in those who received the Watchman versus ACP device (mortality overall: 0% vs. 5.4%; p=0.157; cardiovascular mortality: 0% vs. 2.0%; p=0.519; major bleeding: 1.5% vs. 1.1%; p=1.0). This was similarly seen in the German study[227] comparing these devices. Over a median of 364 days, there was no statistically significant difference in overall mortality between the Watchman group and the ACP device (2.6% vs. 5%; p=1.0). The U.S. study comparing Watchman and Lariat devices[337] had no cases of death attributed to the respective devices.

Reddy and colleagues[341] carried out a 3.8-year follow up of the PROTECT-AF trial to determine whether a local strategy of mechanical left atrial appendage (LAA) closure was noninferior to warfarin. At a mean (SD) followup of 3.8 (1.7) years (2621 patient-years), there were 39 events among 463 patients (8.4%) in the device group for a primary event rate of 2.3 events per 100 patient-years, compared with 34 events among 244 patients (13.9%) for a primary event rate of 3.8 events per 100 patient-years with warfarin (rate ratio, 0.60; 95% credible interval, 0.41 to 1.05), meeting prespecified criteria for both noninferiority (posterior probability, >99.9%) and superiority (posterior probability, 96.0%). Patients in the device group demonstrated lower rates of both cardiovascular mortality (1.0 events per 100 patient-years for the device group [17/463 patients, 3.7%] vs. 2.4 events per 100 patient-years with warfarin [22/244 patients, 9.0%]; HR 0.40; 95% CI 0.21 to 0.75; p=.005) and all-cause mortality (3.2 events per 100 patient-years for the device group [57/466 patients, 12.3%] vs. 4.8 events per 100 patient-years with warfarin [44/244 patients, 18.0%]; HR 0.66; 95% CI 0.45 to 0.98; p=.04). Given the findings across the included studies, there was low SOE for no evidence of a benefit in all-cause mortality.

Adverse Events

The primary composite outcome for safety in the RCT[288] consisted of excessive bleeding or procedure-related complications. This outcome was more frequent in the LAA group (RR 1.69; 95% CI 1.01 to 3.19). At 2 years the cumulative primary safety event rate (events related to excessive bleeding [eg, intracranial or gastrointestinal bleeding] or procedure-related complications [eg, serious pericardial effusion, device embolisation, or procedure-related stroke]) was 10.2 percent and 6.8 percent for the LAA and warfarin groups, respectively. This was driven by two procedure-related complications: pericardial effusion (4.8% in the LAA group and none in the warfarin group) and device embolization (0.6% in the LAA group and none in the warfarin group) (moderate SOE).

In the PROTECT AF (Watchman Left Atrial Appendage Closure Technology for Embolic Protection in Patients With Atrial Fibrillation) trial that evaluated patients with nonvalvular atrial fibrillation (NVAF), left atrial appendage (LAA) occlusion was noninferior to warfarin for stroke prevention, but a periprocedural safety hazard was identified. The PREVAIL trial[289] was carried out to assess the safety and efficacy of LAA occlusion for stroke prevention in patients with

NVAF compared with long-term warfarin therapy. This randomized trial further assessed the efficacy and safety of the Watchman device. Patients with NVAF who had a CHADS2 (congestive heart failure, hypertension, age >75 years, diabetes mellitus, and previous stroke/transient ischemic attack) score ≥2 or 1 and another risk factor were eligible. Patients were randomly assigned (in a 2:1 ratio) to undergo LAA occlusion and subsequent discontinuation of warfarin (intervention group, n = 269) or receive chronic warfarin therapy (control group, n = 138). Two efficacy and 1 safety coprimary endpoints were assessed. At 18 months, the rate of the first coprimary efficacy endpoint (composite of stroke, systemic embolism, and cardiovascular/unexplained death) was 0.064 in the device group versus 0.063 in the control group (rate ratio 1.07 [95% credible interval (CrI) 0.57 to 1.89]) and did not achieve the prespecified criteria noninferiority (upper boundary of 95% CrI ≥1.75). The rate for the second coprimary efficacy endpoint (stroke or systemic embolism >7 days' postrandomization) was 0.0253 versus 0.0200 (risk difference 0.0053 [95% CrI: -0.0190 to 0.0273]), achieving noninferiority. Early safety events occurred in 2.2% of the Watchman arm, significantly lower than in PROTECT AF, satisfying the prespecified safety performance goal. Using a broader, more inclusive definition of adverse effects, these still were lower in PREVAIL (Watchman LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy) trial than in PROTECT AF (4.2% vs. 8.7%; p=0.004). Pericardial effusions requiring surgical repair decreased from 1.6% to 0.4% (p=0.027), and those requiring pericardiocentesis decreased from 2.9% to 1.5% (p=0.36), although the number of events was small.

Two observational studies examined devices leaks following LAA closure.[253,337] Both found a higher incidence of leaks with the Watchman device in comparison to their respective comparators. A U.S. study[337] showed more device leaks in those patients receiving Watchman devices. At the end of the procedure, 5% in the Watchman group versus 2% in the Lariat group had residual leaks (p=0.065) All the leaks were eccentric (toward the periphery of the device) in the Watchman group and centric (middle of the appendage ostium) in the Lariat group. At 30 to 90-day followup TEE, the Watchman group had a statistically higher incidence (25% vs. 13%;P=.001) and size (2.6±0.82 mm vs. 2.28±1.5 mm; p=.005) of leaks compared to the Lariat group. At 9-12 months of followup, the Watchman group continued to have a statistically higher incidence (21% vs. 13%; p=.019) and mean leak size (3.10±1.1 mm vs. 2.15±1.4 mm; p<.001) than did the Lariat group.

An Italian study[253] similarly saw a higher incidence of both severe peri-device leak (>3mm) and moderate peri-device leaks (>1mm) with the Watchman versus Amplatzer device (severe: 18.0% vs. 6.3%; p=0.037; moderate 34% vs. 14%; p=0.004). The use of intraoperative 3D TEE (OR 0.195, 95% CI 0.064 to 0.596; p=0.004) as well as use of Amplatzer device (OR 0.288, 95% CI 0.120 to 0.695; p=0.006) were associated with reduced risk of peri-leak.

Observational studies did not show any statistically significant difference in pericardial effusions between devices. An Italian study[253] showed a numerically higher, but nonsignificant, incidence of pericardial effusions with the Watchman device versus ACP (4.5% vs. 1.0%; p=0.1.0). There was additionally no evidence of a difference in cases of pericardial tamponade (1.5% vs. 0%; p=1.0). This was similarly seen in a German study comparing these devices, with 1 case of delayed tamponade in each of the Watchman and ACP device groups, P=1.00.[227]

Finally, a U.S. study comparing Watchman to Lariat LAA occlusion devices showed no statistically significant difference in pericardial effusions (1% vs. 0%) or cardiac tamponade (0% vs. 1.5%) between the groups, however noted that after switching needles for pericardial access midway through the study no tamponade or effusions occurred.[337]

Quality-of-Life Assessment

Alli and colleagues[212] assessed quality of life parameters in a subset of patients enrolled in the PROTECT AF. QOL using the Short-Form 12 Health Survey, version 2, measurement tool was obtained at baseline and 12 months in a subset of 547 patients in the PROTECT AF trial (361 device and 186 warfarin patients). The analysis cohort consisted of patients for whom either paired quality of life data were available after 12 months of followup or for patients who died. With the device, the total physical score improved in 34.9% and was unchanged in 29.9% versus warfarin in whom 24.7% were improved and 31.7% were unchanged (p = 0.01). Mental health improvement occurred in 33.0% of the device group versus 22.6% in the warfarin group (p = 0.06). There was a significant improvement in QOL in patients randomized to device for total physical score, physical function, and in physical role limitation compared to control. There were significant differences in the change in total physical score among warfarin naive and not-warfarin naive subgroups in the device group compared to control, but larger gains were seen with the warfarin naive subgroup with a 12-month change of 1.3 ± 8.8 versus -3.6 ± 6.7 (p = 0.0004) device compared to warfarin.

Strength of Evidence

Table 73 summarizes the SOE for outcomes of interest for this comparison.

Table 73. Strength of evidence domains for preventing thromboembolic events—percutaneous LAA closure versus warfarin

Outcome	Number of Studies (Subjects)	Risk of Bias	Consistency	Directness	Precision	Reporting Bias	SOE and Effect (95% CI)
Ischemic stroke	1 RCT[288] (707)	Low	NA	Direct	Imprecise	None	**SOE=Low** 9 LAA patients (1.3 events per 100 patient-years) and 6 warfarin patients (1.6 events per 100 patient-years) had ischemic stroke, demonstrating no evidence of a difference between therapies
All strokes	1 RCT[288] (707) 2 Obs[253,337] (643)	Low	Consistent	Direct	Imprecise	None	**SOE=Low** No evidence of a difference
Major bleeding	1 RCT[288] (707)	Low	NA	Direct	Imprecise	None	**SOE=Low** Less frequent with LAA (3.5% vs. 4.1%)
All-cause mortality	1 RCT[288] (707) 4 Obs[227,253,337,341] (1,430)	Low	Consistent	Direct	Imprecise	None	**SOE=Low** No evidence of a difference

Outcome	Number of Studies (Subjects)	Risk of Bias	Consistency	Directness	Precision	Reporting Bias	SOE and Effect (95% CI)
Adverse events	2 RCTs[288] (1,114) 3 Obs[227,253,337] (723)	Low	Consistent	Direct	Imprecise	None	**SOE=Moderate** Higher rate with LAA

Abbreviations: CI=confidence interval; LAA=left atrial appendage; NA=not applicable; Obs=observational; RCT=randomized controlled trial; SOE=strength of evidence

19. Outcomes for Specific Subgroups of Interest

Many of our included studies focused on the comparative safety and effectiveness of specific anticoagulation therapies, antiplatelet therapies, and procedural interventions for preventing thromboembolic events in specific subgroups of interest within patients with nonvalvular AF. We summarize the findings from these studies in Table 74. Given the heterogeneity of these studies and the populations and outcomes that they assessed, we only summarize them qualitatively and do not perform quantitative synthesis. More detailed descriptions of the findings from the individual studies are found in Appendix G.

Table 74. Summary of findings for specific subgroups of interest

Subgroup	Number and Study Design of Studies	Findings
Patients not eligible for warfarin use	2 RCTs[115,233]	Two studies, evaluating very different interventions, included patients with nonvalvular AF who were deemed unsuitable for oral anticoagulation with warfarin. One study found that clopidogrel plus aspirin was superior to aspirin alone for stroke prevention, but was associated with a higher risk of bleeding. A second study found that apixaban compared with aspirin was associated with a lower risk of stroke and no evidence of a difference in risk of bleeding.
Patients with AF and renal impairment	1 primary RCT, 5 substudies from 5 RCTs, and 2 observational studies[26,247,261,281,282,286,376,387]	These studies demonstrated that compared to participants with normal renal function, participants with renal disease had increased risk of ischemic events, bleeding, and all-cause mortality. In all sub-studies, among participants with renal disease, use of the DOACs were consistently similar to or better than warfarin in the prevention of stroke/systemic embolism and bleeding events. One sub-study demonstrated that in patients with stage 3 CKD, compared to aspirin, apixaban was associated with lower risk of stroke and no evidence of a difference in bleeding. One observational study indicated a higher

Subgroup	Number and Study Design of Studies	Findings
		risk of GI bleed for patients on dabigatran as compared to warfarin, though a reduced risk of stroke.
Patients with paroxysmal versus sustained AF	2 substudies from 2 RCTs[211,284]	Analysis of two large RCTs evaluated for differences in treatment effects (clopidogrel plus aspirin vs. warfarin or apixaban vs. warfarin) for stroke prevention/bleeding by type of AF (paroxysmal or persistent). In neither study was there a difference in treatment effect by type of AF.
Patients with recently diagnosed AF	1 substudy of an RCT[270]	Regardless of timing of diagnosis, apixaban had similar benefits on prevention of stroke or systemic embolism and major bleeding compared to warfarin
Patients with AF after stroke	1 RCT and 5 substudies of 5 RCTs[219,241,242,244,274,342], 1 observational study[392]	Studies were inconsistent in terms of the interventions evaluated and their findings. Three studies compared anticoagulation to aspirin therapy. Anticoagulation with either apixaban or warfarin was superior to aspirin therapy in preventing recurrent thromboembolism. Four studies compared direct oral anticoagulants to warfarin therapy. These studies demonstrated that there was no evidence of a difference in risk of stroke or systemic embolism when comparing direct oral anticoagulants (edoxaban, rivaroxaban, apixaban, dabigatran 110mg BID) to warfarin therapy. The only exception was the dabigatran 150mg BID dose showed reduced risk of stroke or systemic embolism compared to warfarin therapy
Patients with acute stroke and known or newly diagnosed AF	1 observational study[375]	There was no statistical difference for patients on dabigatran, apixaban, or rivaroxaban for ischemic outcomes.
Patients with AF and different thromboembolic risks	1 RCT, 2 substudies of 1 RCT, 1 observational studies[141,232,313,333]	The studies were inconsistent in terms of the comparisons evaluated and the findings. Two studies showed a decrease in risk of thromboembolism when comparing warfarin therapy to aspirin and clopidogrel regardless of calculated risk. When comparing direct oral anticoagulants (apixaban or dabigatran) to warfarin therapy, a decrease in risk of thromboembolism was seen with direct oral anticoagulant

Subgroup	Number and Study Design of Studies	Findings
		agents. Lastly, one study looking at only patients with CHA_2DS_2-VASc score=0 showed no evidence of a difference in risk of thromboembolism between those using oral anticoagulation and/or antiplatelet therapy
Patients with AF according to INR control	2 substudies from 2 RCTs and 2 observational studies[127,215,336,364]	The first two studies from this group suggest that compared to aspirin or no therapy, an INR ≥ 2 lowers the risk of ischemic stroke. However, INR values above the therapeutic range may lead to higher rates of hemorrhagic stroke. The second two studies compared treatment with warfarin to a factor Xa inhibitor and showed that there was no evidence of a difference in the treatment effect of rivaroxaban and apixaban across the ranges of INR values examined with regard to stroke or systemic embolism outcomes. There is mixed data regarding the interaction between INR control and treatment with regard to bleeding outcomes.

Subgroup	Number and Study Design of Studies	Findings
Elderly patients with AF	3 RCTs, 5 substudies of 4 RCTs, and 4 observational studies[210,246,262,269,271,272,283,320,339,350,358,376,387,388]	Twelve studies including observational, small RCTs, and sub-studies of large RCTs compared the effect of different strategies to prevent stroke and bleeding in elderly participants with AF. Of 7 studies comparing the effects of warfarin vs. aspirin in older adults, compared to aspirin, warfarin was generally found to be associated with lower risk of stroke/systemic embolism/bleeding for both primary and secondary prevention. In studies comparing the effects of DOACs vs. warfarin, the DOACs were generally found to be associated with similar or decreased risk of stroke/systemic embolism/bleeding compared with warfarin among older adults. One prospective cohort study did find an increased risk of GI bleeding and intracranial hemorrhage with rivaroxaban as compared to dabigatran. Another observational study found higher rates of GI bleeding and myocardial infarction for those on dabigatran compared to warfarin for those aged 75 to 84 years, and for those aged 85 years or older, but lower risk of major non-GI extracranial hemorrhage with dabigatran compared to warfarin..
Patients with AF and myocardial infarction	1 substudy of 1 RCT[23]	In this analysis, the relative effects of dabigatran versus warfarin on myocardial ischemic events were consistent in patients with or without a baseline history of MI or coronary artery disease.
Elderly patients with AF and myocardial infarction	1 observational study[259]	Relative to aspirin alone, antithrombotics were associated with increased bleeding risk. Patients treated with triple therapy of aspirin+clopidogrel+warfarin had the greatest bleeding risk. The rates of major cardiac outcomes (death, readmission for MI, or stroke) were similar between groups, although relative to aspirin alone, there was a trend toward lower risk for the warfarin+aspirin group.
Patients with AF and peripheral artery disease	1 substudy of 1 RCT[290]	Compared to those without PAD, patients with PAD had similar prevention of stroke and systemic embolism with apixaban versus

Subgroup	Number and Study Design of Studies	Findings
		warfarin. There was similarly no statistically significant interaction between presence of PAD and treatment group on major bleeding. While data is only available from one study, this suggests that patients with PAD had similar benefit from treatment with apixaban as compared to those without.
Patients with AF carotid artery disease	1 substudy of 1 RCT[399]	This single study evaluated outcomes in patients with AF and carotid artery disease, treated with either warfarin or rivaroxaban. There was no statistically significant interaction between treatment and presence of carotid artery disease with either ischemic or bleeding outcomes.
Patients with AF and underlying anemia	1 substudy of 1 RCT[367]	There was no evidence of a difference in the benefits of reduced stroke or systemic embolization events with apixaban in patients with anemia. The incidence of new anemia during treatment was lower in patients with apixaban and there was no statistically significant interaction between underlying anemia and treatment group on any of the bleeding outcomes. This single analysis suggests that the same benefits of apixaban, including decreased risk of stroke or systemic embolism, extend to patients with underlying anemia without differential change in bleeding risk.
Patients with AF and history of bleeding	1 substudy of 1 RCT[237]	Patients treated with apixaban had consistently lower rates of bleeding overall and this extended to patients with prior history of bleeding. While only informed by one study, this suggests that the lower rates of bleeding observed with treatment with apixaban compared to warfarin are generally similar for patients with a history of bleeding. This benefit may not include lower rates of major or clinically relevant non-major bleeding; further data is necessary to clarify this borderline result.
Patients with AF and chronic obstructive pulmonary disease	1 substudy of 1 RCT[243]	Overall, all-cause mortality was higher in patients with a diagnosis of COPD while there was no statistically significant difference in major bleeding. There was no statistically significant difference in the effect of apixaban on

Subgroup	Number and Study Design of Studies	Findings
		all-cause mortality, stroke or systemic embolism, or major bleeding in patients with and without COPD. This single analysis suggests that there is no treatment difference in the benefits observed with apixaban in patients with or without COPD.
Patients with AF by sex	2 substudies of 2 RCTs[306,363]	In only two studies assessing potentially differences in treatment effect by sex both included apixaban but the comparators were different – one was warfarin and one was aspirin. No interaction between sex and treatment was found for major bleeding (for either comparator, warfarin or aspirin) or for ischemic stroke (as compared to aspirin).
Patients with AF and diabetes	3 substudies of 3 RCTs and 1 observational[217,223,252,387]	The results from four studies assessing the potential impact of diabetes on treatment effect were inconsistent; in one study no impact on treatment effect was seen between dabigatran and warfarin on any of the included efficacy or safety outcomes; in a second study diabetics did not have the same statistically significant reduction in major bleeding as non-diabetics; and in the third study diabetics had a statistically significant reduction that was not seen in non-diabetics. In the final study there was no evidence of a difference between diabetes and no diabetes in stratified results
Patients with AF and aspirin treatment	3 substudies from 3 RCTs[209,348,368]	From a total of three studies, no impact on treatment effect between apixaban, rivaroxaban, low dose endoxaban or high dose endoxaban vs. warfarin was seen in patients with concomitant aspirin administration.
Patients with AF and hypertension	1 substudy of 1 RCT and 1 observational study[359,387]	There was no statistically significant interaction between treatment and HTN status (no HTN versus controlled hypertension versus uncontrolled hypertension) on all ischemic/thrombotic or bleeding outcomes.
Patients with AF and heart failure	2 substudies from 2 RCTs and 1 observational study[316,356,387]	Data from three studies give similar findings and suggest that patients had similar ischemic and bleeding outcomes based on the treatment received regardless of heart failure status.

Subgroup	Number and Study Design of Studies	Findings
Patients with AF and left ventricular hypertrophy	1 substudy of 1 RCT[360]	In this single study, the treatment effect (reduced risk of stroke or systemic embolism, reduced risk of any stroke and no evidence of a difference in major bleeding) between the FDA approved 150 mg dose of dabigatran and warfarin was not statistically significantly impacted by left ventricular hypertrophy.
Patients with AF and history of falls	1 substudy of 1 RCT[377]	This single study evaluated the comparison of treatment with apixaban versus warfarin in patients with a history of falling. No statistically significant interaction was found between a history of falls and treatment with apixaban versus warfarin for either ischemic (stroke or systemic embolism) or bleeding endpoints.
Patients with AF and a history of cancer	1 substudy of 1 RCT[390]	A single study evaluated the outcomes of patients with AF, a history of cancer and treated with apixaban or warfarin. There was no statistically significant interaction between a history of cancer and treatment with apixaban versus warfarin on either ischemic or bleeding outcomes. There was a trend toward a significant interaction between cancer status and treatment effect only for death from any cause although this did not reach statistical significance.
Patients with AF and reduced kidney function	2 observational studies[376,401]	Compared with warfarin, those on dabigatran, had higher risk of GI bleed but a reduced risk of stroke. DOACs had similar rates of major bleeding, ischemic stroke, GI bleeding, and death among cohort with CKD.
Patients with active cancer	1 observational study[402]	A U.S. propensity-matched observational study using MarketScan specifically looked at outcomes of interest in patients with nonvalvular AF and active cancer. This study found no evidence of a difference in risk for the outcomes of ischemic stroke and major bleeding comparing dabigatran and warfarin. No evidence of a difference in major bleeding was found when comparing rivaroxaban and warfarin, however a reduction was demonstrated with apixaban compared warfarin.

Abbreviations: AF=atrial fibrillation; BID=two times per day; CKD=chronic kidney disease; COPD=chronic obstructive pulmonary disease; DOAC=direct oral anticoagulant; HTN=hypertension; INR=international normalized ratio; MI=myocardial infarction; PAD=peripheral artery disease; RCT=randomized controlled trial

Discussion

Key Findings and Strength of Evidence

In this Comparative Effectiveness Review (CER), we reviewed 185 unique studies represented by 320 publications that evaluated stroke and bleeding prediction tools and stroke prevention strategies in patients with nonvalvular atrial fibrillation (AF).

KQ 1. Predicting Thromboembolic Risk

Our review included 61 studies comparing the diagnostic accuracy and impact on clinical decisionmaking of available clinical and imaging tools for predicting thromboembolic risk. The clinical tools assessed for this question included the $CHADS_2$ score (Congestive heart failure, Hypertension, Age ≥75, Diabetes mellitus, prior Stroke/transient ischemic attack [2 points]), CHA_2DS_2-VASc score (Congestive heart failure/left ventricular ejection fraction ≤ 40%, Hypertension, Age ≥75 [2 points], Diabetes mellitus, prior Stroke/transient ischemic attack/thromboembolism [2 points], Vascular disease, Age 65–74, Sex category female), Framingham risk score, ABC (age, biomarkers, clinical history), imaging tools, as well as individual patient risk factors not included in the existing tools. Current guidelines recommend that oral anticoagulation be considered in patients with $CHADS_2$ or CHA_2DS_2-VASc score ≥2.

The reviewed studies had varying categorical arrangements of risk scores with patients receiving antiplatelet therapy and/or anticoagulant therapy or not, making direct comparisons across studies examining these tools difficult. The $CHADS_2$, CHA_2DS_2-VASc, and ABC scores had the best prediction abilities given available evidence, but this advantage was incremental on an absolute basis. Imaging risk tools found conflicting results when the presence of left atrial thrombus was assessed, and there was insufficient evidence to support conclusions.

Our conclusions may be limited by the limitations in the development and validation of risk scores. Specifically, although many of the studies use clinical data sources to derive or validate these risk scores, some studies relied on billing data and institutional electronic medical records to identify patients with AF and comorbidity information. Since few of these administrative studies used a formal clinical adjudication process to validate the occurrence of a clinical event and may suffer from insufficient coding, the risk scores could underestimate stroke risk, particularly in patients incorrectly identified as having few or no comorbidities. Likewise, lack of validated results or common event definitions for the endpoints of thromboembolism and bleeding could have underestimated the performance of these risk scores. Additionally, lack of standard definitions for comorbidities such as heart failure, diabetes mellitus, hypertension, etc. could also lead to discrepancies across studies validating the various risk scores. Moreover, our review included both ambulatory and hospitalized patients, which inherently introduces bias in comparing studies and results give the heterogeneity with regard to stability of covariates, concomitant medications, stroke inducing procedures, etc.

Table 75 summarizes the strength of evidence (SOE) for the thromboembolic risk prediction abilities of the included tools. This summary table represents only those studies that evaluated the risk prediction abilities of the tools using a c-statistic. Details about the specific components of these ratings (risk of bias, consistency, directness, and precision) are available in the Results section.

Table 75. Summary of strength of evidence and c-statistic estimate for Key Question 1 (prediction of thromboembolic risk)

Tool	Number of Studies (Patients)	Strength of Evidence and Effect Estimate
$CHADS_2$ (Categorical)	16 (548,464)	**SOE=Moderate** Limited risk prediction (c-statistic 0.66, 95% CI -.63 to 0.69)
$CHADS_2$ (Continuous)	14 (489,335)	**SOE=Moderate** Limited risk prediction ability (c-statistic 0.69; 95% CI 0.66 to 0.73)
CHA_2DS_2-VASc (Categorical)	13 (496,683)	**SOE=Low** Limited risk prediction ability (c-statistic 0.64; 95% CI 0.58 to 0.70)
CHA_2DS_2-VASc (Continuous)	16 (511,481)	**SOE=Moderate** Limited risk prediction ability (c-statistic 0.66; 95% CI 0.63 to 0.69)
Framingham (Categorical)	6 (282,572)	**SOE=Moderate** Limited risk prediction ability (c-statistic 0.63; 95% CI 0.62 to 0.65)
Framingham (Continuous)	4 (274,538)	**SOE=Low** Limited risk prediction ability (c-statistic ranges between 0.64 and 0.69 across studies)
ABC (Categorical)	4 (25,614)	**SOE=Moderate** Limited risk prediction ability (c-statistic 0.67; 95% CI 0.63 to 0.71)

Abbreviations: ABC=age, biomarkers, clinical history, CI=confidence interval; $CHADS_2$=Congestive heart failure, Hypertension, Age ≥75, Diabetes mellitus, prior Stroke/transient ischemic attack (2 points); CHA_2DS_2-VASc=Congestive heart failure/left ventricular ejection fraction ≤ 40%, Hypertension, Age ≥75 (2 points), Diabetes mellitus, prior Stroke/transient ischemic attack/thromboembolism (2 points), Vascular disease, Age 65–74, Sex category female; SOE=strength of evidence

KQ 2. Predicting Bleeding Events

Thirty-eight studies were included in our analyses comparing the diagnostic accuracy and impact on clinical decisionmaking of clinical tools and associated risk factors for predicting bleeding events. Five different bleeding risk scores were evaluated in these studies, including ATRIA, ABC, Bleeding Risk Index, HAS-BLED, and $HEMORR_2HAGES$.

Of note, many included studies used administrative data sources to identify patients with AF, as well as comorbidity information. As a result, many of the included studies used different approaches to calculating the risk scores of interest due to unavailable data, particularly for the $HEMORR_2HAGES$ and HAS-BLED scores. For example, in $HEMORR_2HAGES$, due to unavailability of information on genetic factors, multiple database studies left out the "genetic factors" component of the score. To further complicate this issue, not all studies described in detail whether certain factors were omitted from their calculations of these scores. Inter-study differences in approach to calculating some of the bleeding risk scores limited comparison of bleeding risk scores across populations and precluded meta-analysis. Similarly, use of administrative data in some cases prevented validation of clinical bleeding events, and this could have affected studies' estimates of the performance of these risk scores.

Among the tools for predicting risk of major bleeding and ICH, there was a suggestion that HAS-BLED is the most accurate for predicting major bleeds in patients on warfarin although only has modest prediction abilities; but the majority of studies for other patient scenarios showed no statistically significant differences in predictive accuracy among tools. Evaluating these bleeding risk prediction scores was complicated by the fact that, though studies

consistently reported event rates and c-statistics, measures of calibration, strength of association, and diagnostic accuracy were inconsistently reported.

Table 76 summarizes the SOE for the bleeding risk prediction abilities of the included tools. This summary table represents only those studies that evaluated the risk prediction abilities of the tools using a c-statistic. Details about the specific components of these ratings (risk of bias, consistency, directness, and precision) are available in the Results section.

Table 76. Summary of strength of evidence and c-statistic estimate for Key Question 2 (prediction of bleeding risk)

Tool	Number of Studies (Patients)	Strength of Evidence and Effect Estimate[a]
Summary c-statistic		
BRI	4 (11,939)	**SOE=Moderate** Limited risk discrimination ability (c-statistic ranging from 0.56 to 0.65)
$HEMORR_2HAGES$	10 (115,348)	**SOE=Moderate** Limited risk discrimination ability (c-statistic ranging from 0.53 to 0.78)
HAS-BLED	11 (194,839)	**SOE=Moderate** Modest risk discrimination ability (c-statistic ranging from 0.50 to 0.80)
ABC	1 (22,998)	**SOE=Low** Limited risk discrimination (c-statistic of 0.65 in validation study)
Comparative Risk Prediction Abilities		
Major bleeding events among patients with AF on warfarin	13 (351,985)	**SOE=Moderate** Favors HAS-BLED
Intracranial hemorrhage among patients with AF on warfarin	2 (71,597)	**SOE=Low** No evidence of a difference
Major bleeding events among patients with AF on aspirin alone	3 (177,538)	**SOE=Low** No evidence of a difference
Major bleeding events among patients with AF not on antithrombotic therapy	6 (310,607)	**SOE=Low** No evidence of a difference

[a] As a reminder, for a clinical prediction rule, we assumed that a c-statistic <0.6 had no clinical value, 0.6–0.7 had limited value, 0.7–0.8 had modest value, and >0.8 has prediction adequate for genuine clinical utility.[94]

Abbreviations: ABC=age, biomarkers, clinical history; AF=atrial fibrillation; ATRIA=Anticoagulation and Risk Factors in Atrial Fibrillation; BRI=Bleeding Risk Index; CI=confidence interval; HAS-BLED=Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (> 65 years), Drugs/alcohol concomitantly; $HEMORR_2HAGES$=Hepatic or renal disease, Ethanol abuse, Malignancy, Older (age >75 years), Reduced platelet count or function, Rebleeding risk (2 points), Hypertension (uncontrolled), Anemia, Genetic factors, Excessive fall risk, Stroke; KQ=Key Question; SOE=strength of evidence

KQ 3. Interventions for Preventing Thromboembolic Events

Our review included 117 studies comparing the safety and effectiveness of specific anticoagulation therapies, antiplatelet therapies, and procedural interventions for preventing thromboembolic events. Among these studies, several direct oral anticoagulant agents were evaluated including thrombin inhibitors (dabigatran) and Xa inhibitors (apixaban, edoxaban, rivaroxaban, idraparinux). The included RCTs were often very large, of good quality, and considered definitive in the field. These trials were, however, limited to comparing direct oral anticoagulant therapies with warfarin or aspirin and have not involved head-to-head comparison among the newer agents. Based on these trials though, clinical leaders and professional societies

have determined that these newer agents are better than the prior lone treatment of warfarin in terms of stroke prevention, side effects, and risk of bleeding.

In comparative effectiveness analyses, warfarin was found to be superior to aspirin for stroke prevention, and the combination of aspirin and clopidogrel was found to be superior to aspirin alone in patients with warfarin contraindications. Triple therapy with aspirin, clopidogrel, and warfarin did not provide any additional stroke protection beyond warfarin alone, but increased bleeding events significantly. Percutaneous left atrial appendage (LAA) closure is non-inferior to warfarin, while direct oral antithrombotics (apixaban, rivaroxaban, dabigatran) were non-inferior or superior to warfarin for stroke prevention.

Table 77 summarizes the SOE for the various comparisons and outcomes of interest. Details about the specific components of these ratings (risk of bias, consistency, directness, and precision) are available in the Results section.

Table 77. Summary of strength of evidence and effect estimate for Key Question 3 (interventions for preventing thromboembolic events)

Outcome	Number of Studies (Subjects)	SOE and Effect (95% CI)
ASA vs. Warfarin		
Ischemic stroke	5 (251,578)	**SOE=Moderate** Reduction in stroke with warfarin
Bleeding	4 (213,371)	**SOE=Moderate** Warfarin associated with increased rates of bleeding
Warfarin+ASA vs. Warfarin Alone		
Ischemic stroke	1 (69,264)	**SOE=Moderate** HR 1.27 (95% CI 1.14 to 1.40) increase with warfarin+ASA
Stroke or systemic embolism	1 (3,624)	**SOE=Low** No evidence of differences between those with or without ASA regardless of TTR
Bleeding	2 (141,223)	**SOE=Moderate** Increased with warfarin+ASA
Major bleeding	1 (32,770)	**SOE=Low** Increased with TTR < 65% without ASA (HR 1.93; 95% CI 1.29 to 2.87) or with ASA (HR 2.24; 95% CI 1.28 to 3.93) as compared to no ASA + TTR□65%;
All Cause Mortality	1 (3,624)	**SOE=Low** Increased with TTR < 65% without ASA (HR 1.80; 95% CI 1.31 to 2.47) or with ASA (HR 1.74; 95% CI 1.12 to 2.72) as compared to no ASA + TTR≥65%
Clopidogrel+ASA vs. ASA Alone		
Any stroke	2 (8,147)	**SOE=Moderate** Lower rates with combined therapy (HR 0.72; 95% CI 0.62 to 0.83)
Ischemic stroke	2 (8,147)	**SOE=Low** Lower rates with combined therapy (HR 0.68; 95% CI 0.57 to 0.80)
Hemorrhagic stroke	2 (8,147)	**SOE=Moderate** Similar between therapies in both studies
Systemic embolism	1 (7,554)	**SOE=Moderate** Similar between therapies (HR 0.96; 95% CI 0.66 to 1.40)
Major bleeding	1 (7,554)	**SOE=Moderate** Clopidogrel+ASA associated with higher rates (HR 1.57; 95% CI 1.29 to 1.92)

Outcome	Number of Studies (Subjects)	SOE and Effect (95% CI)
Minor bleeding	1 (7,554)	**SOE=Moderate** Clopidogrel+ASA associated with higher rates (HR 2.42; 95% CI 2.03 to 2.89)
Intracranial bleeding	2 (8,147)	**SOE=Low** Higher rate with clopidogrel+ASA (HR 1.87; 95% CI 1.19 to 2.94)
All-cause mortality	2 (8,147)	**SOE=Moderate** No evidence of a difference (HR 0.98 [95% CI 0.89 to 1.08]; and HR 1.12 [95% CI 0.65 to 1.90])
Death from vascular causes	2 (8,147)	**SOE=Low** No evidence of a difference based on large RCT (HR 1.00; 95% CI 0.89 to 1.12), although a smaller study showed a trend toward a benefit of ASA alone (HR 1.68; 95% CI 0.83 to 3.42)
Myocardial infarction	2 (8,147)	**SOE=Low** No evidence of a difference based on large RCT (HR 0.78; 95% CI 0.59 to 1.03), although a smaller study showed a trend toward a benefit of ASA alone (HR 1.43; 95% CI 0.51 to 4.01)
Clopidogrel vs. Warfarin		
Ischemic stroke	1 (54,636)	**SOE=Moderate** Increased risk with clopidogrel (HR 1.86; 95% CI 1.52 to 2.27)
Bleeding	1 (54,636)	**SOE=Moderate** Similar between therapies (HR 1.06; 95% CI 0.87 to 1.29)
Clopidogrel+ASA vs. Warfarin		
Stroke or systemic embolism	2 (60,484)	**SOE=High** Clopidogrel+ASA increased risk in both studies (HR 1.56 [95% CI 1.17 to 2.10]; and HR 1.72 [95% CI 1.24 to 2.37])
Hemorrhagic stroke	1 (6,706)	**SOE=Moderate** Increased risk with warfarin (HR 0.34 [95% CI 0.12 to 0.93])
Major bleeding	2 (60,484)	**SOE=Low** Similar rates between therapies (HR 1.10; 95% CI 0.83 to 1.45),
Minor bleeding	1 (6,706)	**SOE=Moderate** Clopidogrel+ASA increased risk (HR 1.23; 95% CI 1.09 to 1.39)
All-cause mortality	1 (6,706)	**SOE=Moderate** No evidence of a difference (HR 1.01; 95% CI 0.81 to 1.26)
Death from vascular causes	1 (6,706)	**SOE=Moderate** No evidence of a difference (HR 1.14; 95% CI 0.88 to 1.48)
Myocardial infarction	1 (6,706)	**SOE=Moderate** No evidence of a difference (MI occurred at rates of <1% per year with both therapies)
Warfarin+Clopidogrel vs. Warfarin Alone		
Ischemic stroke	1 (52,349)	**SOE=Low** Trend toward benefit of warfarin+clopidogrel (HR 0.70; 95% CI 0.35 to 1.40)
Bleeding	1 (52,349)	**SOE=Moderate** Higher for patients on warfarin+clopidogrel (HR 3.08; 95% CI 2.32 to 3.91)
Warfarin Alone vs. Warfarin+ASA+Clopidogrel		
Ischemic stroke	1 (52,180)	**SOE=Low** Trend toward being higher for patients on triple therapy (HR 1.45; 95% CI 0.84 to 2.52)
Bleeding	1 (52,180)	**SOE=Moderate** Higher for patients on triple therapy (HR 3.70; 95% CI 2.89 to 4.76)
Factor IIa Inhibitor (Dabigatran 150 mg) vs. Warfarin		

Outcome	Number of Studies (Subjects)	SOE and Effect (95% CI)
Stroke or systemic embolism	1 RCT (12,098) 10 Obs (662,920)	**SOE=High** Dabigatran reduced risk (RR 0.66; 95% CI 0.53 to 0.82)
Ischemic or uncertain stroke	1 RCT (12,098) 15 Obs (963,214)	**SOE=Low** Dabigatran reduced risk (RR 0.76; 95% CI 0.60 to 0.98)
Hemorrhagic stroke	1 RCT (12,098) 8 Obs (653,067)	**SOE=High** Dabigatran reduced risk (RR 0.26; 95% CI 0.14 to 0.49)
Major bleeding	1 RCT (12,098) 20 Obs (692,782)	**SOE=High** No evidence of a difference (RR 0.93; 95% CI 0.81 to 1.07)
Minor bleeding	1 RCT (12,098)	**SOE=Moderate** Dabigatran reduced risk (RR 0.91; 95% CI 0.85 to 0.97)
Intracranial bleeding	1 RCT (12,098) 16 Obs (1,037,632)	**SOE=High** Dabigatran reduced risk (RR 0.40; 95% CI 0.27 to 0.60)
GI bleeding	18 Obs (1,222,594)	**SOE-Low** Warfarin increased risk (HR 1.08, 95% CI 1.00 to 1.17)
All-cause mortality	1 RCT (12,098) 8 Obs (460,089)	**SOE=Low** No evidence of a difference (RR 0.88; 95% CI 0.77 to 1.00)
Death from vascular causes	1 RCT (12,098)	**SOE=Moderate** Dabigatran reduced risk (RR 0.85; 95% CI 0.72 to 0.99)
Myocardial infarction	1 RCT (12,098) 10 Obs (689,413)	**SOE=Low** No evidence of a difference
Hospitalization	1 RCT (12,098) 4 Obs (74,029)	**SOE=Moderate** No evidence of a difference (RR 0.97; 95% CI 0.92 to 1.03)
Adverse events	1 RCT (12,098)	**SOE=Moderate** Dyspepsia more common with dabigatran (11.3% of patients with dabigatran 150mg vs. 5.8% with warfarin, p<0.001). No evidence of differences in liver function or other adverse events between therapies.
Factor IIa Inhibitor (Dabigatran 110 mg) vs. Warfarin		
Stroke or systemic embolism	1 RCT (12,098) 10 Obs (662,920)	**SOE=Moderate** No evidence of a difference (RR 0.91; 95% CI 0.74 to 1.11)
Ischemic or uncertain stroke	1 RCT (12,098) 15 Obs (963,214)	**SOE=High** No evidence of a difference (RR 1.11; 95% CI 0.89 to 1.40)
Hemorrhagic stroke	1 RCT (12,098) 8 Obs (653,067)	**SOE=High** Dabigatran reduced risk (RR 0.31; 95% CI 0.17 to 0.56)
Major bleeding	1 RCT (12,098) 20 Obs (692,782)	**SOE=High** Dabigatran reduced risk (RR 0.80; 95% CI 0.69 to 0.93)
Minor bleeding	1 RCT (12,098)	**SOE=Moderate** Dabigatran reduced risk (RR 0.79; 95% CI 0.74 to 0.84)
Intracranial bleeding	1 RCT (12,098) 16 Obs (1,037,632)	**SOE=High** Dabigatran reduced risk (RR 0.31; 95% CI 0.20 to 0.47)

Outcome	Number of Studies (Subjects)	SOE and Effect (95% CI)
GI bleeding	18 Obs (1,222,594)	**SOE=Low** Increase in GI bleeding with warfarin as compared to dabigatran (HR 1.08, 95% CI 1.00 to 1.17)
All-cause mortality	1 RCT (12,098) 8 Obs (460,089)	**SOE=Low** No evidence of a difference (RR 0.91; 95% CI 0.80 to 1.03)
Death from vascular causes	1 RCT (12,098)	**SOE=Moderate** No evidence of a difference (RR 0.90; 95% CI 0.77 to 1.06)
Myocardial infarction	1 RCT (12,098) 10 Obs (689,413)	**SOE=Low** No evidence of a difference in risk. SOE was reduced given conflicting evidence between RCT and observational studies
Hospitalization	1 RCT (12,098) 4 Obs (74,029)	**SOE=High** Dabigatran reduced risk (RR 0.92; 95% CI 0.87 to 0.97)
Adverse events	1 RCT (12,098)	**SOE=Moderate** Dyspepsia more common with dabigatran (11.8% of patients with dabigatran 110mg vs. 5.8% with warfarin, p<0.001). No evidence of differences in liver function or other adverse events between therapies.
Xa Inhibitor (Apixaban) vs. Warfarin		
Stroke or systemic embolism	1 RCT (18,201) 9 Obs (652,156)	**SOE=High** Apixaban reduced risk (HR 0.79; 95% CI 0.66 to 0.95)
Ischemic stroke	1 RCT (18,201) 8 Obs (407,778)	**SOE=High** No evidence of a difference (HR 0.92; 95% CI 0.74 to 1.13)
Hemorrhagic stroke	1 RCT (18,201) 6 Obs (499,683)	**SOE=High** Apixaban reduced risk (HR 0.51; 95% CI 0.35 to 0.75)
Systemic embolism	1 RCT (18,201) 1 Obs (76,940)	**SOE=Moderate** No evidence of a difference (HR 0.87; 95% CI 0.44 to 1.75)
Major bleeding	1 RCT (18,201) 13 Obs (713,345)	**SOE=High** Apixaban reduced risk (HR 0.69; 95% CI 0.60 to 0.80)
Intracranial bleeding	1 RCT (18,201) 11 Obs (636,093)	**SOE=High** Apixaban reduced risk (HR 0.42; 95% CI 0.30 to 0.58)
GI bleeding	11 Obs (686,396)	**SOE=Low** Reduction in GI bleeding with apixaban (HR 0.67, 95% CI 0.56 to 0.79)
All-cause mortality	1 RCT (18,201) 5 Obs (214,745)	**SOE=Low** Apixaban reduced risk (HR 0.89; 95% CI 0.80 to 0.998), SOE was reduced given inconsistency with findings from observational studies
Death from cardiovascular causes	1 RCT (18,201)	**SOE=Moderate** No evidence of a difference (HR 0.89; 95% CI 0.76 to 1.04)

Outcome	Number of Studies (Subjects)	SOE and Effect (95% CI)
Myocardial infarction	1 RCT (18,201) 1 Obs (1,670)	**SOE=High** No evidence of a difference (HR 0.88; 95% CI 0.66 to 1.17)
Adverse events	1 RCT (18,201)	**SOE=Moderate** Adverse events occurred in almost equal proportions of patients in the apixaban and the warfarin therapy arms
Xa Inhibitor (Rivaroxaban) vs. Warfarin		
Stroke or systemic embolism	1 RCT (14,264) 10 Obs (556,370)	**SOE=Moderate** No evidence of a difference (HR 0.88; 95% CI 0.74 to 1.03)
Ischemic stroke	1 RCT (14,264) 8 Obs (484,891)	**SOE=Moderate** No evidence of a difference in on-treatment analyses (HR 0.94; 95% CI 0.75 to 1.17), SOE was reduced since analysis was on-treatment rather than ITT
Hemorrhagic stroke	1 RCT (14,264) 3 Obs (364,159)	**SOE=Low** In on-treatment analyses, one large RCT demonstrated benefit of rivaroxaban (HR 0.59; 95% CI 0.37 to 0.93); a smaller study showed a trend toward no evidence of a difference (HR 0.73; 95% CI 0.16 to 3.25)
Systemic embolism	1 RCT (14,264) 1 Obs (186,132)	**SOE=Moderate** Rivaroxaban reduced risk in on-treatment analyses (HR 0.23; 95% CI 0.09 to 0.61). SOE was reduced since on treatment analysis rather than ITT
Major bleeding	1 RCT (14,264) 11 Obs (529,053)	**SOE=Low** No evidence of a difference in RCT (HR 1.04, 95% CI 0.90 to 1.20). Observational studies support a trend towards a small increase (HR 1.09, 95% CI 1.03 to 1.16)
Intracranial bleeding	1 RCT (14,264) 15 Obs (897,011)	**SOE=High** Rivaroxaban reduced risk in on-treatment analyses (HR 0.67; 95% CI 0.47 to 0.93)
GI bleeding	1 RCT (14,264) 14 Obs (1,145,385)	**SOE=Low** Increased GI bleeding with rivaroxaban compared with warfarin (HR 1.42; 95% CI 1.22 to 1.66)
All-cause mortality	1 RCT (14,264) 6 Obs (237,103)	**SOE=Moderate** No evidence of a difference (HR 0.92; 95% CI 0.82 to 1.03)
Death from cardiovascular causes	1 RCT (14,264)	**SOE=Moderate** No evidence of a difference in on-treatment analyses (HR 0.89; 95% CI 0.73 to 1.10)
Myocardial infarction	1 RCT (14,264) 2 Obs (169,377)	**SOE=High** No evidence of a difference in on-treatment analyses (HR 0.81; 95% CI 0.63 to 1.06)
Medication adherence	3 Obs (65,422)	**SOE=Moderate** Better adherence with rivaroxaban compared with warfarin (HR 0.63; 95% CI 0.59 to 0.67)
Xa Inhibitor (Edoxaban) vs. Warfarin		
Stroke or systemic embolism	1 RCT (21,105)	**SOE=Moderate** No evidence of a difference for either dose (low dose HR 1.13, 95% CI 0.96 to 1.34; high dose HR 0.87 95% CI 0.73 to 1.04)

Outcome	Number of Studies (Subjects)	SOE and Effect (95% CI)
Ischemic stroke	1 RCT (21,105)	**SOE=Moderate** No evidence of a difference for high dose, increase for low dose (low dose HR 1.41, 95% CI 1.19 to 1.67; high dose HR 1.00 95% CI 0.83 to 1.19)
Hemorrhagic stroke	1 RCT (21,105)	**SOE=Moderate** Reduction in risk with either dose (low dose HR 0.33, 95% CI 0.22 to 0.50; high dose HR 0.54 95% CI 0.38 to 0.77)
Systemic embolism	1 RCT (21,105)	**SOE=Moderate** No evidence of a difference either dose
Major bleeding	1 RCT (21,105)	**SOE=Moderate** Lower bleeding on either dose (low dose HR 0.47, 95% CI 0.41 to 0.55; high dose HR 0.80 95% CI 0.71 to 0.91)
Intracranial bleeding	1 RCT (21,105)	**SOE=Moderate** Lower intracranial bleeding with either dose (low dose HR 0.30, 95% CI 0.21 to 0.43; high dose HR 0.47 95% CI 0.34 to 0.63)
All-cause mortality	1 RCT (21,105)	**SOE=Low** Reduction in risk for low dose (HR 0.87, 95% CI 0.79 to 0.96) **SOE=Moderate** No evidence of a difference in risk for high dose (HR 0.92, 95% CI 0.83 to 1.01)
Death from cardiovascular causes	1 RCT (21,105)	**SOE=Moderate** Reduction in risk for either dose (low dose HR 0.85, 95% CI 0.76 to 0.96; high dose HR 0.86 95% CI 0.77 to 0.97)
Myocardial infarction	1 RCT (21,105)	**SOE=Moderate** No evidence of a difference in risk for either dose (low dose HR 1.19, 95% CI 0.95 to 1.49; high dose HR 0.94 95% CI 0.74 to 1.19)
Xa Inhibitor (Apixaban) vs. ASA		
Stroke or systemic embolism	1 (5,599)	**SOE=Moderate** Apixaban reduced risk; HR 0.45 (0.32 to 0.62)
Ischemic stroke	1 (5,599)	**SOE=Moderate** Apixaban reduced risk; HR 0.37 (0.25 to 0.55)
Hemorrhagic stroke	1 (5,599)	**SOE=Moderate** Trend toward a reduction in risk with apixaban; HR 0.67 (0.24 to 1.88)
Major bleeding	1 (5,599)	**SOE=Moderate** No evidence of a difference; HR 1.13 (0.74 to 1.75)
Minor bleeding	1 (5,599)	**SOE=Moderate** Apixaban increased risk; HR 1.20 (1.00 to 1.53)
Intracranial bleeding	1 (5,599)	**SOE=Low** Trend toward a reduction in risk with apixaban; HR 0.85 (0.38 to 1.90); SOE is reduced since effect did not reach statistical significance
All-cause mortality	1 (5,599)	**SOE=Low** Trend toward a reduction in risk with apixaban; HR 0.79 (0.62 to 1.02); SOE is reduced given the closeness of the HR to 1
Death from vascular causes	1 (5,599)	**SOE=Moderate** No evidence of a difference; HR 0.87 (0.66 to 1.17)
Myocardial infarction	1 (5,599)	**SOE=Moderate** No evidence of a difference; HR 0.86 (0.50 to 1.48)
Hospitalization	1 (5,599)	**SOE=Moderate** Apixaban reduced risk; HR 0.79 (0.69 to 0.91)

Outcome	Number of Studies (Subjects)	SOE and Effect (95% CI)
Adverse events	1 (5,599)	**SOE=Moderate** No evidence of differences in liver function or other adverse events between therapies
Percutaneous LAA Closure vs. Warfarin		
Ischemic stroke	1 RCT (707)	**SOE=Low** 9 LAA patients (1.3 events per 100 patient-years) and 6 warfarin patients (1.6 events per 100 patient-years) had ischemic stroke, demonstrating no evidence of a difference between therapies
All strokes	1 RCT (707) 2 Obs (643)	**SOE=Low** No evidence of a difference
Major bleeding	1 RCT (707)	**SOE=Low** Less frequent with LAA (3.5% vs. 4.1%)
All-cause mortality	1 RCT (707) 4 Obs (1,430)	**SOE=Low** No evidence of a difference
Adverse events	2 RCTs (1,114) 3 Obs (723)	**SOE=Moderate** Higher rate with LAA

Abbreviations: ASA=aspirin; CI=confidence interval; HR hazard ratio; LAA=left atrial appendage; Obs=observational; RCT=randomized controlled trial; RR=relative risk; SOE=strength of evidence; TTR=time in therapeutic range

Contextual Question: Shared Decisionmaking Tools for Patients and Providers

Shared decisionmaking is now being recognized as one of the most important components of clinical care. This process involves an open exchange of information provided by clinicians on the risks and benefits of available treatment options and patients sharing their values and preferences regarding the presented options. Through an interactive process of reflection and discussion, clinicians and patients come to an agreement on a plan of care that best fits the patients' goals and preferences. Clinical decision support tools have been developed to facilitate shared decisionmaking by helping patients understand their medical options. Some of these tools tackle stroke prevention in atrial fibrillation as this arena involves the consideration of tradeoffs among the benefits, risks, and inconveniences of several different treatment options. We performed a non–systematic review of the literature and summarize here some of the available tools, their relative strengths and weaknesses, and then discuss existing reviews of the available evidence in shared decisionmaking. Note that these tools are all in early stages of development and none of these tools have been validated by large studies. As such they are not in clinical use.

One tool by Fraenkel and colleagues aimed at improving decisionmaking in patients with atrial fibrillation was developed based on the provision of individualized risk estimates for stroke and bleeding over 5 years associated with no treatment, aspirin, and warfarin.[411] The tool aims to provide education that incorporates patients' perceptions about their illness to explain the relationship between AF and stroke. Using this tool, patients are encouraged to state how they value the incremental risks and benefits associated with each treatment option and document specific concerns to address with their healthcare providers. However, this tool has been pilot-

tested in only 11 participants, of whom 8 (72%) rated ease of use as "very easy," and 9 (81%) rated the amount of information as "just right."[411]

A second clinical decision support tool by Lahaye and colleagues involved an iPad questionnaire intended to determine the minimal clinically important difference and the maximum number of major bleeding events that a patient is willing to accept in order to prevent one stroke for the initiation of antithrombotic therapy.[412] This tool was tested in 172 hospitalized patients with NVAF in whom anticoagulation was being considered. Testing showed that 12 percent of patients were not willing to consider antithrombotic therapy even if it was 100 percent effective in preventing stroke. Of patients willing to consider antithrombotic therapy, 42 percent were identified as "risk averse," (not willing to accept any risk of major bleed to prevent one stroke) and 15 percent were "risk tolerant" (willing to accept 20% risk of major bleed to prevent one stroke). Patients required at least a 0.8-percent (number needed to treat [NNT]=125) annual absolute risk reduction (or 15-percent relative risk reduction) in the risk of stroke in order to agree to initiate antithrombotic therapy, and patients were willing to accept the risk of 4.4 major bleeds in order to prevent one stroke.[412]

A third decision aid tool by Fatima and colleagues was developed to assist patients in selecting an antithrombotic agent such as an antiplatelet, warfarin, or a direct-acting oral anticoagulant (DOAC) for AF. Testing the tool in 81 patients with a mean age of 75 years and 77 percent taking warfarin or a DOAC, the mean decisional conflict score was low, indicating that patients' decisionmaking was improved with the use of the tool. In addition, the mean knowledge score improved and the mean helpfulness score in making a treatment choice was high. Therefore, the decision aid tool appeared to help patients participate in shared decisions about anticoagulation.[413]

One study evaluated a mobile application to support shared decisionmaking regarding stroke prophylaxis in patients with AF. The application included a video on AF, thromboembolic risk calculators, explanatory graphics, and information on available oral anticoagulants. The application was pilot tested in 30 patients. The number of correct answers in the questionnaire increased significantly after using the application (from 4.7 ± 1.8 to 7.2 ± 1.0, $p < 0.001$). The decisional conflict scale showed a low decisional conflict associated with use of the application. Whether these improvements in patient knowledge and decisional conflict translate to clinical benefit remains to be seen.[414]

It is important to understand factors that influence patients' decisions about starting an OAC for NVAF. A cross-sectional study attempted to accomplish this goal by studying veterans in the primary care clinics and the international normalized ratio laboratory. The survey used in the study was developed with input from patients and physicians and was intended to measure patient values and preferences. A hypothetical scenario of the risk of NVAF was presented, and the attributes of different anticoagulants were reviewed. Patients were offered the following list of priorities: (1) has better efficacy at reducing stroke risk; (2) has been on the market for a long time; (3) has an antidote to reverse bleeding; (4) leads to better quality of life with no need for frequent laboratory tests; or (5) I want to follow recommendations made by my physician. The results were stratified by whether a patient was taking an OAC at the time of the survey. Of 173 veterans approached, 137 completed the survey (79% response rate). Ninety patients were not on any type of OAC, 46 reported being on warfarin, and one reported being on dabigatran. Importantly, 98 percent of subjects stated they would like to participate in the decisionmaking process of selecting an OAC. About 36 percent of patients (on an OAC or not) reported they would select a medication that has an antidote even if the risk of bleeding were very small.

Twenty-three percent of patients not on an OAC and 22 percent of patients on an OAC reported a preference for the medication that results in the best quality of life.[415]

While a complete environmental scan of existing decision support tools has not been published, a review of 33 resources is available.[416] This analysis showed that warfarin was the most frequently mentioned treatment option among the OACs, being cited in all resources, followed by the DOACs dabigatran (82.3% of resources), rivaroxaban (73.5%), and apixaban (67.6%). Only one-third of resources discussed the role of stroke risk and/or bleeding risk within decisionmaking. Three noteworthy observations were made: (1) the practical ease of using DOACs over warfarin, (2) uneven explanation about stroke versus bleeding risk, and (3) individualized selection of antithrombotic therapy.[416]

Another recent systematic review examined the existence, accessibility, and outcomes associated with patient decision aids for stroke prevention in NVAF. The seven included studies provided data on six decision aids that displayed combinations of aspirin, warfarin, or no therapy; only one included a DOAC. These tools were associated with increased patient knowledge, increased likelihood of making a choice, and low decisional conflict. Use of decision aids in this review was associated with less selection of warfarin. Given the early stages of development and lack of validation, none of the tested decision aids are currently available for clinical use.[417]

A multicenter, encounter-level, randomized trial is currently underway to compare a conversation tool on anticoagulation choices with usual care in patients with AF. The trial aims to enroll 999 patients with ongoing nonvalvular AF at risk of stroke. The primary outcome is the quality of shared decisionmaking as assessed by patients. Other endpoints of interest include anticoagulant use, choice of and adherence to an oral anticoagulant, stroke, and bleeding events.[418]

Finally, a National Coverage Determination released by the Centers for Medicare and Medicaid Services (CMS) brought shared decisionmaking discussions to the forefront. In the Coverage Determination, CMS prescriptively outlined the healthcare delivery processes required to take place before left atrial appendage closure (LAAC). They stipulated that referring physicians must document evidence of a shared decisionmaking interaction regarding anticoagulation choices with an evidence-based decision aid. This led to an appreciable amount of anxiety and confusion among healthcare providers, and it was later clarified that the shared decisionmaking mandate relates to the choice of oral anticoagulation including the rationale behind not using an OAC. However, the process is far from ideal as when shared decisionmaking occurs upstream, it is possible that given the large amount of potentially relevant information the initial interactions may not include information on all choices appropriate for the patient.[419]

While many studies have examined decision support tools about anticoagulation for patients with NVAF, future studies are required to evaluate how decision aids influence actual choices and clinical outcomes.

Findings in Relation to What Is Already Known

Several scores have been developed to risk stratify patients with AF for stroke and other thromboembolic events. Given the known bleeding risks of oral anticoagulants that are used to reduce the risk of thromboembolism in patients with AF, risk scores for bleeding have also been developed to help inform therapeutic decisions. Risk scores for prediction of these events have been touted as a way of guiding antithrombotic therapy in patients with AF. In the current CER, we found that of the available risk scores, the $CHADS_2$ and CHA_2DS_2VASc scores are the most

commonly studied. Several factors limited our ability to compare the different risk scores. Such factors included the heterogeneous patient populations and the variability in treating patients with antiplatelets and oral anticoagulants. Also, few studies used clinical validation in reporting main outcomes especially stroke, and although event rates were consistently reported, measures of predictability, calibration, and strength of association were inconsistently reported. Despite these limitations, the $CHADS_2$, CHA_2DS_2-VASc, and ABC risk scores appeared to be similar and to have the most prediction ability of stroke events. While some studies have explored the inclusion of biomarkers in stroke risk scores (i.e. the ABC stroke risk score), and preliminary evidence supports this score being comparable to $CHADS_2$ and CHA_2DS_2-VASc, the experience with ABC is limited and more data are needed on the contribution of these biomarkers to the overall risk assessment. Note that this differs from the current 2014 AHA/ACC/HRS Guidelines for the Management of Patients with Atrial Fibrillation which concludes that CHA_2DS_2-VASc was superior.

Similar to comparisons of stroke risk scores, comparisons of bleeding risk scores in our CER were hard to interpret. The difficulty in interpreting comparisons of bleeding risk scores stemmed from the different approaches to calculating bleeding risk scores, the inability to validate clinical bleeding events, and the inconsistency in reporting measures of calibration, strength of association, and diagnostic accuracy. Limited evidence favored the HAS-BLED risk score based on two studies demonstrating that it has significantly higher prediction ability for major bleeding events than other scores among patients on warfarin, but the majority of studies showed no statistically significant differences in prediction, reducing the SOE. Bleeding risk scores are currently not included in the American Heart Association/American College of Cardiology guideline recommendations on AF, and they are generally not used to decide whether to prescribe an oral anticoagulant to individual patients. However, bleeding risk scores may inform shared decision making discussions of the risks of stroke and bleeding incorporating patients' values and preferences. As more data on stroke and bleeding risk scores emerge, it is possible that improvement in the tools and methods for risk stratification of both stroke and bleeding will be important to better individualize treatment using different oral anticoagulants in patients with AF.

With more available treatments, our review found that not only do risk algorithms need to be updated, but physician decisionmaking about when to use which agent does as well. Until recently, there was only one established oral anticoagulant available for stroke prevention in patients with AF. This single agent—warfarin—while effective when compared with placebo or antiplatelet agents such as aspirin, is associated with significant limitations from both the health system and patient perspectives. Limitations of warfarin and other vitamin K antagonists (VKAs) led to the development of several direct oral anticoagulants for stroke prevention in nonvalvular AF. It is important to note that for warfarin to be effective, time in the therapeutic range has to be high; patients in whom this is hard to achieve should be considered for other types of oral anticoagulants. Trials of dabigatran, rivaroxaban, apixaban, and edoxaban have demonstrated favorable efficacy and safety results compared with warfarin, but direct comparisons of their efficacy and safety have not been done. In addition, the trials used different dosing strategies, were performed in different health systems, used varying event definitions, and recruited populations at varying risk for stroke and bleeding. Thus, it is not possible to affirm here which medication is better, and cross-trial comparisons may not be reliable. The direct oral anticoagulants do, however, have different attributes and important advantages over warfarin and offer, after many years without options, new alternatives for the treatment of patients with

nonvalvular AF who are at risk for stroke. Notably, approved doses of these medications for stroke prevention in patients with AF are: 150 and 75 mgs twice a day for dabigatran, 20 and 15 mgs once a day for rivaroxaban, 5 and 2.5 mgs twice a day for apixaban and 60 and 30 mgs once a day for edoxaban. Lower doses are generally recommended in patients with moderate to severe kidney disease.

Specifically, our review provides evidence of the following within the field of stroke prevention for patients with AF, as follows.

Dabigatran

- Dabigatran at a 150mg dose is superior to warfarin in reducing the incidence of the composite outcome of stroke (including hemorrhagic) or systemic embolism, with no statistically significant difference in the occurrence of major bleeding, all-cause mortality, or MI risk.
- Dabigatran at a 110mg dose is equivalent to warfarin in reducing stroke with less major bleeding, an issue of substantial importance in the care of older adults.

Edoxaban

- From a good-quality RCT of 21,105 patients with AF showed that both lower (30 mg) and higher (60 mg) once-daily doses of edoxaban were similar to warfarin in preventing stroke or systemic embolism and resulted in significantly lower rates of bleeding including intracranial hemorrhage and death from cardiovascular causes. Note that the 60 mg once-daily dose of edoxaban is approved by the FDA to treat only NVAF patients with creatinine clearance (CrCL) >50 to ≤ 95 mL/min, while 30 mg once-daily dose of edoxaban is approved to treat NVAF in patients with renal dysfunction (CrCL 15 to 50 mL/min).

Apixaban

- The risk of minor and major bleeding including intracranial, intracerebral and subdural intracranial bleeding is significantly lower with apixaban than warfarin, and patients are significantly less likely to die within 30 days of a major hemorrhagic event (other than intracranial bleeding) on apixaban compared with warfarin.
- The efficacy and safety profiles of apixaban are similar for different types of AF (persistent, paroxysmal, permanent) as well as for AF first diagnosed within 30 days prior to randomization.
- Apixaban leads to similar reductions in stroke or systemic embolism and consistent reductions in major bleeding in patients treated with and without aspirin.

Rivaroxaban

- From a good quality-RCT of 14,264 patients, rivaroxaban is similar to warfarin in preventing stroke or systemic embolism, with similar rates of major bleeding, and all-cause mortality. Note that there was inconsistency between the observational and RCT evidence related to major bleeding with the observational studies demonstrating a trend toward increased major bleeding with rivaroxaban.

Observational Versus RCT Evidence

- Within the included set of observational studies, use of direct oral anticoagulants and comparative effectiveness analyses of the different oral anticoagulants often have inconsistent findings. These inconsistencies likely resulted from confounding, selection bias, different endpoint definitions, rigor and completeness of followup, and variations in decisionmaking practice between trial populations and real world scenarios.
- When considered together, the findings from observational and RCT studies were inconsistent related to all-cause mortality and myocardial infarction for dabigatran versus warfarin.
    - The observational studies demonstrated a benefit in all-cause mortality for patients on dabigatran compared with warfarin. RCT evidence, however did not demonstrate evidence of a difference. In addition, observational studies did not show a difference in myocardial infarction while RCT studies suggested an increase with dabigatran.
- Xa inhibitors (all-cause mortality): The observational studies did not show a reduction in all-cause mortality across Xa inhibitors, whereas RCTs showed reduction in all-cause mortality across Xa inhibitors.
- Other RCT findings were supported by existing observational studies.

Left Atrial Appendage Closure Devices

- Observational studies comparing different left atrial appendage (LAA) closure devices have suggested no statistically significant differences in risk of stroke, thromboembolism, or mortality among the different devices; however, those studies were limited by small sample sizes and short followup.
- Based on these observational studies, LAA shows a trend toward a benefit over warfarin for all strokes (including ischemic or hemorrhagic) and all-cause mortality. Although LAA with percutaneous closure results in less frequent major bleeding than warfarin, it is also associated with a higher rate of adverse safety events such as pericardial effusion and device embolization

Applicability

Efficacy of interventions as determined in RCTs does not always translate to usual practice, where patient characteristics, provider clinical training, and available resources may differ from trial conditions. Additionally, the availability and/or specific features of interventions studied in our review may differ from those available to patients within the United States. Table 78 illustrates the specific issues with the applicability of our included evidence base by KQ.

Table 78. Potential issues with applicability of included studies

Issues	KQ 1 (N=61)	KQ 2 (N=38)	KQ 3 (N=117)	Total[a] (N=185)
Population (P)				
Narrow eligibility criteria and exclusion of those with comorbidities	2	0	2	3
Large differences between demographics of study population and community patients	3	1	4	7

Issues	KQ 1 (N=61)	KQ 2 (N=38)	KQ 3 (N=117)	Total[a] (N=185)
Narrow or unrepresentative severity, stage of illness, or comorbidities	2	0	2	4
Run-in period with high exclusion rate for non-adherence or side effects	1	1	1	2
Event rates much higher or lower than observed in population-based studies	0	0	0	0
Intervention (I)				
Doses or schedules not reflected in current practice	0	0	2	2
Monitoring practices or visit frequency not used in typical practice	2	1	0	2
Older versions of an intervention no longer in common use	2	1	0	2
Cointerventions that are likely to modify effectiveness of therapy	0	0	0	0
Highly selected intervention team or level of training/proficiency not widely available	0	0	0	0
Comparator (C)				
Inadequate comparison therapy	2	2	1	5
Use of substandard alternative therapy	1	0	0	1
Outcomes (O)				
Composite outcomes that mix outcomes of different significance	4	2	1	5
Short-term or surrogate outcomes	1	0	4	5
Setting (S)				
Standards of care differ markedly from setting of interest	1	0	0	1
Specialty population or level of care differs from that seen in community	1	0	1	2

[a]Some studies were relevant to more than one KQ.

Abbreviations: KQ=Key Question; N=number of studies

In general, concerns about study applicability were not a major factor for this project's body of evidence. The main issues related to applicability were concerns about short-term outcomes; concerns about large differences between demographics of study populations and community patients in terms of age, renal function, and comorbidities; and concerns about inadequate comparison therapies.

Implications for Clinical and Policy Decisionmaking

Although stroke prevention in patients with nonvalvular AF in contemporary clinical practice is complex and challenging, it is critically important given the morbidity and mortality associated with stroke events. It is noteworthy that aspirin is not an effective treatment for stroke prevention in patients with AF. The European Society of Cardiology guideline on AF confirms that

evidence supporting antiplatelet monotherapy for stroke prevention in AF is very limited. It also clarifies that the bleeding risk on aspirin is not different from the bleeding risk on apixaban (AVERROES trial) while VKA and DOACs, but not aspirin, effectively prevent strokes in AF patients.[27] Although traditional anticoagulants like warfarin can significantly reduce the risk of stroke in patients with AF, the bleeding risk is increased with these agents, potentially attenuating their effects. In addition, use of warfarin is further challenged by numerous interactions with food items and other medications, inability to predict the best dose in an individual patient, and the need for regular monitoring of INR. The direct oral anticoagulants promise improved efficacy with reduction in bleeding events, especially intracranial bleeding, and more predictable pharmacokinetics. However, the long-term effects of these agents in broad populations have not been established. Therefore, clinicians are constantly struggling to find the right balance between efficacy and risk in the use of these therapies in this patient population. Also while bleeding risk scores are generally not used to decide whether or not to use an oral anticoagulant in a given patient, high scores may help guide intensity of patient follow-up and monitoring.

Despite the availability and validation of numerous tools for both stroke and bleeding risk assessment in patients with nonvalvular AF, meaningful comparisons of the tools could not be performed in this CER due to the heterogeneous patient populations, the variability in treating patients with antiplatelets and oral anticoagulants, the lack of clinical validation of endpoints, and the underreporting of measures of predictability, calibration, and strength of association. In their most recent update in 2014, the AHA/ACC published guidelines that acknowledge the limitation of current risk tools to identify patients at high risk for thromboembolic risk. The 2014 guideline recommends all patients with a CHA_2DS_2-VASc score of ≥ 2 be considered for oral anticoagulant therapy. This guideline, along with other professional guidelines, recommends use of the CHA_2DS_2-VASc score for assessment of stroke risk in AF patients. Our review highlights the similar evidence supporting the prediction abilities of CHA_2DS_2-VASc, $CHADS_2$, and the ABC stroke risk scores. Whether biomarkers such as brain natriuretic peptide, C-reactive protein or troponin can enhance clinically-based scores and as a result be incorporated in guideline recommendations remains to be seen. Also, the current ACC/AHA guidelines[17] do not recommend use of bleeding risk scores. Whether biomarkers (e.g., brain natriuretic peptide, C-reactive protein or troponin) can enhance these scores is uncertain. Another gap in the evidence is the absence of randomized controlled trials comparing the direct oral anticoagulants head-to-head. For effective stroke prevention in patients with AF, clinicians will have to understand the risk and benefits, indications, side effects, and monitoring patients taking direct oral anticoagulants (e.g. renal function as dose may need to be adjusted), further complicating treatment decisions in patients with AF.

With the growing prevalence of digitized medical records, there is an opportunity to monitor the real world uptake of the direct oral anticoagulants. Additionally, with these electronic records, there will be the opportunity to continue to evaluate and modify risk prediction tools to improve their prediction for stroke and bleeding risk, particularly with these newer anticoagulants diffusing into clinical practice. Also, newer clinical markers (e.g. MRI to assess scar), comorbidities (i.e., renal failure, etc.) and biomarkers should be tested and validated with or alongside current risk tools to improve their prediction of both stroke and bleeding risks. Additionally, more prescriptive guidelines on how to use risk scores and apply necessary therapies, possibly in the form of physician decision support tools, will be important for clinical decisionmaking. Data on efficacy, effectiveness and safety of direct oral anticoagulants are

needed on important patient groups such as patients with severe kidney disease including end stage renal disease on dialysis and patients older than 75 years of age. Also, although not part of this review, the best strategies should be defined for patients undergoing procedures including cardioversion and catheter ablation of AF, switching among anticoagulant therapies, and starting or restarting anticoagulant therapy in patients with previous major bleeding events.

As new interventions are introduced, determining their relative risks and benefits in the overall scheme for stroke prevention in AF is critically important in order to minimize the use of less efficacious, less safe, and more expensive therapies. Although the results of the current review are largely consistent with existing guidelines, they do help identify gaps in the evidence base and areas of needed future research, particularly as agents are rapidly entering into broader clinical practice.

We also explored relevant ongoing studies within clincialtrials.gov to determine whether any of these studies could impact our findings. One such study targeted KQ1 and KQ2. The "Thromboembolic and Bleeding Risk Stratification in Patients With Nonvalvular Atrial Fibrillation" or FASTRHAC study is currently listed as recruiting (target enrollment of 825 patients) and is looking to be complete at the end of 2020. Twenty additional studies evaluated the safety and effectiveness of different treatment strategies. These studies are summarized in Table 79 and represent 13 ongoing RCTs and 7 ongoing observational studies. Of note are the four ongoing studies of devices representing over 4000 patients—three of these studies however will not be completed until 2020. Also note that there are two RCTs which directly compare direct oral anticoagulants although the first of these studies will not be finished until December 2018.

Table 79. Ongoing studies potentially relevant to Key Questions

Study Name	NCT	Interventions	Enrollment Goal	Planned Completion Date (Month-Year)
RCTs				
Assessment of the WATCHMAN Device in Patients Unsuitable for Oral Anticoagulation	NCT02928497	WATCHMAN LAAC Implant, Single Antiplatelet Therapy	888	Dec 2023
WAveCrest Vs. Watchman TranssEptal LAA Closure to REduce AF-Mediated STroke 2	NCT03302494	Coherex WaveCrest,: Watchman LAA Closure Device	1250	Dec 2020
Comparison of Efficacy and Safety Among Dabigatran, Rivaroxaban, and Apixaban in Non-Valvular Atrial Fibrillation	NCT02666157	Dabigatran etexilate, Rivaroxaban, Apixaban	3672	Dec 2018
Efficacy and Safety of Aspirin and Clopidogrel in the Atrial Fibrillation With Low or Moderate Stroke Risk	NCT02960126	Aspirin, Clopidogrel	1500	Oct 2020
The Danish Non-vitamin K Antagonist Oral Anticoagulation Study in Patients With Atrial Fibrillation	NCT03129490	Dabigatran etexilate, Rivaroxaban, Edoxaban, Apixaban	11,000	Sep 2021
Compare Apixaban and Vitamin-K Antagonists in Patients With Atrial Fibrillation (AF) and End-Stage Kidney Disease (ESKD)	NCT02933697	Apixaban, Phenprocoumon	222	Sep 2018
Left Atrial Appendage Closure vs. Novel Anticoagulation Agents in Atrial Fibrillation	NCT02426944	DOAC, Left atrial appendage closure	400	May 2018

Study Name	NCT	Interventions	Enrollment Goal	Planned Completion Date (Month-Year)
Impact of Anticoagulation Therapy on the Cognitive Decline and Dementia in Patients With Non-Valvular Atrial Fibrillation	NCT03061006	Dabigatran etexilate, Warfarin	120	Apr 2021
Blinded Randomized Trial of Anticoagulation to Prevent Ischemic Stroke and Neurocognitive Impairment in AF	NCT02387229	Rivaroxaban, Acetylsalicylic acid	6,396	Feb 2021
AMPLATZER Amulet LAA Occluder Trial	NCT02879448	Amulet Left Atrial Appendage Occluder, WATCHMAN Left Atrial Appendage Closure	1,600	Feb 2020
Trial to Evaluate Anticoagulation Therapy in Hemodialysis Patients With Atrial Fibrillation	NCT02942407	Apixaban, warfarin	762	Feb 2019
Oral Anticoagulation in Haemodialysis Patients	NCT02886962	No oral anticoagulation, oral anticoagulation with vitamin K antagonists	855	Jan 2023
The Efficacy and Safety Study of Dabigatran and Warfarin to Non-valvular Atrial Fibrillation Patients	NCT02646267	Warfarin, dabigatran etexilate	210	Jan 2018
WAveCrest Vs. Watchman TranssEptal LAA Closure to REduce AF-Mediated STroke 2	NCT03302494	Coherex WaveCrest® Left Atrial Appendage Occlusion System, WATCHMAN Left Atrial Appendage Closure	1,250	Dec 2020
Observational				
Benefit/Risk in Real Life of New Oral Anticoagulants and Vitamin K Antagonists in Patients Aged 80 Years and Over	NCT02286414	Dabigatran, rivaroxaban, apixaban, warfarin, fluindione, acenocoumarol	2,193	Dec 2019
Study of Rivaroxaban Use and Potential Adverse Outcomes in Routine Clinical Practice (Sweden)	NCT02468102	Rivaroxaban, Standard of care drugs	40,000	Dec 2018
Comparative Effectiveness and Safety Between Warfarin and Dabigatran	NCT03254134	Warfarin, dabigatran	8,000	Dec 2017
LAA Excision With AF Ablation Versus Oral Anticoagulants for Secondary Prevention of Stroke	NCT02478294	Thoracoscopic LAA Excision plus AF Ablation, Warfarin, Novel Oral Anticoagulants	300	Dec 2017
Benefit/Risk in Real Life of New Oral Anticoagulants and Vitamin K Antagonists in Patients Aged 75 Years and Over Suffering From Non Valvular Atrial Fibrillation (nv AF)	NCT02906527	Non-exposed group, exposed group	150,000	Dec 2016
Sequential Expansion of Comparative Effectiveness of Anticoagulants	NCT02081807		99,999	Oct 2017
Left Atrial Appendage Occlusion Versus New Oral Anticoagulants for Stroke Prevention in Patients With Non-valvular Atrial Fibrillation	NCT03108872	Left atrial appendage occlusion, New oral anticoagulants	300	Sep 2017

Study Name	NCT	Interventions	Enrollment Goal	Planned Completion Date (Month-Year)
Clinical Outcomes Among Non-valvular Atrial Fibrillation Patients With Renal Dysfunction	NCT03359876	Rivaroxaban, Warfarin	11,000	Dec 2018
Benefit/Risk in Real Life of New Oral Anticoagulants and Vitamin K Antagonists in Patients Aged 80 Years and Over	NCT02286414	Dabigatran, Rivaroxaban, Apixaban Warfarin, fluindione, acenocoumarol	2,193	Apr 2018
Rivaroxaban vs Warfarin for SPAF in Multi-morbid Patients	NCT03374540	Rivaroxaban, Vitamin K antagonist(VKA)	99,999	Nov 2018

Abbreviations: AF=atrial fibrillation; LAA=left atrial appendage; LAAC=left atrial appendage closure; nvAF=nonvaluvular atrial fibrillation; SPAF=stroke prevention in atrial fibrillation

Limitations of the Evidence Base and the Comparative Effectiveness Review Process

Our findings have limitations related to the literature and our approach. Important limitations of the literature across the KQs include inconsistency across studies that assess prediction tools for thromboembolic or bleeding risk in terms of the methods used and findings reported; and the lack of RCTs which directly compare specific stroke prevention therapies.

Our review methods also had limitations. Our study was limited to English-language publications and excluded studies conducted exclusively in Asia, Africa, or the Middle East and observational studies with less than 1000 patients which studied only pharmacological interventions. It was the opinion of the investigators that the resources required to translate non-English articles, to include areas of the world where clinical practice differs significantly from standards in the United States, or findings from small pharmacologic observational studies would not be justified by the low potential likelihood of identifying relevant data which would change decisionmaking. Note this exclusion does not restrict observational studies that target nonpharmacologic interventions where evidence is more sparse and smaller studies may have a larger impact on the review findings. We also limited our analysis to studies published since 2000. Given the rapidly changing treatment alternatives for stroke prevention for patients with AF this recent literature was considered the most relevant to today's clinical and policy uncertainties.

Research Recommendations

In our analyses, we have identified several areas for recommended future research. Specifically, many of the available studies for KQ 1 and KQ 2 had methodological issues that point to limitations of the current evidence base. Many studies' utilization of administrative data sources led to different approaches to calculating the risk scores of interest due to unavailable data (notably for the HEMORR$_2$HAGES and HAS-BLED scores). Similarly, use of administrative data in some cases prevented validation of clinical stroke/bleeding events, which could have affected studies' estimates of the performance of these risk scores. Finally, though studies consistently reported c-statistic as a measure of model prediction, other relevant statistics (including measures of calibration, strength of association and diagnostic accuracy) were inconsistently reported. Further studies are needed that: (1) utilize complete data; (2) use

validated clinical outcomes; and (3) compare all available risk scores using consistent and appropriate statistical evaluations.

We can identify well patients at risk for stroke, who usually are the same patients at high risk for bleeding. Thus, there is a need for a score that could be used for decisionmaking about antithrombotic therapy in AF patients taking into account both thromboembolic and bleeding risks. Scores that identify only patients at risk for stroke or only those at risk for bleeding are not so helpful since the clinical factors in these scores are usually similar and treatments which reduce one or the other risk may increase the other for the same patient. Another challenge is that both stroke events and bleeding events are on a spectrum of severity and therefore predicting overall stroke might not align with outcomes that matter most to patients. For example, some strokes may have symptoms lasting <24 hours with complete resolution, whereas others can cause death. Additional studies utilizing prospectively constructed databases with longer-term outcomes data that compare all available risk prediction scores would be of great use in better clarifying which risk score system is superior in predicting major bleeding or thromboembolic risk. Specific to bleeding risk, additional prospective comparisons of the standard deviation of transformed international normalized ratio (SDT_{INR}) and time in therapeutic range (TTR) are needed to establish which variable has better predictive accuracy for major bleeding.

Additionally, even assuming an optimal risk prediction score can be identified, further work is needed to clarify how scores should be used prospectively in clinical practice.

Specific to treatment strategies, although recent years have been exciting in stroke prevention and development of new agents as alternatives to warfarin, there are several evidence gaps that remain and should inform future research. It is important to have new studies with head-to-head comparisons of available prevention strategies. Given variability in patient populations, concomitant therapies, and underlying patient care, cross-trial comparisons in this field is of limited use. Patients with AF usually have other comorbidities that also require the use of other antithrombotic agents. There are many antithrombotic agents available at different doses for different clinical indications. There is a need for further study of these agents, particularly focusing on methods of monitoring adequacy of anticoagulation, as well as the development of antidotes for severe bleeding events. There is a need for studies assessing the safety and effectiveness of different combinations of antithrombotics (anticoagulants and antiplatelet agents) at different doses, as well as their duration. In frail older patients, there may be concerns about using anticoagulation in the presence of multimorbidity due to a higher prevalence of pre-existing conditions that predispose to bleeding, concomitant interacting medications (antiplatelet therapy, nonsteroidal anti-inflammatory drugs), and additional complicating conditions such as risk of falls. Such a patient population needs further study.

There are also many novel invasive treatments for AF but the evidence remains sparse about these interventions. Studies need to be conducted in patients who receive these procedures to determine if and how anticoagulation strategies should be modified in patients receiving these procedures.

Finally, despite all the potential advantages of the direct oral anticoagulants demonstrated in the clinical trials when compared with warfarin, except for dabigatran, these drugs still do not have an approved immediate antidote. Similarly, for warfarin-treated patients, although there are data showing that fresh frozen plasma or vitamin K can help in normalizing INRs, there are not good data on actually stopping or reversing bleeding events for such warfarin-treated patients. Once a bleed occurs, the event has happened, and regardless of the original treatment strategy, it is not clear that any reversal or antidote will alter patient outcomes. Therefore, a focus should be

on preventing bleeds—in particular, fatal bleeds. The shorter half-life of the direct oral anticoagulants may help in the management of bleeding episodes in patients receiving these drugs and should provide comfort that bleeding can be controlled without an antidote. Other areas worthy of further study relate to the use of the direct oral anticoagulants in patients with severe kidney disease.

Conclusions

Overall, we found that $CHADS_{2,}$ CHA_2DS_2-VASc, and ABC scores have similar evidence regarding their ability to predict stroke risk in patients with AF, whereas HAS-BLED has the best evidence to predict bleeding risk. Imaging tools require further evidence in regard to their appropriate use in clinical decisionmaking. Additionally, simple clinical decision tools are needed that incorporate both stroke risk and bleeding risk to assist providers choosing agents in patients with AF. Additional work will be required to develop risk tools for patients to discriminate those individuals with AF where the bleeding risk may be high enough to warrant more intensive follow-up and monitoring. These tools could be embedded into electronic medical record systems for point-of-care decisionmaking, developed into applications for smartphones and tablets, or be delivered via web-based interfaces. Additional evidence of the use of these stroke and bleeding risk scores (and clinical decision tools which balance these risks) among patients on therapy is also required.

DOACs (specifically apixaban and dabigatran) demonstrate reductions in stroke events and reductions (apixaban) or similar (dabigatran) rates in bleeding events when compared with warfarin while rivaroxaban was similar in both benefits and harms with warfarin. Comparative effectiveness of these direct oral anticoagulants as compared to one another however is limited by the lack of randomized studies directly comparing their safety and effectiveness.

Acronyms and Abbreviations

Acronym	Definition
ABC	Age, biomarkers, clinical history
ACC	American College of Cardiology
ACTIVE-A	Effect of Clopidogrel Added to Aspirin in Patients with Atrial Fibrillation (trial)
ACTIVE-W	Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (trial)
ACP	Amplatzer cardiac plug
ACTS	Anti-Clot Treatment Scale
AF	Atrial fibrillation
AHA	American Heart Association
AHRQ	Agency for Healthcare Research and Quality
AMADAEUS	Evaluating the Use of SR34006 Compared to Warfarin or Acenocoumarol in Patients With Atrial Fibrillation (trial)
ApoE	Apolipoprotein E
ARISTOTLE	Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (trial)
ASA	Acetylsalicylic acid
ASD	Atrial septal defect
ATRIA	Age, female, diabetes, congestive heart failure, hypertension, proteinuria
AV	Aortic valve
AVERROES	Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (trial)
BAFTA	Birmingham Atrial Fibrillation Treatment of the Aged Study
BRI	Bleeding risk index
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CDSR	Cochrane Database of Systematic Reviews
CER	Comparative effectiveness research/review
$CHADS_2$	Congestive heart failure, hypertension, age >75, diabetes, stroke/TIA (2 points)
CHA_2DS_2-VASc	Congestive heart failure/left ventricular ejection fraction ≤40%, hypertension, age ≥75 (2 points), diabetes, stroke/TIA/thromboembolism (2 points), vascular disease, age 65-74, sex

Acronym	Definition
CI	Confidence interval
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CQ	Contextual question
CrCl	Creatinine clearance
CT	Computed tomography
cTnT-hs	High-sensitivity cardiac troponin T
DM	Diabetes mellitus
DOAC	Direct oral anticoagulant
DSMB	Data safety and monitoring board
DTI	Direct thrombin inhibitor
DVT	Deep vein thrombosis
eGFR	Estimated glomerular filtration rate
EHC	Effective Healthcare
ENGAGE-AF TIMI-48	Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48 (trial)
EPC	Evidence-based Practice Center
eQ-5D-3L	EuroQol 5 dimensions questionnaire, level 3 version
ER	Emergency room
ESRD	End-stage renal disease
FASTRHAC	Thromboembolic and Bleeding Risk Stratification in Patients With Nonvalvular Atrial Fibrillation
GDF-15	Growth differentiation factor 15
GI	Gastrointestinal
HAEST	Heparin in Acute Embolic Stroke Trial
HAS-BLED	Hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly (> 65), drugs/alcohol concomitantly
HEMORR$_2$HAGES	Hepatic or renal disease, ethanol (alcohol) abuse, malignancy, older (> 75), reduced platelet count or function, rebleeding risk (2 points), hypertension (uncontrolled), anemia, genetic factors, excessive fall risk, stroke history
HF	Heart failure
HFpEF	Heart Failure with a Preserved Ejection Fraction
HIV	Human immunodeficiency virus

Acronym	Definition
HR	Hazard ratio
HRQOL	Health-related quality of life
HTN	Hypertension
INR	International normalized ratio
IQR	Interquartile ratio
IRR	Interrater reliability
ISTH	International Society on Thrombosis and Haemostasis
ITT	Intention to treat
KQ	Key Question
LAA	Left atrial appendage
LAAC	Left atrial appendage closure
LV	Left ventricular
LVEF	Left ventricular ejection fraction
LVH	Left ventricular hypertrophy
LVS	Left ventricular systolic
LVSD	Left ventricular systolic dysfunction
mg	Milligram
MI	Myocardial infarction
mL/min	Milliliter per minute
MMSE	Mini-Mental State Examination
MR	Mitral regurgitation
MRI	Magnetic resonance imaging
MV	Mitral valve
NDA	Nondedicated Amplatzer
NMCR	Non-major clinically relevant
NNT	Number needed to treat
NR	Not reported
NVAF	Nonvalvular atrial fibrillation
NYHA	New York Heart Association
OAC	Oral anticoagulant
OR	Odds ratio
PAD	Peripheral artery disease
PCI	Percutaneous coronary intervention
PCORI	Patient-Centered Outcomes Research Institute

Acronym	Definition
PE	Pulmonary embolism
PICOTS	Populations, Interventions, Comparators, Outcomes, Timing, Settings
PFO	Patent foramen ovale
PLAATO	Percutaneous Left Atrial Appendage Transcatheter Occlusion
PREVAIL	Watchman LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy (trial)
PROTECT-AF	Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation (trial)
QOL	Quality of life
QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies-2
RCT	Randomized controlled trial
RE-LY	Randomized Evaluation of Long-Term Anticoagulation Therapy (trial)
ROB	Risk of bias
ROCKET-AF	Rivaroxaban Once-daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation
RR	Relative risk
SAT-Q	Satisfaction Questionnaire
SD	Standard deviation
SE	Standard error
SEC	Spontaneous echocardiographic contrast
SEE	Systemic embolic event
SOE	Strength of evidence
SR	Systematic review
SRF	Stable renal function
TE	Thromboembolic
TEE	Transesophageal echocardiography
TIA	Transient ischemic attack
TnC	Troponin C
TnI	Troponin I
TnT	Troponin T
TTE	Transthoracic echocardiography
TTE-LAWV	Transthoracic echocardiographic LAA wall velocity
TTR	Time in therapeutic range
VKA	Vitamin K antagonist

Acronym	Definition
VSD	Ventricular septal defect
WRF	Worsening renal function

Appendix A. Exact Search Strings

PubMed® Search Strategy (February 14, 2018)

KQ 1 & KQ 2: In patients with nonvalvular atrial fibrillation, what are the comparative diagnostic accuracy and impact on clinical decisionmaking (diagnostic thinking, therapeutic and patient outcome efficacy) of available clinical and imaging tools and associated risk factors for predicting thromboembolic risk? In patients with nonvalvular atrial fibrillation, what are the comparative diagnostic accuracy and impact on clinical decisionmaking (diagnostic thinking, therapeutic, and patient outcome efficacy) of clinical tools and associated risk factos for predicting bleeding events?

#1	"Atrial Fibrillation"[Mesh] OR "atrial fibrillation"[tiab] OR "Atrial Flutter"[Mesh] OR "atrial flutter"[tiab]
#2	"Cerebrovascular Disorders"[Majr:NoExp] OR "Stroke"[Mesh] OR "Thromboembolism"[Mesh] OR "Hemorrhage"[Mesh:NoExp] OR "Intracranial Hemorrhages"[Mesh] OR "Brain Ischemia"[Mesh] OR "Prothrombin Time"[Mesh] OR stroke[tiab] OR strokes[tiab] OR thromboembolism[tiab] OR thromboembolisms[tiab] OR thromboembolic[tiab] OR thromboses[tiab] OR hemorrhage[tiab] OR hemorrhages[tiab] OR hemorrhaging[tiab] OR hemorrhagic[tiab] OR haemorrhage[tiab] OR haemorrhages[tiab] OR haemorrhaging[tiab] OR haemorrhagic[tiab] OR (("bleeding"[tiab] OR bleed[tiab] OR bleeds[tiab]) AND (major[tiab] OR risk[tiab] OR event[tiab])) OR ((Systemic[tiab] OR paradoxical[tiab] OR crossed[tiab]) AND (embolism[tiab] OR embolisms[tiab])) OR ((brain[tiab] OR cerebral[tiab] OR brainstem[tiab] OR "brain stem"[tiab]) AND (ischemia[tiab] OR ischaemia[tiab] OR ischemias[tiab] OR ischaemias[tiab] OR infarction[tiab] OR infarctions[tiab])) OR (transient[tiab] AND (ischemic[tiab] OR ischaemic[tiab] OR ischaemia[tiab] OR ischemia[tiab]) AND (attack[tiab] OR attacks[tiab])) OR TIA[tiab] OR TIAs[tiab] OR "cerebrovascular accident"[tiab] OR "cerebrovascular accidents"[tiab] OR CVA[tiab] OR CVAs[tiab] OR "brain vascular accident"[tiab] OR "brain vascular accidents"[tiab]
#3	"Risk"[Mesh] OR risk[tiab] OR risks[tiab] OR "Predictive Value of Tests"[Mesh] OR predict[tiab] OR predicts[tiab] OR predicting[tiab] OR predictor[tiab] OR predictors[tiab] OR predictive[tiab]
#4	#1 AND #2 AND #3
#5	#4 NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp])
#6	#5 NOT ("Animals"[MeSH Terms] NOT "Humans"[MeSH Terms])
#7	#6 NOT (("Adolescent"[Mesh] OR "Child"[Mesh] OR "Infant"[Mesh]) NOT "Adult"[Mesh])

#8	"Randomized Controlled Trial"[Publication Type] OR "Controlled Clinical Trial"[Publication Type] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR "Clinical Trial"[Publication Type] OR "clinical trial"[tiab] OR "clinical trials"[tiab] OR "Evaluation Studies"[Publication Type] OR "Evaluation Studies as Topic"[MeSH Terms] OR "evaluation study"[tiab] OR "evaluation studies"[tiab] OR "intervention study"[tiab] OR "intervention studies"[tiab] OR "Case-control Studies"[MeSH Terms] OR "case-control"[tiab] OR "Cohort Studies"[Mesh Terms] OR cohort[tiab] OR "Longitudinal Studies"[MeSH Terms] OR longitudinal[tiab] OR longitudinally[tiab] OR "Prospective Studies"[Mesh Terms] OR "prospective"[tiab] OR prospectively[tiab] OR "Retrospective Studies"[MeSH Terms] OR "retrospective"[tiab] OR "Follow-Up Studies"[Mesh Terms] OR "follow up"[tiab] OR "Comparative Study"[Publication Type] OR "comparative study"[tiab] OR systematic[subset] OR "systematic review"[tiab] OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[tiab] OR "meta-analyses"[tiab] OR "meta synthesis"[tiab] OR "meta syntheses"[tiab] OR "Multicenter Study"[Publication Type] OR "Multicenter Study"[tiab] OR multicentre[tiab] OR "Registries"[Mesh Terms] OR registry[tiab] OR registries[tiab] OR "Sensitivity and Specificity"[Mesh] OR Sensitivity[tiab] OR specificity[tiab] OR valid[tiab] OR validity[tiab] OR validation[tiab] OR "validation studies"[publication type]
#9	#7 AND #8
#10	#9 AND ("2011/08/01"[Date - Publication] : "3000"[Date - Publication])

KQ 3: What are the comparative safety and effectiveness of specific anticoagulation therapies, antiplatelet therapies, and procedural interventions for preventing thromboembolic events:

a) In patients with nonvalvular atrial fibrillation?
b) In specific subpopulations of patients with nonvalvular atrial fibrillation?

#1	"Atrial Fibrillation"[Mesh] OR "atrial fibrillation"[tiab] OR "Atrial Flutter"[Mesh] OR "atrial flutter"[tiab]
#2	"Cerebrovascular Disorders"[Majr:NoExp] OR "Stroke"[Mesh] OR "Thromboembolism"[Mesh] OR "Hemorrhage"[Mesh:NoExp] OR "Intracranial Hemorrhages"[Mesh] OR "Brain Ischemia"[Mesh] OR "Prothrombin Time"[Mesh] OR stroke[tiab] OR strokes[tiab] OR thromboembolism[tiab] OR thromboembolisms[tiab] OR thromboembolic[tiab] OR thromboses[tiab] OR hemorrhage[tiab] OR hemorrhages[tiab] OR hemorrhaging[tiab] OR hemorrhagic[tiab] OR haemorrhage[tiab] OR haemorrhages[tiab] OR haemorrhaging[tiab] OR haemorrhagic[tiab] OR (("bleeding"[tiab] OR bleed[tiab] OR bleeds[tiab]) AND (major[tiab] OR risk[tiab] OR event[tiab])) OR ((Systemic[tiab] OR paradoxical[tiab] OR crossed[tiab]) AND (embolism[tiab] OR embolisms[tiab])) OR ((brain[tiab] OR cerebral[tiab] OR brainstem[tiab] OR "brain stem"[tiab]) AND (ischemia[tiab] OR ischaemia[tiab] OR ischemias[tiab] OR ischaemias[tiab] OR infarction[tiab] OR infarctions[tiab])) OR (transient[tiab] AND (ischemic[tiab] OR ischaemic[tiab] OR ischaemia[tiab] OR ischemia[tiab]) AND (attack[tiab] OR attacks[tiab])) OR TIA[tiab] OR TIAs[tiab] OR "cerebrovascular accident"[tiab] OR "cerebrovascular accidents"[tiab] OR CVA[tiab] OR CVAs[tiab] OR "brain vascular accident"[tiab] OR "brain vascular accidents"[tiab]

#3	"Risk"[Mesh] OR risk[tiab] OR risks[tiab] OR "Safety"[Mesh] OR safety[tiab] OR safe[tiab] OR "Incidence"[Mesh] OR efficacy[tiab] OR efficacious[tiab] OR "prevention and control"[Subheading] OR prevent[tiab] OR prevents[tiab] OR preventing[tiab] OR prevention[tiab] OR "Treatment Outcome"[Mesh] OR "adverse effects"[Subheading] OR side effect*[tiab] OR (adverse[tiab] AND (interaction*[tiab] or response*[tiab] or effect*[tiab] or event*[tiab] or reaction*[tiab] or outcome*[tiab])) OR (unintended[tiab] AND (interaction*[tiab] or response*[tiab] or effect*[tiab] or event*[tiab] or reaction*[tiab] or outcome*[tiab])) OR (unintentional[tiab] AND (interaction*[tiab] or response*[tiab] or effect*[tiab] or event*[tiab] or reaction*[tiab] or outcome*[tiab])) OR (unwanted[tiab] AND (interaction*[tiab] or response*[tiab] or effect*[tiab] or event*[tiab] or reaction*[tiab] or outcome*[tiab])) OR (unexpected AND (interaction*[tiab] or response*[tiab] or effect*[tiab] or event*[tiab] or reaction*[tiab] or outcome*[tiab])) OR (undesirable AND (interaction*[tiab] or response*[tiab] or effect*[tiab] or event*[tiab] or reaction*[tiab] or outcome*[tiab])) OR "drug safety"[tiab] OR "drug toxicity"[tiab] OR tolerability[tiab] OR harm[tiab] OR harms[tiab] OR harmful[tiab] OR "treatment emergent"[tiab] OR complication*[tiab] OR toxicity[tiab]
#4	#1 AND #2 AND #3
#5	"Anticoagulants"[Mesh] OR "Warfarin"[Mesh] OR "Heparin"[Mesh] OR "Vitamin K/antagonists and inhibitors"[Mesh] OR "Rivaroxaban"[Mesh] OR Antithrombins[Pharmacological Action] OR "Dabigatran"[Mesh] OR "Blood Coagulation Factor Inhibitors"[Mesh] OR "Anticoagulants"[Pharmacological Action] OR "Factor Xa Inhibitors"[Pharmacological Action] OR "apixaban"[Supplementary Concept] OR "edoxaban"[Supplementary Concept] OR warfarin[tiab] OR coumadin[tiab] OR "vitamin k"[tiab] OR enoxaparin[tiab] OR lovenox[tiab] OR rivaroxaban[tiab] OR xarelto[tiab] OR dabigatran[tiab] OR pradaxa[tiab] OR heparin[tiab] OR apixaban[tiab] OR eliquis[tiab] OR edoxaban[tiab] OR lixiana[tiab] OR anticoagulant[tiab] OR anticoagulants[tiab] OR anticoagulation[tiab] OR "thrombin inhibitor"[tiab] OR "thrombin inhibitors"[tiab] OR antithrombin[tiab] OR antithrombins[tiab] OR antithrombotic[tiab] OR "factor Xa inhibitor"[tiab] OR "factor Xa inhibitors"[tiab] OR "Blood clotting inhibitor"[tiab] OR "blood clotting inhibitors"[tiab]
#6	#4 AND #5
#7	"Platelet Aggregation Inhibitors"[Mesh] OR "Aspirin"[Mesh] OR "Dipyridamole"[Mesh] OR "Platelet Aggregation Inhibitors"[Pharmacological Action] OR clopidogrel[Supplementary Concept] OR clopidogrel[tiab] OR plavix[tiab] OR aspirin[tiab] OR dipyridamole[tiab] OR aggrenox[tiab] OR persantine[tiab] OR curantil[tiab] OR antiplatelet[tiab] OR anti-platelet[tiab] OR antiplatelets[tiab] OR anti-platelets[tiab] OR "platelet aggregation inhibitors"[tiab] OR "platelet aggregation inhibitor"[tiab] OR "platelet inhibitors"[tiab] OR "platelet inhibitor"[tiab] OR "platelet antagonists"[tiab] OR "platelet antagonist"[tiab]
#8	#4 AND #7
#9	"atrial appendage/surgery"[Mesh Terms] OR "Septal Occluder Device"[Mesh] OR "atrial appendage"[tiab] OR "atrial appendages"[tiab] OR "atrium appendage"[tiab] OR "auricular appendage"[tiab] OR "auricular appendages"[tiab] OR LAA[tiab] OR occluder[tiab] OR occluders[tiab] OR occlusion[tiab] OR AMPLATZER[tiab] OR AtriClip[tiab] OR PLAATO[tiab] OR Watchman[tiab] OR (atrial[tiab] AND modification[tiab]) OR lariat[tiab] OR atricure[tiab]
#10	#4 AND #9
#11	#6 OR #8 OR #10
#12	#11 NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp])
#13	#12 NOT ("Animals"[MeSH Terms] NOT "Humans"[MeSH Terms])
#14	#13 NOT (("Adolescent"[Mesh] OR "Child"[Mesh] OR "Infant"[Mesh]) NOT "Adult"[Mesh])

#15	"Randomized Controlled Trial"[Publication Type] OR "Controlled Clinical Trial"[Publication Type] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR "Clinical Trial"[Publication Type] OR "clinical trial"[tiab] OR "clinical trials"[tiab] OR "Evaluation Studies"[Publication Type] OR "Evaluation Studies as Topic"[MeSH Terms] OR "evaluation study"[tiab] OR "evaluation studies"[tiab] OR "intervention study"[tiab] OR "intervention studies"[tiab] OR "Case-control Studies"[MeSH Terms] OR "case-control"[tiab] OR "Cohort Studies"[Mesh Terms] OR cohort[tiab] OR "Longitudinal Studies"[MeSH Terms] OR longitudinal[tiab] OR longitudinally[tiab] OR "Prospective Studies"[Mesh Terms] OR "prospective"[tiab] OR prospectively[tiab] OR "Retrospective Studies"[MeSH Terms] OR "retrospective"[tiab] OR "Follow-Up Studies"[Mesh Terms] OR "follow up"[tiab] OR "Comparative Study"[Publication Type] OR "comparative study"[tiab] OR systematic[subset] OR "systematic review"[tiab] OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[tiab] OR "meta-analyses"[tiab] OR "meta synthesis"[tiab] OR "meta syntheses"[tiab] OR "Multicenter Study"[Publication Type] OR "Multicenter Study"[tiab] OR multicentre[tiab] OR "Registries"[Mesh Terms] OR registry[tiab] OR registries[tiab] OR "Sensitivity and Specificity"[Mesh] OR Sensitivity[tiab] OR specificity[tiab] OR valid[tiab] OR validity[tiab] OR validation[tiab] OR "validation studies"[publication type]
#16	#14 AND #15
#17	#16 AND ("2011/08/01"[Date - Publication] : "3000"[Date - Publication])

PubMed® Search Strategy (August 14, 2012)

KQ 1: In patients with nonvalvular atrial fibrillation, what are the comparative diagnostic accuracy and impact on clinical decisionmaking (diagnostic thinking, therapeutic, and patient outcome efficacy) of available clinical and imaging tools for predicting thromboembolic risk?

#1	"Atrial Fibrillation"[Mesh] OR "atrial fibrillation"[tiab] OR (atrial[tiab] AND fibrillation[tiab]) OR afib[tiab] OR "atrial flutter"[MeSH Terms] OR "atrial flutter"[tiab]
#2	chads2[tw] OR chads2-vasc[tw] OR "Magnetic Resonance Imaging"[Mesh] OR MRI[tw] OR "Cardiac Imaging Techniques"[Mesh] OR "Tomography, X-Ray Computed"[Mesh] OR "Echocardiography"[Mesh] OR ((transthoracic[tw] OR transesophageal[tw]) AND echo[tw]) OR TTE[tw] OR TEE[tw] OR CT-scan[tw]
#3	"Stroke"[Mesh] OR stroke[tw] OR thromboembolism[tw] OR "Thromboembolism"[Mesh] OR thromboembolic[tw] OR "brain ischemia"[MeSH Terms] OR (brain[tw] AND ischemia[tw]) OR (brain[tw] AND ischaemia[tw]) OR (transient[tw] AND (ischemic[tw] OR ischaemic[tw] OR ischaemia[tw] OR ischemia[tw]) AND attack[tw]) OR TIA[tw]
#4	#1 AND #2 AND #3
#5	(("diagnosis"[Subheading] OR "diagnosis"[tiab] OR "diagnosis"[MeSH Terms]) OR "treatment outcome"[MeSH Terms] OR outcome[tiab] OR outcomes[tiab]) OR (reliability[tw] OR accuracy[tw] OR accurate[tw] OR Sensitivity[tw] OR specificity[tw] OR "Sensitivity and Specificity"[Mesh] OR valid[tw] OR validity[tw] OR validation[tw] OR decision[tw] OR decisions[tw] OR "decision making"[MeSH Terms] OR assessment[tw])
#6	#5 AND #4
#7	#6 NOT (animals[mh] NOT humans[mh]), Limits: English, Publication Date from 2000 to present

KQ 2: In patients with nonvalvular atrial fibrillation, what are the comparative diagnostic accuracy and impact on clinical decisionmaking (diagnostic thinking, therapeutic, and patient outcome efficacy) of clinical tools and associated risk factors for predicting bleeding events?

#1	"Atrial Fibrillation"[Mesh] OR "atrial fibrillation"[tiab] OR (atrial[tiab] AND fibrillation[tiab]) OR afib[tiab] OR "atrial flutter"[MeSH Terms] OR "atrial flutter"[tiab]

#2	"Age Factors"[Mesh] OR "Dementia"[Mesh] OR "Accidental Falls"[Mesh] OR "International Normalized Ratio"[Mesh] OR age[tiab] OR dementia[tiab] OR INR[tiab] OR fall[tiab] OR falls[tiab] OR "international normalized ratio"[tiab] OR paroxysmal[tiab] OR persistent[tiab] OR permanent[tiab] OR stratification[tiab] OR classification[tiab] OR schema[tiab] OR has-bled[tiab] OR (cognitive[tw] AND impairment[tw]) OR cognition[tw] OR ((prior[tiab] OR previous[tiab] OR first[tiab]) AND stroke[tiab])
#3	"Intracranial Hemorrhages"[Mesh] OR "Hemorrhage"[Mesh:noexp] OR hemorrhage[tw] OR hemorrhaging[tw] OR bleeding[tw] OR bleed[tw] OR hemorrhagic[tw] OR haemorrhage[tw] OR haemorrhaging[tw] OR haemorrhagic[tw]
#4	#1 AND #2 AND #3
#5	(("diagnosis"[Subheading] OR "diagnosis"[tiab] OR "diagnosis"[MeSH Terms]) OR "treatment outcome"[MeSH Terms] OR outcome[tiab] OR outcomes[tiab]) OR (reliability[tw] OR accuracy[tw] OR accurate[tw] OR Sensitivity[tw] OR specificity[tw] OR "Sensitivity and Specificity"[Mesh] OR valid[tw] OR validity[tw] OR validation[tw] OR decision[tw] OR decisions[tw] OR "decision making"[MeSH Terms] OR assessment[tw])
#6	#5 AND #4
#7	#6 NOT (animals[mh] NOT humans[mh]), Limits: English, Publication Date from 2000 to present

KQ 3: What are the comparative safety and effectiveness of specific anticoagulation therapies, antiplatelet therapies, and procedural interventions for preventing thromboembolic events:

(a) In patients with nonvalvular atrial fibrillation?

(b) In specific subpopulations of patients with nonvalvular atrial fibrillation?

#1	"Atrial Fibrillation"[Mesh] OR "atrial fibrillation"[tiab] OR (atrial[tiab] AND fibrillation[tiab]) OR afib[tiab] OR "atrial flutter"[MeSH Terms] OR "atrial flutter"[tiab]
#2	"Anticoagulants"[Mesh] OR "Anticoagulants"[Pharmacological Action] OR warfarin[tw] OR "Warfarin"[Mesh] OR coumadin[tw] OR "Vitamin K/antagonists and inhibitors"[Mesh] OR vitamin k[tw] OR "Heparin"[Mesh] OR "Enoxaparin"[Mesh] OR enoxaparin[tw] OR lovenox[tw] OR "rivaroxaban" [Supplementary Concept] OR rivaroxaban[tw] OR xarelto[tw] OR "dabigatran etexilate" [Supplementary Concept] OR dabigatran[tw] OR pradaxa[tw] OR heparin[tw] OR "apixaban" [Supplementary Concept] OR apixaban[tw] OR eliquis[tw] OR "edoxaban" [Supplementary Concept] OR edoxaban[tw] OR lixiana[tw]
#3	**"Platelet Aggregation Inhibitors"[Mesh] OR "Platelet Aggregation Inhibitors"[Pharmacological Action] OR "clopidogrel" [Supplementary Concept]OR clopidogrel[tw] OR plavix[tw] OR "Aspirin"[Mesh] OR aspirin[tw] OR "Dipyridamole"[Mesh] OR dipyridamole[tw] OR aggrenox[tw] OR persantine[tw] OR antiplatelet[tw] OR anti-platelet[tw] OR antiplatelets[tw] OR anti-platelets[tw]**
#4	Atrial Appendage/surgery[mesh] OR atrial appendage[tw] OR LAA[tw] OR occluder[tw] OR AMPLATZER[tw] OR AtriClip[tw] OR PLAATO[tw] OR Watchman[tw] OR (atrial[tw] AND modification[tw]) OR “atriacure isolator”[tw]
#5	"Stroke"[Mesh] OR stroke[tw] OR thromboembolism[tw] OR "Thromboembolism"[Mesh] OR thromboembolic[tw] OR "brain ischemia"[MeSH Terms] OR (brain[tw] AND ischemia[tw]) OR (brain[tw] AND ischaemia[tw]) OR (transient[tw] AND (ischemic[tw] OR ischaemic[tw] OR ischaemia[tw] OR ischemia[tw]) AND attack[tw]) OR TIA[tw]
#6	#1 AND (#2 OR #3 OR #4) AND #5

#7	"evaluation studies"[Publication Type] OR "evaluation studies as topic"[MeSH Terms] OR "evaluation study"[tw] OR evaluation studies[tw] OR "intervention studies"[MeSH Terms] OR "intervention study"[tw] OR "intervention studies"[tw] OR "case-control studies"[MeSH Terms] OR "case-control"[tw] OR "cohort studies"[MeSH Terms] OR cohort[tw] OR "longitudinal studies"[MeSH Terms] OR "longitudinal"[tw] OR longitudinally[tw] OR "prospective"[tw] OR prospectively[tw] OR "retrospective studies"[MeSH Terms] OR "retrospective"[tw] OR "follow up"[tw] OR "comparative study"[Publication Type] OR "comparative study"[tw] OR systematic[subset] OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[tw] OR "meta-analyses"[tw] OR randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR "drug therapy"[Subheading] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Clinical trial[pt] OR "clinical trial"[tw] OR "clinical trials"[tw] NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp])
#8	#7 AND #6
#9	#8 NOT (animals[mh] NOT humans[mh]), Limits: English, Publication Date from 2000 to present

KQ 4: What are the comparative safety and effectiveness of available strategies for anticoagulation in patients with nonvalvular atrial fibrillation who are undergoing invasive procedures?

#1	"Atrial Fibrillation"[Mesh] OR "atrial fibrillation"[tiab] OR (atrial[tiab] AND fibrillation[tiab]) OR afib[tiab] OR "atrial flutter"[MeSH Terms] OR "atrial flutter"[tiab]
#2	"Anticoagulants"[Mesh] OR "Anticoagulants"[Pharmacological Action] OR warfarin[tw] OR "Warfarin"[Mesh] OR coumadin[tw] OR "Vitamin K/antagonists and inhibitors"[Mesh] OR vitamin k[tw] OR "Heparin"[Mesh] OR "Enoxaparin"[Mesh] OR enoxaparin[tw] OR lovenox[tw] OR "rivaroxaban" [Supplementary Concept] OR rivaroxaban[tw] OR xarelto[tw] OR "dabigatran etexilate" [Supplementary Concept] OR dabigatran[tw] OR pradaxa[tw] OR heparin[tw] OR "apixaban" [Supplementary Concept] OR apixaban[tw] OR eliquis[tw] OR "edoxaban" [Supplementary Concept] OR edoxaban[tw] OR lixiana[tw]
#3	"Surgical Procedures, Operative"[Mesh] OR /surgery[mesh] OR ((surgical[tw] OR invasive[tw]) AND (procedure[tw] OR procedures[tw])) OR "dental care"[MeSH Terms] OR (dental[tw] AND (procedure[tw] OR procedures[tw])) OR surgery[tw] OR procedures[tiab] OR procedure[tiab]
#4	#1 AND #2 AND #3
#5	"evaluation studies"[Publication Type] OR "evaluation studies as topic"[MeSH Terms] OR "evaluation study"[tw] OR evaluation studies[tw] OR "intervention studies"[MeSH Terms] OR "intervention study"[tw] OR "intervention studies"[tw] OR "case-control studies"[MeSH Terms] OR "case-control"[tw] OR "cohort studies"[MeSH Terms] OR cohort[tw] OR "longitudinal studies"[MeSH Terms] OR "longitudinal"[tw] OR longitudinally[tw] OR "prospective"[tw] OR prospectively[tw] OR "retrospective studies"[MeSH Terms] OR "retrospective"[tw] OR "follow up"[tw] OR "comparative study"[Publication Type] OR "comparative study"[tw] OR systematic[subset] OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[tw] OR "meta-analyses"[tw] OR randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR "drug therapy"[Subheading] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Clinical trial[pt] OR "clinical trial"[tw] OR "clinical trials"[tw] NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp])
#6	#5 AND #4
#7	#7 NOT (animals[mh] NOT humans[mh]), Limits: English, Publication Date from 2000 to present

KQ 5: What are the comparative safety and effectiveness of available strategies for switching between warfarin and other novel oral anticoagulants, in patients with nonvalvular atrial fibrillation?

#1	"Atrial Fibrillation"[Mesh] OR "atrial fibrillation"[tiab] OR (atrial[tiab] AND fibrillation[tiab]) OR afib[tiab] OR "atrial flutter"[MeSH Terms] OR "atrial flutter"[tiab]
#2	"warfarin"[MeSH Terms] OR warfarin[tw] OR coumadin[tw]
#3	"antithrombins"[MeSH Terms] OR "antithrombins"[tiab] OR ("direct"[tiab] AND "thrombin"[tiab] AND "inhibitors"[tiab]) OR "direct thrombin inhibitors"[tiab] OR "antithrombins"[Pharmacological Action]
#4	"Anticoagulants"[Mesh] OR "Anticoagulants" [Pharmacological Action] OR anticoagulant[tiab] OR anticoagulants[tiab]
#5	"evaluation studies"[Publication Type] OR "evaluation studies as topic"[MeSH Terms] OR "evaluation study"[tw] OR evaluation studies[tw] OR "intervention studies"[MeSH Terms] OR "intervention study"[tw] OR "intervention studies"[tw] OR "case-control studies"[MeSH Terms] OR "case-control"[tw] OR "cohort studies"[MeSH Terms] OR cohort[tw] OR "longitudinal studies"[MeSH Terms] OR "longitudinal"[tw] OR longitudinally[tw] OR "prospective"[tw] OR prospectively[tw] OR "retrospective studies"[MeSH Terms] OR "retrospective"[tw] OR "follow up"[tw] OR "comparative study"[Publication Type] OR "comparative study"[tw] OR systematic[subset] OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[tw] OR "meta-analyses"[tw] OR randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR "drug therapy"[Subheading] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Clinical trial[pt] OR "clinical trial"[tw] OR "clinical trials"[tw] NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp])
#6	#1 AND #2 AND (#3 OR #4) AND #5
#7	#6 NOT (animals[mh] NOT humans[mh]), Limits: English, Publication Date from 2000 to present

KQ 6: What are the comparative safety and effectiveness of available strategies for resuming anticoagulation therapy or performing a procedural intervention as a stroke prevention strategy following a hemorrhagic event (stroke, major bleed, or minor bleed) in patients with nonvalvular atrial fibrillation?

#1	"Atrial Fibrillation"[Mesh] OR "atrial fibrillation"[tiab] OR (atrial[tiab] AND fibrillation[tiab]) OR afib[tiab] OR "atrial flutter"[MeSH Terms] OR "atrial flutter"[tiab]
#2	"Anticoagulants"[Mesh] OR "Anticoagulants"[Pharmacological Action] OR warfarin[tw] OR "Warfarin"[Mesh] OR coumadin[tw] OR "Vitamin K/antagonists and inhibitors"[Mesh] OR vitamin k[tw] OR "Heparin"[Mesh] OR "Enoxaparin"[Mesh] OR enoxaparin[tw] OR lovenox[tw] OR "rivaroxaban" [Supplementary Concept] OR rivaroxaban[tw] OR xarelto[tw] OR "dabigatran etexilate" [Supplementary Concept] OR dabigatran[tw] OR pradaxa[tw] OR heparin[tw] OR "apixaban" [Supplementary Concept] OR apixaban[tw] OR eliquis[tw] OR "edoxaban" [Supplementary Concept] OR edoxaban[tw] OR lixiana[tw]
#3	"Intracranial Hemorrhages"[Mesh] OR "Hemorrhage"[Mesh:noexp] OR hemorrhage[tw] OR hemorrhaging[tw] OR bleeding[tw] OR bleed[tw] OR hemorrhagic[tw] OR haemorrhage[tw] OR haemorrhaging[tw] OR haemorrhagic[tw]
#4	Resume[tiab] OR resumed[tiab] OR restart[tiab] OR restarted[tiab] OR restarting[tiab] OR re-initiate[tiab] OR reinitiate[tiab] OR continue[tiab] OR continued[tiab] OR start[tiab] OR "time factors"[MeSH Terms] OR resumption[tiab] OR reinitiating[tiab] OR resuming[tiab] OR continuing[tiab]
#5	#1 AND #2 AND #3 AND #4

#6	"evaluation studies"[Publication Type] OR "evaluation studies as topic"[MeSH Terms] OR "evaluation study"[tw] OR evaluation studies[tw] OR "intervention studies"[MeSH Terms] OR "intervention study"[tw] OR "intervention studies"[tw] OR "case-control studies"[MeSH Terms] OR "case-control"[tw] OR "cohort studies"[MeSH Terms] OR cohort[tw] OR "longitudinal studies"[MeSH Terms] OR "longitudinal"[tw] OR longitudinally[tw] OR "prospective"[tw] OR prospectively[tw] OR "retrospective studies"[MeSH Terms] OR "retrospective"[tw] OR "follow up"[tw] OR "comparative study"[Publication Type] OR "comparative study"[tw] OR systematic[subset] OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[tw] OR "meta-analyses"[tw] OR randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR "drug therapy"[Subheading] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Clinical trial[pt] OR "clinical trial"[tw] OR "clinical trials"[tw] NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp])
#7	#5 AND #6
#8	#7 NOT (animals[mh] NOT humans[mh]), Limits: English, Publication Date from 2000 to present

Embase® Search Strategy (February 14, 2018)

Platform: Embase.com

KQ 1 & KQ 2: In patients with nonvalvular atrial fibrillation, what are the comparative diagnostic accuracy and impact on clinical decisionmaking (diagnostic thinking, therapeutic and patient outcome efficacy) of available clinical and imaging tools and associated risk factors for predictin thromboembolic risk? & In patients with nonvalvular atrial fibrillation, what are the comparative diagnostic accuracy and impact on clinical decisionmaking (diagnostic thinking, therapeutic, and patient outcome efficacy) of clinical tools and associated risk factos for predicting bleeding events?

#1	'atrial fibrillation'/exp OR 'heart atrium flutter'/exp OR 'atrial fibrillation':ab,ti OR 'atrial flutter':ab,ti
#2	'cerebrovascular disease'/de OR 'cerebrovascular accident'/exp OR 'thromboembolism'/exp OR 'bleeding'/de OR 'brain hemorrhage'/exp OR 'brain ischemia'/exp OR 'prothrombin time'/exp OR stroke:ab,ti OR strokes:ab,ti OR thromboembolism:ab,ti OR thromboembolisms:ab,ti OR thromboembolic:ab,ti OR thromboses:ab,ti OR hemorrhage:ab,ti OR hemorrhages:ab,ti OR hemorrhaging:ab,ti OR hemorrhagic:ab,ti OR haemorrhage:ab,ti OR haemorrhages:ab,ti OR haemorrhaging:ab,ti OR haemorrhagic:ab,ti OR ((bleeding OR bleed OR bleeds) NEAR/2 (major OR risk OR event)):ab,ti OR ((systemic OR paradoxical OR crossed) NEXT/2 (embolism OR embolisms)):ab,ti OR ((brain OR cerebral OR brainstem OR 'brain stem') NEXT/2 (ischemia OR ischaemia OR ischemias OR ischaemias OR infarction OR infarctions)):ab,ti OR (transient NEXT/2 (ischemic OR ischaemic OR ischaemia OR ischemia) NEXT/2 (attack OR attacks)):ab,ti OR tia:ab,ti OR tias:ab,ti OR 'cerebrovascular accident':ab,ti OR 'cerebrovascular accidents':ab,ti OR cva:ab,ti OR cvas:ab,ti OR 'brain vascular accident':ab,ti OR 'brain vascular accidents':ab,ti
#3	'risk'/exp OR risk:ab,ti OR risks:ab,ti OR 'prediction and forecasting'/exp OR predict:ab,ti OR predicts:ab,ti OR predicting:ab,ti OR predictor:ab,ti OR predictors:ab,ti OR predictive:ab,ti
#4	#1 AND #2 AND #3
#5	#4 NOT ('case report'/exp OR 'case study'/exp OR 'a case report':ti OR ': case report':ti OR 'editorial'/exp OR 'letter'/exp OR 'note'/exp OR [conference abstract]/lim)
#6	#5 AND [humans]/lim
#7	#6 NOT (('adolescent'/exp OR 'child'/exp) NOT 'adult'/exp)

#8	'clinical trial'/exp OR 'clinical study'/exp OR 'controlled study'/exp OR randomized:ab,ti OR randomised:ab,ti OR randomization:ab,ti OR randomisation:ab,ti OR randomly:ab,ti OR placebo:ab,ti OR trial:ab,ti OR groups:ab,ti OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR crossover*:ab,ti OR (cross NEXT/1 over*):ab,ti OR 'clinical trial':ab,ti OR 'clinical trials':ab,ti OR 'clinical study':ab,ti OR 'clinical studies':ab,ti OR 'evaluation study'/exp OR 'evaluation study':ab,ti OR 'evaluation studies':ab,ti OR 'intervention study':ab,ti OR 'intervention studies':ab,ti OR 'case-control':ab,ti OR 'cohort analysis'/exp OR cohort:ab,ti OR longitudinal:ab,ti OR longitudinally:ab,ti OR 'prospective':ab,ti OR prospectively:ab,ti OR 'retrospective':ab,ti OR 'follow up'/exp OR 'follow up':ab,ti OR 'comparative study'/exp OR 'comparative study':ab,ti OR 'comparative studies':ab,ti OR 'systematic review':ab,ti OR 'meta-analysis':ab,ti OR 'meta-analyses':ab,ti OR 'meta synthesis':ab,ti OR 'meta syntheses':ab,ti OR 'survival analysis'/exp OR 'multicenter study'/exp OR 'multicenter study':ab,ti OR multicentre:ab,ti OR 'register'/exp OR registry:ab,ti OR registries:ab,ti OR 'sensitivity and specificity'/exp OR sensitivity:ab,ti OR specificity:ab,ti OR valid:ab,ti OR validity:ab,ti OR validation:ab,ti OR 'validation study'/exp
#9	#7 AND #8
#10	#9 AND [1-8-2011]/sd
#11	#10 AND [embase]/lim NOT [medline]/lim

KQ 3: What are the comparative safety and effectiveness of specific anticoagulation therapies, antiplatelet therapies, and procedural interventions for preventing thromboembolic events:

a) In patients with nonvalvular atrial fibrillation?
b) In specific subpopulations of patients with nonvalvular atrial fibrillation?

#1	'atrial fibrillation'/exp OR 'heart atrium flutter'/exp OR 'atrial fibrillation':ab,ti OR 'atrial flutter':ab,ti
#2	'cerebrovascular disease'/de OR 'cerebrovascular accident'/exp OR 'thromboembolism'/exp OR 'bleeding'/de OR 'brain hemorrhage'/exp OR 'brain ischemia'/exp OR 'prothrombin time'/exp OR stroke:ab,ti OR strokes:ab,ti OR thromboembolism:ab,ti OR thromboembolisms:ab,ti OR thromboembolic:ab,ti OR thromboses:ab,ti OR hemorrhage:ab,ti OR hemorrhages:ab,ti OR hemorrhaging:ab,ti OR hemorrhagic:ab,ti OR haemorrhage:ab,ti OR haemorrhages:ab,ti OR haemorrhaging:ab,ti OR haemorrhagic:ab,ti OR ((bleeding OR bleed OR bleeds) NEAR/2 (major OR risk OR event)):ab,ti OR ((systemic OR paradoxical OR crossed) NEXT/2 (embolism OR embolisms)):ab,ti OR ((brain OR cerebral OR brainstem OR 'brain stem') NEXT/2 (ischemia OR ischaemia OR ischemias OR ischaemias OR infarction OR infarctions)):ab,ti OR (transient NEXT/2 (ischemic OR ischaemic OR ischaemia OR ischemia) NEXT/2 (attack OR attacks)):ab,ti OR tia:ab,ti OR tias:ab,ti OR 'cerebrovascular accident':ab,ti OR 'cerebrovascular accidents':ab,ti OR cva:ab,ti OR cvas:ab,ti OR 'brain vascular accident':ab,ti OR 'brain vascular accidents':ab,ti
#3	'risk'/exp OR risk:ab,ti OR risks:ab,ti OR 'safety'/exp OR safety:ab,ti OR safe:ab,ti OR 'incidence'/exp OR efficacy:ab,ti OR efficacious:ab,ti OR 'prevention':lnk OR prevent:ab,ti OR prevents:ab,ti OR preventing:ab,ti OR prevention:ab,ti OR 'treatment outcome'/exp OR 'adverse drug reaction':lnk OR (side NEXT/1 effect*):ab,ti OR (adverse NEXT/3 (interaction* OR response* OR effect* OR event* OR reaction* OR outcome*)):ab,ti OR (unintended NEXT/3 (interaction* OR response* OR effect* OR event* OR reaction* OR outcome*)):ab,ti OR (unintentional NEXT/3 (interaction* OR response* OR effect* OR event* OR reaction* OR outcome*)):ab,ti OR (unwanted NEXT/3 (interaction* OR response* OR effect* OR event* OR reaction* OR outcome*)):ab,ti OR (unexpected NEXT/3 (interaction* OR response* OR effect* OR event* OR reaction* OR outcome*)):ab,ti OR (undesirable NEXT/3 (interaction* OR response* OR effect* OR event* OR reaction* OR outcome*)):ab,ti OR 'drug safety':ab,ti OR 'drug toxicity':ab,ti OR tolerability:ab,ti OR harm:ab,ti OR harms:ab,ti OR harmful:ab,ti OR 'treatment emergent':ab,ti OR complication*:ab,ti OR toxicity:ab,ti
#4	#1 AND #2 AND #3

#5	'anticoagulant agent'/exp OR warfarin:ab,ti OR coumadin:ab,ti OR 'vitamin k':ab,ti OR enoxaparin:ab,ti OR lovenox:ab,ti OR rivaroxaban:ab,ti OR xarelto:ab,ti OR dabigatran:ab,ti OR pradaxa:ab,ti OR heparin:ab,ti OR apixaban:ab,ti OR eliquis:ab,ti OR edoxaban:ab,ti OR lixiana:ab,ti OR anticoagulant:ab,ti OR anticoagulants:ab,ti OR anticoagulation:ab,ti OR 'thrombin inhibitor':ab,ti OR 'thrombin inhibitors':ab,ti OR antithrombin:ab,ti OR antithrombins:ab,ti OR antithrombotic:ab,ti OR 'factor Xa inhibitor':ab,ti OR 'factor Xa inhibitors':ab,ti OR 'Blood clotting inhibitor':ab,ti OR 'blood clotting inhibitors':ab,ti OR clopidogrel:ab,ti OR plavix:ab,ti OR aspirin:ab,ti OR dipyridamole:ab,ti OR aggrenox:ab,ti OR persantine:ab,ti OR curantil:ab,ti OR antiplatelet:ab,ti OR anti-platelet:ab,ti OR antiplatelets:ab,ti OR anti-platelets:ab,ti OR 'platelet aggregation inhibitors':ab,ti OR 'platelet aggregation inhibitor':ab,ti OR 'platelet inhibitors':ab,ti OR 'platelet inhibitor':ab,ti OR 'platelet antagonists':ab,ti OR 'platelet antagonist':ab,ti
#6	('heart atrium appendage'/de AND 'surgery':lnk) OR 'septal occluder'/exp OR 'atrial appendage':ab,ti OR 'atrial appendages':ab,ti OR 'atrium appendage':ab,ti OR 'auricular appendage':ab,ti OR 'auricular appendages':ab,ti OR LAA:ab,ti OR occluder:ab,ti OR occluders:ab,ti OR occlusion:ab,ti OR AMPLATZER:ab,ti OR AtriClip:ab,ti OR PLAATO:ab,ti OR Watchman:ab,ti OR (atrial:ab,ti AND modification:ab,ti) OR lariat:ab,ti OR atricure:ab,ti
#7	#4 AND (#5 OR #6)
#8	#7 NOT ('case report'/exp OR 'case study'/exp OR 'editorial'/exp OR 'letter'/exp OR 'note'/exp OR [conference abstract]/lim)
#9	#8 AND [humans]/lim
#10	#9 NOT (('adolescent'/exp OR 'child'/exp) NOT 'adult'/exp)
#11	'clinical trial'/exp OR 'clinical study'/exp OR 'controlled study'/exp OR randomized:ab,ti OR randomised:ab,ti OR randomization:ab,ti OR randomisation:ab,ti OR randomly:ab,ti OR placebo:ab,ti OR trial:ab,ti OR groups:ab,ti OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR crossover*:ab,ti OR (cross NEXT/1 over*):ab,ti OR 'clinical trial':ab,ti OR 'clinical trials':ab,ti OR 'clinical study':ab,ti OR 'clinical studies':ab,ti OR 'evaluation study'/exp OR 'evaluation study':ab,ti OR 'evaluation studies':ab,ti OR 'intervention study':ab,ti OR 'intervention studies':ab,ti OR 'case-control':ab,ti OR 'cohort analysis'/exp OR cohort:ab,ti OR longitudinal:ab,ti OR longitudinally:ab,ti OR 'prospective':ab,ti OR prospectively:ab,ti OR 'retrospective':ab,ti OR 'follow up'/exp OR 'follow up':ab,ti OR 'comparative study'/exp OR 'comparative study':ab,ti OR 'comparative studies':ab,ti OR 'systematic review':ab,ti OR 'meta-analysis':ab,ti OR 'meta-analyses':ab,ti OR 'meta synthesis':ab,ti OR 'meta syntheses':ab,ti OR 'survival analysis'/exp OR 'multicenter study'/exp OR 'multicenter study':ab,ti OR multicentre:ab,ti OR 'register'/exp OR registry:ab,ti OR registries:ab,ti OR 'sensitivity and specificity'/exp OR sensitivity:ab,ti OR specificity:ab,ti OR valid:ab,ti OR validity:ab,ti OR validation:ab,ti OR 'validation study'/exp
#12	#10 AND #11
#13	#12 AND [1-8-2011]/sd
#14	#13 AND [embase]/lim NOT [medline]/lim

Embase® Search Strategy (August 14, 2012)

Platform: Embase.com

KQ 1: In patients with nonvalvular atrial fibrillation, what are the comparative diagnostic accuracy and impact on clinical decisionmaking (diagnostic thinking, therapeutic, and patient outcome efficacy) of available clinical and imaging tools for predicting thromboembolic risk?

#1	'heart atrium fibrillation'/exp OR 'heart atrium flutter'/exp OR “atrial fibrillation”:ab,ti OR (atrial:ab,ti AND fibrillation:ab,ti) OR afib:ab,ti OR “atrial flutter”:ab,ti

#2	'nuclear magnetic resonance imaging'/exp OR 'cardiac imaging'/exp OR 'computer assisted tomography'/exp OR 'echocardiography'/exp OR chads2:ab,ti OR 'chads2 vasc':ab,ti OR (transthoracic:ab,ti AND echo:ab,ti) OR (transesophageal:ab,ti AND echo:ab,ti) OR tte:ab,ti OR tee:ab,ti OR 'ct scan':ab,ti
#3	'stroke'/exp OR 'thromboembolism'/exp OR 'brain ischemia'/exp OR stroke:ab,ti OR thromboembolism:ab,ti OR thromboembolic:ab,ti OR (brain:ab,ti AND ischemia:ab,ti) OR (brain:ab,ti AND ischaemia:ab,ti) OR (transient:ab,ti AND (ischemic:ab,ti OR ischaemic:ab,ti OR ischaemia:ab,ti OR ischemia:ab,ti) AND attack:ab,ti) OR TIA:ab,ti
#4	#1 AND #2 AND #3
#5	'diagnosis'/exp OR 'treatment outcome'/exp OR 'sensitivity and specificity'/exp OR 'clinical decision making'/exp OR 'decision making'/exp OR diagnosis:ab,ti OR outcome:ab,ti OR outcomes:ab,ti OR reliability:ab,ti OR accuracy:ab,ti OR accurate:ab,ti OR Sensitivity:ab,ti OR specificity:ab,ti OR valid:ab,ti OR validity:ab,ti OR validation:ab,ti OR decision:ab,ti OR decisions:ab,ti OR assessment:ab,ti
#6	#5 AND #4
#7	#6 Limits: Humans, English, 2000 - present
#8	#7 AND [embase]/lim NOT [medline]/lim

KQ 2: In patients with nonvalvular atrial fibrillation, what are the comparative diagnostic accuracy and impact on clinical decisionmaking (diagnostic thinking, therapeutic, and patient outcome efficacy) of clinical tools and associated risk factors for predicting bleeding events?

#1	'heart atrium fibrillation'/exp OR 'heart atrium flutter'/exp OR “atrial fibrillation”:ab,ti OR (atrial:ab,ti AND fibrillation:ab,ti) OR afib:ab,ti OR “atrial flutter”:ab,ti
#2	'age'/exp OR 'dementia'/exp OR 'falling'/exp OR 'international normalized ratio'/exp OR “age factors”:ab,ti OR “age factor”:ab,ti OR age:ab,ti OR dementia:ab,ti OR INR:ab,ti OR fall:ab,ti OR falls:ab,ti OR "international normalized ratio":ab,ti OR paroxysmal:ab,ti OR persistent:ab,ti OR permanent:ab,ti OR stratification:ab,ti OR classification:ab,ti OR schema:ab,ti OR has-bled:ab,ti OR (cognitive:ab,ti AND impairment:ab,ti) OR cognition:ab,ti OR ((prior:ab,ti OR previous:ab,ti OR first:ab,ti) AND stroke:ab,ti)
#3	'brain hemorrhage'/exp OR 'bleeding'/exp OR hemorrhage:ab,ti OR hemorrhaging:ab,ti OR bleeding:ab,ti OR bleed:ab,ti OR hemorrhagic:ab,ti OR haemorrhage:ab,ti OR haemorrhaging:ab,ti OR haemorrhagic:ab,ti
#4	#1 AND #2 AND #3
#5	'diagnosis'/exp OR 'treatment outcome'/exp OR 'sensitivity and specificity'/exp OR 'clinical decision making'/exp OR 'decision making'/exp OR diagnosis:ab,ti OR outcome:ab,ti OR outcomes:ab,ti OR reliability:ab,ti OR accuracy:ab,ti OR accurate:ab,ti OR Sensitivity:ab,ti OR specificity:ab,ti OR valid:ab,ti OR validity:ab,ti OR validation:ab,ti OR decision:ab,ti OR decisions:ab,ti OR assessment:ab,ti
#6	#5 AND #4
#7	#6 Limits: Humans, English, 2000 - present
#8	#7 AND [embase]/lim NOT [medline]/lim

KQ 3: What are the comparative safety and effectiveness of specific anticoagulation therapies, antiplatelet therapies, and procedural interventions for preventing thromboembolic events:

(a) In patients with nonvalvular atrial fibrillation?

(b) In specific subpopulations of patients with nonvalvular atrial fibrillation?

#1	'heart atrium fibrillation'/exp OR 'heart atrium flutter'/exp OR “atrial fibrillation”:ab,ti OR (atrial:ab,ti AND fibrillation:ab,ti) OR afib:ab,ti OR “atrial flutter”:ab,ti

#2	'anticoagulant agent'/exp OR 'warfarin'/exp OR 'vitamin K group'/exp OR 'heparin'/exp OR 'enoxaparin'/exp OR 'rivaroxaban'/exp OR 'dabigatran etexilate'/exp OR 'apixaban'/exp OR 'edoxaban'/exp
#3	warfarin:ab,ti OR coumadin:ab,ti OR vitamin k:ab,ti OR enoxaparin:ab,ti OR lovenox:ab,ti OR rivaroxaban:ab,ti OR xarelto:ab,ti OR dabigatran:ab,ti OR pradaxa:ab,ti OR heparin:ab,ti OR apixaban:ab,ti OR eliquis:ab,ti OR edoxaban:ab,ti OR lixiana:ab,ti
#4	#2 OR #3
#5	**'antithrombocytic agent'/exp OR 'clopidogrel'/exp OR 'acetylsalicylic acid'/exp OR 'dipyridamole'/exp OR clopidogrel:ab,ti OR plavix:ab,ti OR aspirin:ab,ti OR dipyridamole:ab,ti OR aggrenox:ab,ti OR persantine:ab,ti OR antiplatelet:ab,ti OR anti-platelet:ab,ti OR antiplatelets:ab,ti OR anti-platelets:ab,ti**
#6	'heart atrium appendage'/exp OR atrial appendage:ab,ti OR LAA:ab,ti OR occluder:ab,ti OR AMPLATZER:ab,ti OR AtriClip:ab,ti OR PLAATO:ab,ti OR Watchman:ab,ti OR (atrial:ab,ti AND modification:ab,ti) OR “atriacure isolator”:ab,ti
#7	'stroke'/exp OR 'thromboembolism'/exp OR 'brain ischemia'/exp OR stroke:ab,ti OR thromboembolism:ab,ti OR thromboembolic:ab,ti OR (brain:ab,ti AND ischemia:ab,ti) OR (brain:ab,ti AND ischaemia:ab,ti) OR (transient:ab,ti AND (ischemic:ab,ti OR ischaemic:ab,ti OR ischaemia:ab,ti OR ischemia:ab,ti) AND attack:ab,ti) OR TIA:ab,ti
#8	#1 AND (#4 OR #5 OR #6) AND #7
#9	('randomized controlled trial'/exp OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR random*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR (cross NEAR/1 over*):ab,ti OR placebo*:ab,ti OR (doubl* NEAR/1 blind*):ab,ti OR (singl* NEAR/1 blind*):ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR volunteer*:ab,ti OR 'clinical study'/exp OR “clinical trial”:ti,ab OR “clinical trials”:ti,ab OR 'controlled study'/exp OR 'evaluation'/exp OR “evaluation study”:ab,ti OR “evaluation studies”:ab,ti OR “intervention study”:ab,ti OR “intervention studies”:ab,ti OR “case control”:ab,ti OR 'cohort analysis'/exp OR cohort:ab,ti OR longitudinal*:ab,ti OR prospective:ab,ti OR prospectively:ab,ti OR retrospective:ab,ti OR 'follow up'/exp OR “follow up”:ab,ti OR 'comparative effectiveness'/exp OR 'comparative study'/exp OR “comparative study”:ab,ti OR “comparative studies”:ab,ti OR 'evidence based medicine'/exp OR “systematic review”:ab,ti OR “meta-analysis”:ab,ti OR “meta-analyses”:ab,ti) NOT ('editorial'/exp OR 'letter'/exp OR 'case report'/exp)
#10	#8 AND #9
#11	#10 Limits: Humans, English, 2000 - present
#12	#11 AND [embase]/lim NOT [medline]/lim

KQ 4: What are the comparative safety and effectiveness of available strategies for anticoagulation in patients with nonvalvular atrial fibrillation who are undergoing invasive procedures?

#1	'heart atrium fibrillation'/exp OR 'heart atrium flutter'/exp OR “atrial fibrillation”:ab,ti OR (atrial:ab,ti AND fibrillation:ab,ti) OR afib:ab,ti OR “atrial flutter”:ab,ti
#2	'anticoagulant agent'/exp OR 'warfarin'/exp OR 'vitamin K group'/exp OR 'heparin'/exp OR 'enoxaparin'/exp OR 'rivaroxaban'/exp OR 'dabigatran etexilate'/exp OR 'apixaban'/exp OR 'edoxaban'/exp
#3	warfarin:ab,ti OR coumadin:ab,ti OR vitamin k:ab,ti OR enoxaparin:ab,ti OR lovenox:ab,ti OR rivaroxaban:ab,ti OR xarelto:ab,ti OR dabigatran:ab,ti OR pradaxa:ab,ti OR heparin:ab,ti OR apixaban:ab,ti OR eliquis:ab,ti OR edoxaban:ab,ti OR lixiana:ab,ti
#4	#2 OR #3
#5	'surgery'/exp OR 'dental care'/exp OR ((surgical:ab,ti OR invasive:ab,ti) AND (procedure:ab,ti OR procedures:ab,ti)) OR (dental:ab,ti AND (procedure:ab,ti OR procedures:ab,ti)) OR surgery:ab,ti OR procedures:ab,ti OR procedure:ab,ti
#6	#1 AND #4 AND #5

#7	('randomized controlled trial'/exp OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR random*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR (cross NEAR/1 over*):ab,ti OR placebo*:ab,ti OR (doubl* NEAR/1 blind*):ab,ti OR (singl* NEAR/1 blind*):ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR volunteer*:ab,ti OR 'clinical study'/exp OR "clinical trial":ti,ab OR "clinical trials":ti,ab OR 'controlled study'/exp OR 'evaluation'/exp OR "evaluation study":ab,ti OR "evaluation studies":ab,ti OR "intervention study":ab,ti OR "intervention studies":ab,ti OR "case control":ab,ti OR 'cohort analysis'/exp OR cohort:ab,ti OR longitudinal*:ab,ti OR prospective:ab,ti OR prospectively:ab,ti OR retrospective:ab,ti OR 'follow up'/exp OR "follow up":ab,ti OR 'comparative effectiveness'/exp OR 'comparative study'/exp OR "comparative study":ab,ti OR "comparative studies":ab,ti OR 'evidence based medicine'/exp OR "systematic review":ab,ti OR "meta-analysis":ab,ti OR "meta-analyses":ab,ti) NOT ('editorial'/exp OR 'letter'/exp OR 'case report'/exp)
#8	#6 AND #7
#9	#8 Limits: Humans, English, 2000 - present
#10	#9 AND [embase]/lim NOT [medline]/lim

KQ 5: What are the comparative safety and effectiveness of available strategies for switching between warfarin and other novel oral anticoagulants, in patients with nonvalvular atrial fibrillation?

#1	'heart atrium fibrillation'/exp OR 'heart atrium flutter'/exp OR "atrial fibrillation":ab,ti OR (atrial:ab,ti AND fibrillation:ab,ti) OR afib:ab,ti OR "atrial flutter":ab,ti
#2	'warfarin'/exp OR warfarin:ab,ti OR coumadin:ab,ti
#3	antithrombins:ab,ti OR (direct:ab,ti AND thrombin:ab,ti AND inhibitors:ab,ti) OR (direct:ab,ti AND thrombin:ab,ti AND inhibitor:ab,ti) OR "direct thrombin inhibitors":ab,ti OR "Antithrombin III":ab,ti OR "Antithrombin Proteins":ab,ti OR argatroban:ab,ti OR bivalirudin:ab,ti OR "Heparin Cofactor II":ab,ti OR Hirudins:ab,ti OR inogatran:ab,ti OR lepirudin:ab,ti OR melagatran:ab,ti OR "SDZ MTH 958":ab,ti OR ximelagatran:ab,ti
#4	'anticoagulant agent'/exp OR anticoagulant:ab,ti OR anticoagulants:ab,ti
#5	('randomized controlled trial'/exp OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR random*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR (cross NEAR/1 over*):ab,ti OR placebo*:ab,ti OR (doubl* NEAR/1 blind*):ab,ti OR (singl* NEAR/1 blind*):ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR volunteer*:ab,ti OR 'clinical study'/exp OR "clinical trial":ti,ab OR "clinical trials":ti,ab OR 'controlled study'/exp OR 'evaluation'/exp OR "evaluation study":ab,ti OR "evaluation studies":ab,ti OR "intervention study":ab,ti OR "intervention studies":ab,ti OR "case control":ab,ti OR 'cohort analysis'/exp OR cohort:ab,ti OR longitudinal*:ab,ti OR prospective:ab,ti OR prospectively:ab,ti OR retrospective:ab,ti OR 'follow up'/exp OR "follow up":ab,ti OR 'comparative effectiveness'/exp OR 'comparative study'/exp OR "comparative study":ab,ti OR "comparative studies":ab,ti OR 'evidence based medicine'/exp OR "systematic review":ab,ti OR "meta-analysis":ab,ti OR "meta-analyses":ab,ti) NOT ('editorial'/exp OR 'letter'/exp OR 'case report'/exp)
#6	#1 AND #2 AND (#3 OR #4) AND #5
#7	#6 Limits: Humans, English, 2000 - present
#8	#7 AND [embase]/lim NOT [medline]/lim

KQ 6: What are the comparative safety and effectiveness of available strategies for resuming anticoagulation therapy or performing a procedural intervention as a stroke prevention strategy following a hemorrhagic event (stroke, major bleed, or minor bleed) in patients with nonvalvular atrial fibrillation?

#1	'heart atrium fibrillation'/exp OR 'heart atrium flutter'/exp OR "atrial fibrillation":ab,ti OR (atrial:ab,ti AND fibrillation:ab,ti) OR afib:ab,ti OR "atrial flutter":ab,ti
#2	'anticoagulant agent'/exp OR 'warfarin'/exp OR 'vitamin K group'/exp OR 'heparin'/exp OR 'enoxaparin'/exp OR 'rivaroxaban'/exp OR 'dabigatran etexilate'/exp OR 'apixaban'/exp OR 'edoxaban'/exp
#3	warfarin:ab,ti OR coumadin:ab,ti OR vitamin k:ab,ti OR enoxaparin:ab,ti OR lovenox:ab,ti OR rivaroxaban:ab,ti OR xarelto:ab,ti OR dabigatran:ab,ti OR pradaxa:ab,ti OR heparin:ab,ti OR apixaban:ab,ti OR eliquis:ab,ti OR edoxaban:ab,ti OR lixiana:ab,ti
#4	#2 OR #3
#5	'brain hemorrhage'/exp OR 'bleeding'/exp OR hemorrhage:ab,ti OR hemorrhaging:ab,ti OR bleeding:ab,ti OR bleed:ab,ti OR hemorrhagic:ab,ti OR haemorrhage:ab,ti OR haemorrhaging:ab,ti OR haemorrhagic:ab,ti
#6	'time'/exp OR resume:ab,ti OR resumed:ab,ti OR restart:ab,ti OR restarted:ab,ti OR restarting:ab,ti OR re-initiate:ab,ti OR reinitiate:ab,ti OR continue:ab,ti OR continued:ab,ti OR start:ab,ti OR resumption:ab,ti OR reinitiating:ab,ti OR resuming:ab,ti OR continuing:ab,ti
#7	#1 AND #4 AND #5 AND #6
#8	('randomized controlled trial'/exp OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR random*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR (cross NEAR/1 over*):ab,ti OR placebo*:ab,ti OR (doubl* NEAR/1 blind*):ab,ti OR (singl* NEAR/1 blind*):ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR volunteer*:ab,ti OR 'clinical study'/exp OR "clinical trial":ti,ab OR "clinical trials":ti,ab OR 'controlled study'/exp OR 'evaluation'/exp OR "evaluation study":ab,ti OR "evaluation studies":ab,ti OR "intervention study":ab,ti OR "intervention studies":ab,ti OR "case control":ab,ti OR 'cohort analysis'/exp OR cohort:ab,ti OR longitudinal*:ab,ti OR prospective:ab,ti OR prospectively:ab,ti OR retrospective:ab,ti OR 'follow up'/exp OR "follow up":ab,ti OR 'comparative effectiveness'/exp OR 'comparative study'/exp OR "comparative study":ab,ti OR "comparative studies":ab,ti OR 'evidence based medicine'/exp OR "systematic review":ab,ti OR "meta-analysis":ab,ti OR "meta-analyses":ab,ti) NOT ('editorial'/exp OR 'letter'/exp OR 'case report'/exp)
#9	#7 AND #8
#10	#9 Limits: Humans, English, 2000 - present
#11	#10 AND [embase]/lim NOT [medline]/lim

Cochrane Search Strategy (February 14, 2018)

Platform: Wiley
Database searched: Cochrane Database of Systematic Reviews

KQ 1 & KQ 2: In patients with nonvalvular atrial fibrillation, what are the comparative diagnostic accuracy and impact on clinical decisionmaking (diagnostic thinking, therapeutic and patient outcome efficacy) of available clinical and imaging tools and associated risk factors for predictin thromboembolic risk? & In patients with nonvalvular atrial fibrillation, what are the comparative diagnostic accuracy and impact on clinical decisionmaking (diagnostic thinking, therapeutic, and patient outcome efficacy) of clinical tools and associated risk factos for predicting bleeding events?

#1	[mh "Atrial Fibrillation"] OR "atrial fibrillation":ab,ti OR [mh "Atrial Flutter"] OR "atrial flutter":ab,ti
#2	[mh ^"Cerebrovascular Disorders"[mj]] or [mh Stroke] or [mh Thromboembolism] or [mh ^Hemorrhage] or [mh "Intracranial Hemorrhages"] or [mh "Brain Ischemia"] or [mh "Prothrombin Time"] or stroke:ab,ti or strokes:ab,ti or thromboembolism:ab,ti or thromboembolisms:ab,ti or thromboembolic:ab,ti or thromboses:ab,ti or hemorrhage:ab,ti or hemorrhages:ab,ti or hemorrhaging:ab,ti or hemorrhagic:ab,ti or haemorrhage:ab,ti or haemorrhages:ab,ti or haemorrhaging:ab,ti or haemorrhagic:ab,ti or ((bleeding or bleed or bleeds) near/2 (major or risk or event)):ab,ti or ((systemic or paradoxical or crossed) next/2 (embolism or embolisms)):ab,ti or ((brain or cerebral or brainstem or 'brain stem') next/2 (ischemia or ischaemia or ischemias or ischaemias or infarction or infarctions)):ab,ti or (transient next/2 (ischemic or ischaemic or ischaemia or ischemia) next/2 (attack or attacks)):ab,ti or TIA:ab,ti or TIAs:ab,ti or "cerebrovascular accident":ab,ti or "cerebrovascular accidents":ab,ti or CVA:ab,ti or CVAs:ab,ti or "brain vascular accident":ab,ti or "brain vascular accidents":ab,ti
#3	[mh Risk] or risk:ab,ti or risks:ab,ti or [mh "Predictive Value of Tests"] or predict:ab,ti or predicts:ab,ti or predicting:ab,ti or predictor:ab,ti or predictors:ab,ti or predictive:ab,ti
#4	{and #1-#3}
#5	#4 Publication Year from 2011

KQ 3: What are the comparative safety and effectiveness of specific anticoagulation therapies, antiplatelet therapies, and procedural interventions for preventing thromboembolic events:

a) In patients with nonvalvular atrial fibrillation?
b) In specific subpopulations of patients with nonvalvular atrial fibrillation?

#1	[mh "Atrial Fibrillation"] OR "atrial fibrillation":ab,ti OR [mh "Atrial Flutter"] OR "atrial flutter":ab,ti
#2	[mh ^"Cerebrovascular Disorders"[mj]] or [mh Stroke] or [mh Thromboembolism] or [mh ^Hemorrhage] or [mh "Intracranial Hemorrhages"] or [mh "Brain Ischemia"] or [mh "Prothrombin Time"] or stroke:ab,ti or strokes:ab,ti or thromboembolism:ab,ti or thromboembolisms:ab,ti or thromboembolic:ab,ti or thromboses:ab,ti or hemorrhage:ab,ti or hemorrhages:ab,ti or hemorrhaging:ab,ti or hemorrhagic:ab,ti or haemorrhage:ab,ti or haemorrhages:ab,ti or haemorrhaging:ab,ti or haemorrhagic:ab,ti or ((bleeding or bleed or bleeds) near/2 (major or risk or event)):ab,ti or ((systemic or paradoxical or crossed) next/2 (embolism or embolisms)):ab,ti or ((brain or cerebral or brainstem or 'brain stem') next/2 (ischemia or ischaemia or ischemias or ischaemias or infarction or infarctions)):ab,ti or (transient next/2 (ischemic or ischaemic or ischaemia or ischemia) next/2 (attack or attacks)):ab,ti or TIA:ab,ti or TIAs:ab,ti or "cerebrovascular accident":ab,ti or "cerebrovascular accidents":ab,ti or CVA:ab,ti or CVAs:ab,ti or "brain vascular accident":ab,ti or "brain vascular accidents":ab,ti
#3	[mh Risk] or risk:ab,ti or risks:ab,ti or [mh Safety] or safety:ab,ti or safe:ab,ti or [mh Incidence] or efficacy:ab,ti or efficacious:ab,ti or [mh /PC] or prevent:ab,ti or prevents:ab,ti or preventing:ab,ti or prevention:ab,ti or [mh "Treatment Outcome"] or [mh /AE] or (side next/1 effect*):ab,ti or (adverse next/3 (interaction* or response* or effect* or event* or reaction* or outcome*)):ab,ti or (unintended next/3 (interaction* or response* or effect* or event* or reaction* or outcome*)):ab,ti or (unintentional next/3 (interaction* or response* or effect* or event* or reaction* or outcome*)):ab,ti or (unwanted next/3 (interaction* or response* or effect* or event* or reaction* or outcome*)):ab,ti or (unexpected next/3 (interaction* or response* or effect* or event* or reaction* or outcome*)):ab,ti or (undesirable next/3 (interaction* or response* or effect* or event* or reaction* or outcome*)):ab,ti or "drug safety":ab,ti or "drug toxicity":ab,ti or tolerability:ab,ti or harm:ab,ti or harms:ab,ti or harmful:ab,ti or "treatment emergent":ab,ti or complication*:ab,ti or toxicity:ab,ti
#4	{and #1-#3}
#5	[mh Anticoagulants] or [mh Warfarin] or [mh Heparin] or [mh "Vitamin K"/AI] or [mh Rivaroxaban] or [mh Antithrombins] or [mh Dabigatran] or [mh "Blood Coagulation Factor Inhibitors"] or [mh "Factor Xa Inhibitors"] or warfarin:ab,ti or coumadin:ab,ti or "vitamin k":ab,ti or enoxaparin:ab,ti or lovenox:ab,ti or rivaroxaban:ab,ti or xarelto:ab,ti or dabigatran:ab,ti or pradaxa:ab,ti or heparin:ab,ti or apixaban:ab,ti or eliquis:ab,ti or edoxaban:ab,ti or lixiana:ab,ti or

	anticoagulant:ab,ti or anticoagulants:ab,ti or anticoagulation:ab,ti or "thrombin inhibitor":ab,ti or "thrombin inhibitors":ab,ti or antithrombin:ab,ti or antithrombins:ab,ti or antithrombotic:ab,ti or "factor Xa inhibitor":ab,ti or "factor Xa inhibitors":ab,ti or "Blood clotting inhibitor":ab,ti or "blood clotting inhibitors":ab,ti
#6	[mh "Platelet Aggregation Inhibitors"] or [mh Aspirin] or [mh Dipyridamole] or clopidogrel:ab,ti or plavix:ab,ti or aspirin:ab,ti or dipyridamole:ab,ti or aggrenox:ab,ti or persantine:ab,ti or curantil:ab,ti or antiplatelet:ab,ti or anti-platelet:ab,ti or antiplatelets:ab,ti or anti-platelets:ab,ti or "platelet aggregation inhibitors":ab,ti or "platelet aggregation inhibitor":ab,ti or "platelet inhibitors":ab,ti or "platelet inhibitor":ab,ti or "platelet antagonists":ab,ti or "platelet antagonist":ab,ti
#7	[mh "atrial appendage"/SU] or [mh "Septal Occluder Device"] or "atrial appendage":ab,ti or "atrial appendages":ab,ti or "atrium appendage":ab,ti or "auricular appendage":ab,ti or "auricular appendages":ab,ti or LAA:ab,ti or occluder:ab,ti or occluders:ab,ti or occlusion:ab,ti or AMPLATZER:ab,ti or AtriClip:ab,ti or PLAATO:ab,ti or Watchman:ab,ti or (atrial:ab,ti and modification:ab,ti) or lariat:ab,ti or atricure:ab,ti
#8	#4 and {or #5-#7}
#9	#8 Publication Year from 2011

Cochrane Search Strategy (August 14, 2012)

Platform: Wiley
Database searched: Cochrane Database of Systematic Reviews

KQ 1: In patients with nonvalvular atrial fibrillation, what are the comparative diagnostic accuracy and impact on clinical decisionmaking (diagnostic thinking, therapeutic, and patient outcome efficacy) of available clinical and imaging tools for predicting thromboembolic risk?

#1	(atrial fibrillation OR atrial flutter):ti,ab,kw
#2	Magnetic Resonance Imaging explode all trees OR MeSH descriptor Cardiac Imaging Techniques explode all trees OR MeSH descriptor Tomography, X-Ray Computed explode all trees OR MeSH descriptor Echocardiography explode all trees OR (chads2 OR chads2-vasc OR TEE OR TTE OR ct-scan OR transthoracic echo OR transesophageal echo):ti,ab,kw
#3	MeSH descriptor Stroke explode all trees OR MeSH descriptor Thromboembolism explode all trees OR MeSH descriptor Brain Ischemia explode all trees OR (thromboembolism OR thromboembolic OR brain ischemia OR brain ischaemia OR tia):ti,ab,kw OR (transient ischemic attack):ti,ab,kw or (transient ischaemic attack):ti,ab,kw or (transient ischemia attack):ti,ab,kw or (transient ischaemic attack):ti,ab,kw
#4	#1 AND #2 AND #3
#5	#4, Limits: Cochrane Reviews, 2000 to 2012

KQ 2: In patients with nonvalvular atrial fibrillation, what are the comparative diagnostic accuracy and impact on clinical decisionmaking (diagnostic thinking, therapeutic, and patient outcome efficacy) of clinical tools and associated risk factors for predicting bleeding events?

#1	(atrial fibrillation OR atrial flutter):ti,ab,kw
#2	MeSH descriptor Age Factors explode all trees OR MeSH descriptor Dementia explode all trees OR MeSH descriptor Accidental Falls explode all trees OR MeSH descriptor International Normalized Ratio explode all trees OR age:ti,ab,kw OR dementia:ti,ab,kw OR INR:ti,ab,kw OR fall:ti,ab,kw OR falls:ti,ab,kw OR "international normalized ratio":ti,ab,kw OR paroxysmal:ti,ab,kw OR persistent:ti,ab,kw OR permanent:ti,ab,kw OR stratification:ti,ab,kw OR classification:ti,ab,kw OR schema:ti,ab,kw OR has-bled:ti,ab,kw OR cognitive impairment:ti,ab,kw OR cognition:ti,ab,kw OR ((prior:ti,ab,kw OR previous:ti,ab,kw OR first:ti,ab,kw) AND stroke:ti,ab,kw)

#3	MeSH descriptor Intracranial Hemorrhages explode all trees OR MeSH descriptor Hemorrhage explode all trees OR hemorrhage:ti,ab,kw OR hemorrhaging:ti,ab,kw OR bleeding:ti,ab,kw OR bleed:ti,ab,kw OR hemorrhagic:ti,ab,kw OR haemorrhage:ti,ab,kw OR haemorrhaging:ti,ab,kw OR haemorrhagic:ti,ab,kw
#4	#1 AND #2 AND #3
#5	MeSH descriptor Diagnosis explode all trees OR MeSH descriptor Treatment Outcome explode all trees OR MeSH descriptor Sensitivity and Specificity explode all trees OR MeSH descriptor Decision Making explode all trees OR diagnosis:ti,ab,kw OR outcome:ti,ab,kw OR outcomes:ti,ab,kw OR reliability:ti,ab,kw OR accuracy:ti,ab,kw OR accurate:ti,ab,kw OR Sensitivity:ti,ab,kw OR specificity:ti,ab,kw OR valid:ti,ab,kw OR validity:ti,ab,kw OR validation:ti,ab,kw OR decision:ti,ab,kw OR decisions:ti,ab,kw OR assessment:ti,ab,kw
#6	#4 AND #5
#7	#6, Limits: Cochrane Reviews, 2000 to 2012

KQ 3: What are the comparative safety and effectiveness of specific anticoagulation therapies, antiplatelet therapies, and procedural interventions for preventing thromboembolic events:

(a) In patients with nonvalvular atrial fibrillation?

(b) In specific subpopulations of patients with nonvalvular atrial fibrillation?

#1	(atrial fibrillation OR atrial flutter):ti,ab,kw
#2	MeSH descriptor Anticoagulants explode all trees OR warfarin:ti,ab,kw OR coumadin:ti,ab,kw OR vitamin k:ti,ab,kw OR enoxaparin:ti,ab,kw OR lovenox:ti,ab,kw OR rivaroxaban:ti,ab,kw OR xarelto:ti,ab,kw OR dabigatran:ti,ab,kw OR pradaxa:ti,ab,kw OR heparin:ti,ab,kw OR apixaban:ti,ab,kw OR eliquis:ti,ab,kw OR edoxaban:ti,ab,kw OR lixiana:ti,ab,kw OR anticoagulants:ti,ab,kw OR OR anticoagulant:ti,ab,kw
#3	MeSH descriptor Platelet Aggregation Inhibitors explode all trees OR clopidogrel:ti,ab,kw OR plavix:ti,ab,kw OR aspirin:ti,ab,kw OR dipyridamole:ti,ab,kw OR aggrenox:ti,ab,kw OR persantine:ti,ab,kw OR antiplatelet:ti,ab,kw OR anti-platelet:ti,ab,kw OR antiplatelets:ti,ab,kw OR anti-platelets:ti,ab,kw
#4	MeSH descriptor Atrial Appendage explode all trees OR atrial appendage:ti,ab,kw OR LAA:ti,ab,kw OR occluder:ti,ab,kw OR AMPLATZER:ti,ab,kw OR AtriClip:ti,ab,kw OR PLAATO:ti,ab,kw OR Watchman:ti,ab,kw OR (atrial:ti,ab,kw AND modification:ti,ab,kw) OR "atriacure isolator":ti,ab,kw
#5	MeSH descriptor Stroke explode all trees OR MeSH descriptor Thromboembolism explode all trees OR MeSH descriptor Brain Ischemia explode all trees OR (thromboembolism OR thromboembolic OR brain ischemia OR brain ischaemia OR tia):ti,ab,kw OR (transient ischemic attack):ti,ab,kw or (transient ischaemic attack):ti,ab,kw or (transient ischemia attack):ti,ab,kw or (transient ischaemic attack):ti,ab,kw
#6	#1 AND (#2 OR #3 OR #4) AND #5
#7	#6, Limits: Cochrane Reviews, 2000 to 2012

KQ 4: What are the comparative safety and effectiveness of available strategies for anticoagulation in patients with nonvalvular atrial fibrillation who are undergoing invasive procedures?

#1	(atrial fibrillation OR atrial flutter):ti,ab,kw
#2	MeSH descriptor Anticoagulants explode all trees OR warfarin:ti,ab,kw OR coumadin:ti,ab,kw OR vitamin k:ti,ab,kw OR enoxaparin:ti,ab,kw OR lovenox:ti,ab,kw OR rivaroxaban:ti,ab,kw OR xarelto:ti,ab,kw OR dabigatran:ti,ab,kw OR pradaxa:ti,ab,kw OR heparin:ti,ab,kw OR apixaban:ti,ab,kw OR eliquis:ti,ab,kw OR edoxaban:ti,ab,kw OR lixiana:ti,ab,kw OR anticoagulants:ti,ab,kw OR OR anticoagulant:ti,ab,kw

#3	MeSH descriptor Surgical Procedures, Operative explode all trees OR MeSH descriptor Dental Care explode all trees OR surgical:ti,ab,kw OR invasive:ti,ab,kw OR procedures:ti,ab,kw OR surgery:ti,ab,kw OR procedure:ti,ab,kw
#4	#1 AND #2 AND #3
#5	#4, Limits: Cochrane Reviews, 2000 to 2012

KQ 5: What are the comparative safety and effectiveness of available strategies for switching between warfarin and other novel oral anticoagulants, in patients with nonvalvular atrial fibrillation?

#1	(atrial fibrillation OR atrial flutter):ti,ab,kw
#2	warfarin:ti,ab,kw OR coumadin:ti,ab,kw
#3	MeSH descriptor Antithrombins explode all trees OR antithrombins:ti,ab,kw OR (direct:ti,ab,kw AND thrombin:ti,ab,kw AND inhibitors:ti,ab,kw) OR "direct thrombin inhibitors":ti,ab,kw OR "direct thrombin inhibitor":ti,ab,kw
#4	MeSH descriptor Anticoagulants explode all trees OR anticoagulant:ti,ab,kw OR anticoagulants:ti,ab,kw OR vitamin k:ti,ab,kw OR enoxaparin:ti,ab,kw OR lovenox:ti,ab,kw OR rivaroxaban:ti,ab,kw OR xarelto:ti,ab,kw OR dabigatran:ti,ab,kw OR pradaxa:ti,ab,kw OR heparin:ti,ab,kw OR apixaban:ti,ab,kw OR eliquis:ti,ab,kw OR edoxaban:ti,ab,kw OR lixiana:ti,ab,kw
#5	#1 AND #2 AND (#3 OR #4)
#6	#5, Limits: Cochrane Reviews, 2000 to 2012

KQ 6: What are the comparative safety and effectiveness of available strategies for resuming anticoagulation therapy or performing a procedural intervention as a stroke prevention strategy following a hemorrhagic event (stroke, major bleed, or minor bleed) in patients with nonvalvular atrial fibrillation?

#1	(atrial fibrillation OR atrial flutter):ti,ab,kw
#2	MeSH descriptor Anticoagulants explode all trees OR warfarin:ti,ab,kw OR coumadin:ti,ab,kw OR vitamin k:ti,ab,kw OR enoxaparin:ti,ab,kw OR lovenox:ti,ab,kw OR rivaroxaban:ti,ab,kw OR xarelto:ti,ab,kw OR dabigatran:ti,ab,kw OR pradaxa:ti,ab,kw OR heparin:ti,ab,kw OR apixaban:ti,ab,kw OR eliquis:ti,ab,kw OR edoxaban:ti,ab,kw OR lixiana:ti,ab,kw OR anticoagulant:ti,ab,kw OR anticoagulants:ti,ab,kw
#3	MeSH descriptor Intracranial Hemorrhages explode all trees OR MeSH descriptor Hemorrhage explode all trees OR hemorrhage:ti,ab,kw OR hemorrhaging:ti,ab,kw OR bleeding:ti,ab,kw OR bleed:ti,ab,kw OR hemorrhagic:ti,ab,kw OR haemorrhage:ti,ab,kw OR haemorrhaging:ti,ab,kw OR haemorrhagic:ti,ab,kw
#4	MeSH descriptor Time Factors explode all trees OR Resume:ti,ab,kw OR resumed:ti,ab,kw OR restart:ti,ab,kw OR restarted:ti,ab,kw OR restarting:ti,ab,kw OR re-initiate:ti,ab,kw OR reinitiate:ti,ab,kw OR continue:ti,ab,kw OR continued:ti,ab,kw OR start:ti,ab,kw OR resumption:ti,ab,kw OR reinitiating:ti,ab,kw OR resuming:ti,ab,kw OR continuing:ti,ab,kw
#5	#1 AND #2 AND #3 AND #4
#6	#5, Limits: Cochrane Reviews, 2000 to 2012

PubMed® Search Strategy (February 12, 2018)

Contextual Question: What are currently available shared decision-making tools for patient and provider use for stroke prophylaxis in atrial fibrillation, and what are their relative strengths and weaknesses?

((("Atrial Fibrillation"[Mesh] OR "Atrial Flutter"[Mesh] OR "atrial fibrillation"[tiab] OR afib[tiab] OR "atrial flutter"[tiab])) AND ("Stroke"[Mesh] OR "Thromboembolism"[Mesh] OR "brain ischemia"[Mesh] OR stroke[tiab] OR strokes[tiab] OR thromboembolism[tiab] OR thromboembolisms[tiab] OR thromboembolic[tiab] OR ((brain[tiab] OR cerebral[tiab]) AND (ischemia[tiab] OR ischaemia[tiab] OR ischemias[tiab] OR ischaemias[tiab])) OR (transient[tiab] AND (ischemic[tiab] OR ischaemic[tiab] OR ischaemia[tiab] OR ischemia[tiab]) AND (attack[tiab] OR attacks[tiab])) OR TIA[tiab] OR TIAs[tiab] OR “cerebrovascular accident”[tiab] OR “cerebrovascular accidents”[tiab] OR CVA[tiab] OR CVAs[tiab] OR “brain vascular accident”[tiab] OR “brain vascular accidents”[tiab])) AND ("Clinical Decision-Making"[Mesh] OR "Decision Support Systems, Clinical"[Mesh] OR "Decision Making, Computer-Assisted"[Mesh] OR "Decision Support Techniques"[Mesh] OR "Decision Making"[Mesh] OR "Decision Theory"[Mesh] OR "Medical Order Entry Systems"[Mesh] OR "Point-of-Care Systems"[Mesh] OR “decision”[tiab] OR "decision-making"[tiab]) AND ("2011/08/01"[Date - Publication] : "3000"[Date - Publication])

Grey Literature Searches

ClinicalTrials.gov (February 9, 2018)

KQ1, KQ2, KQ3	
Condition	atrial fibrillation OR afib OR atrial flutter
Outcome	stroke OR thromboembolism OR thromboembolic OR "brain ischemia" OR “brain ischaemia” OR (transient AND ischemic AND attack) OR TIA OR hemorrhage OR hemorrhaging OR bleeding OR bleed OR hemorrhagic OR haemorrhage OR haemorrhaging OR haemorrhagic

Total number of results: 343

ClinicalTrials.gov (August 22, 2012)

KQ1, KQ2, KQ3, KQ6	
Condition	atrial fibrillation OR afib OR atrial flutter
Outcome	stroke OR thromboembolism OR thromboembolic OR "brain ischemia" OR “brain ischaemia” OR (transient AND ischemic AND attack) OR TIA OR hemorrhage OR hemorrhaging OR bleeding OR bleed OR hemorrhagic OR haemorrhage OR haemorrhaging OR haemorrhagic

KQ4	
Condition	atrial fibrillation OR afib OR atrial flutter
Intervention	Anticoagulants OR anticoagulation OR warfarin OR coumadin OR vitamin k OR Heparin OR enoxaparin OR lovenox OR rivaroxaban OR xarelto OR dabigatran OR pradaxa OR apixaban OR eliquis OR edoxaban OR lixiana
Search Terms	Surgery OR procedures OR procedure

KQ5	
Condition	atrial fibrillation OR afib OR atrial flutter
Intervention	(warfarin OR Coumadin) AND (Antithrombins OR antithrombin OR (direct AND thrombin AND (inhibitors OR inhibitor)) OR anticoagulant OR anticoagulants)

Total number of results: 186

WHO: International Clinical Trials Registry Platform Search Portal (August 17, 2012)

KQs 1-6	
Condition	atrial fibrillation OR afib OR atrial flutter
Recruiting status	ALL

Total number of results: 858

ProQuest COS Conference Papers Index (August 14, 2012)

KQ1, KQ2, KQ3, KQ6	
#1	All (atrial fibrillation OR afib OR atrial flutter)
#3	All (stroke OR thromboembolism OR thromboembolic OR "brain ischemia" OR “brain ischaemia” OR (transient AND (ischemic OR ischaemic) AND attack) OR TIA OR hemorrhage OR hemorrhaging OR bleeding OR bleed OR hemorrhagic OR haemorrhage OR haemorrhaging OR haemorrhagic)
#4	#1 AND #2 AND #3

KQ4	
#1	All (atrial fibrillation OR afib OR atrial flutter)
#2	All (Anticoagulants OR anticoagulation OR warfarin OR coumadin OR vitamin k OR Heparin OR enoxaparin OR lovenox OR rivaroxaban OR xarelto OR dabigatran OR pradaxa OR apixaban OR eliquis OR edoxaban OR lixiana)
#3	All (Surgery OR procedures OR procedure)
#4	#1 AND #2 AND #3

KQ5	
#1	All (atrial fibrillation OR afib OR atrial flutter)
#2	All (warfarin OR Coumadin)
#3	All (Antithrombins OR antithrombin OR (direct AND thrombin AND (inhibitors OR inhibitor)) OR anticoagulant OR anticoagulants)
#6	#1 AND #2 AND #3

Total number of results: 352

Appendix B. Data Abstraction Elements

Study Characteristics

- Study Identifiers
  - Study Name or Acronym
  - Last name of first author
  - Publication Year
- Additional Articles Used in This Abstraction
- Study Objective(s)
- Study Dates
  - Enrollment start (Mon and YYYY)
  - Enrollment end (Mon and YYYY)
  - Follow-up end (Mon and YYYY)
- Study Sites
  - Single center, Multicenter, Unclear/Not reported
  - Number of sites
- Geographic Location (Select all that apply)
  - US, Canada, UK, Europe, S. America, C. America, Asia, Africa, Australia/NZ, Unclear/Not reported, Other (specify)
- Study Design
  - Prospective RCT
  - Prospective Cohort
  - Retrospective Cohort
  - Case-control
  - Cross-sectional
  - Other (specify)
- Funding Source (Select all that apply)
  - Government, Industry, Non-government/non-industry, Unclear/Not reported, Other (specify)
- Setting (Select all that apply)
  - In-patient, Out-patient, Emergency Room, Unclear/Not reported, Other (specify)
- Enrollment Approach (Select all that apply)
  - Consecutive patients, Convenience sample, Unclear/Not reported, Other (specify)
- Study Inclusion and Exclusion Criteria
  - Copy/paste inclusion and exclusion criteria as reported
  - Is the study entirely composed of patients with any of the following characteristics/conditions?
    - Paroxysmal Atrial Fibrillation (AF)
    - Persistent AF
    - Permanent AF
    - Patients with atrial fibrillation who experience acute coronary syndrome
    - Age
    - Women
    - Pregnant women
    - Race/ethnicity
    - Presence of heart disease

        - Type of AF
        - Patients in the therapeutic range
        - Patients with prior bleed
        - Patients with prior stroke
        - Patients with comorbid conditions such as dementia, renal failure, or hepatic failure
        - Patients with multiple coexisting conditions (e.g. combinations of hypertension, diabetes, CHF, CAD, and high cholesterol)
        - Patients non-compliant with treatment
        - None of the above
- Study Enrollment/Study Completion
    - N assessed for eligibility
    - N eligible
    - N enrolled/included
    - N completed follow-up (most distal timepoint of the primary outcome)
    - N analyzed
- Key Question Applicability (Select all that apply)
    - KQ1, KQ2, KQ3, KQ4, KQ5, KQ6
- Comments

Baseline Characteristics – Record the following elements for Total Population, Arm 1, Arm 2, Arm 3, and Arm 4 (as applicable)

- Number of Patients, Age, Ethnicity, and Race
    - Number of Patients
        - Total
        - Female
        - Male
    - Percentage
        - Female
        - Male
    - Age
        - Mean
        - Standard Deviation
        - Standard Error
        - Median
        - IQR
        - Min
        - Max
        - NR
    - Ethnicity
        - Hispanic or Latino
        - Not Hispanic or Latino
        - NR
    - Race
        - Black/African American
        - American Indian or Alaska Native

        - Asian
        - Native Hawaiian or other Pacific Islander
        - White
        - Multiracial
        - Other (specify)
        - NR
- Baseline Characteristics
    - Diabetes
        - N
        - %
    - Heart failure (NYHA Class), N and % for the following:
        - Class I
        - Class II
        - Class III
        - Class IV
        - All classes
    - Sleep apnea
        - N
        - %
    - Hyperlipidemia
        - N
        - %
    - Hypertension
        - N
        - %
    - Kidney disease
        - N
        - %
    - Congestive Heart Failure (CHF)
        - N
        - %
    - Coronary Artery Disease (CAD)
        - N
        - %
    - Prior Myocardial Infarction (MI)
        - N
        - %
    - Prior Percutaneous Coronary Intervention (PCI)
        - N
        - %
    - Prior CABG
        - N
        - %
    - Left Ventricular Ejection Fraction (LVEF), Mean or median
        - Mean or median
        - SD, SE, or IQR

- LVEF, Number of patients (<35% or other [define])
  - N
  - %
- Evidence of Left Atrial Appendage (LAA) thrombus
  - N
  - %
- Any Left Ventricular (LV) dysfunction
  - N
  - %
- Prior stroke or Transient Ischemic Attack (TIA), N and % for the following types:
  - Ischemic
  - Hemorrhagic
  - TIA
  - All types
- Tobacco use
  - N
  - %
- Obesity (define)
  - N
  - %
- Patients non-compliant with treatment
  - N
  - %
- Prior vascular disease
  - N
  - %
- Prior bleed
  - N
  - %
- $CHADS_2$ score
  - Mean or median
  - SD, SE, or IQR
- $CHADS_2$, N and % of patients with the following scores:
  - 0
  - 1
  - 2+
- CHA_2DS_2-VASc score
  - Mean or median
  - SD, SE, or IQR
- CHA_2DS_2-VASc, N and % of patients with the following scores:
  - 0
  - 1
  - 2+
- HAS-BLED score
  - Mean or median
  - SD, SE, or IQR

- HAS-BLED, N and % of patients with the following scores:
  - <3
  - 3+
- Duration of AF
  - Mean or median
  - SD, SE, or IQR
- Paroxysmal AF
  - N
  - %
- Persistent AF
  - N
  - %
- Permanent AF
  - N
  - %

- Comments

Intervention Characteristics – Record the following elements for Total Population, Arm 1, Arm 2, Arm 3, and Arm 4 (as applicable)

- Interventions (Check all that apply)
  - Placebo or control; Clinical & imaging tools for thromboembolic risk; Clinical tools & individual factors for bleeding risk; Anticoagulation therapy (all oral anticoagulants); Procedural interventions; Antiplatelet therapy; Anticoagulation bridging therapies
    - If 'Placebo or control' selected:
      - Placebo/control
        - Placebo, Usual care/Optimal medical therapy (OMT), Other (specify)
    - If 'Clinical & imagine tools for thromboembolic risk' selected:
      - Thromboembolic risk tools
        - $CHADS_2$ score, CHA_2DS_2-VASc score, Transthoracic echo (TTE), Transesophageal echo (TEE), CT scan, Cardiac MRI, Framingham Score
    - If 'Clinical tools & individual factors for bleeding risk' selected:
      - Intracerebral bleeding risk tools/factors
        - Patient age, Prior stroke, Type of AF (paroxysmal, persistent, permanent), International normalized ratio (INR), Dementia/cognitive impairment, Falls risk, $CHADS_2$ score, CHA_2DS_2-VASc score, $HEMORR_2HAGES$, HAS-BLED, ATRIA, Bleeding Risk Index, Framingham
    - If 'Anticoagulation therapy (all oral anticoagulants)' selected:
      - Anticoagulation therapy
        - Vitamin K antagonists
          - If 'Vitamin K antagonists' selected:
            - Warfarin (Coumadin), Other
              - Newer anticoagulants (direct oral anticoagulants [DOACS])
              - Direct thrombin Inh-DTI:
                - Dabigatran (Pradaxa)
              - Factor Xa inhibitors:

        - Rivaroxaban (Xarelto), Apixaban (Eliquis), Edoxaban (DU-176b)
    - If 'Procedural interventions' selected:
        - Procedural interventions
            - Surgical LAA resection, Surgical LAA ligation, Surgical LAA occlusion, Surgical – other (specify), Minimally invasive – Atriclip, Minimally invasive – LARIAT, Minimally invasive – other (specify), Transcatheter – WATCHMAN, Transcatheter – AMPLATZER, Transcatheter – PLAATO, Transcatheter – Other (specify)
    - If 'Antiplatelet therapy' selected:
        - Antiplatelet therapy
            - Clopidogrel (Plavix), Aspirin (ASA), ASA + dipyridamole (Aggrenox), Dipyridamole (Persantine), Other (specify)
    - If 'Anticoagulation bridging therapies' selected:
        - Anticoagulation bridging
            - Unfractionated Heparin, Low Molecular Weight Heparin (LMWH), Factor IIa Inhibitors, Factor Xa Inhibitors, Other (specify)
                - If 'Unfractionated Heparin' selected:
                    - IV Heparin, Other
                - If 'LMWH' selected:
                    - Bemiparin, Certoparin, Dalteparin, Enoxaparin, Nadroparin, Parnaparin, Reviparin, Tinzaparin, Other
                - If 'Factor IIa Inhibitors' selected:
                    - Dabigatran, Other
                - If 'Factor Xa Inhibitors' selected:
                    - Apixaban, Edoxaban, Rivaroxaban, Other
- Intervention Descriptors
    - Describe the intervention received by each patient group. If the intervention includes medication(s), include pertinent details such as dose, frequency, and potential for adjustment.
- Duration of Follow-up: Record the following elements for Arm 1, Arm 2, Arm 3, and Arm 4 (as applicable)
    - Mean or median (include units)
    - SD, SE, or IQR
    - NR

Clinical/ Patient-Centered Outcomes

- Select the outcome reported on this form:
    - Cerebrovascular infarction
    - Transient ischemic attack (TIA)
    - Systemic embolism (excludes pulmonary embolism and deep vein thrombosis)
    - CV infarction/stroke
    - Ischemic stroke
    - Hemorrhagic stroke
    - Intercerebral hemorrhage
    - Extracranial hemorrhage

    - Subdural hematoma
    - Major bleed
    - Minor bleed
    - Myocardial infarction
    - All-cause mortality
    - CV mortality
    - Infection
    - Heart block
    - Esophageal fistula
    - Cardiac tamponade
    - Health-related QOL/Functional capacity
    - Healthcare utilization – Hospital admissions
    - Healthcare utilization – Other measures
    - Long-term adherence to therapy
    - Cognitive function
    - Time in therapeutic range
    - Composite outcome
    - No clinical or patient-centered outcomes of interest reported
- Define/specify the following for the outcome, if applicable
    - Major bleed type and location
    - Minor bleed type and location
    - Health-related QOL/Functional capacity measure/scale
    - Other Healthcare utilization measure/scale
    - Components of composite outcomes:
        - Cerebrovascualr infarction; Transient ischemic attach (TIA); Systemic embolism (excludes pulmonary embolism and deep vein thrombosis); CV infarction/stroke; Intercerebral hemorrhage; Subdural hematoma; Major bleed; Minor bleed; Myocardial infarction; All-cause mortality; CV mortality; Infection; Heart block; Esophageal fistula; Tamponade; Dyspepsia; Health-related QOL/Functional capacity; Healthcare utilization – Hospital admissions; Healthcare utilization – Other measures; Long-term adherence to therapy; Time in therapeutic range; Ischemic stroke
- Record additional details to describe outcome measure, as needed
- Timepoints to be abstracted (Check all that apply)
    - Close to 1 month
    - Close to 3 months
    - Close to 6 months
    - Close to 1 yr
    - Most distal timepoint after one year
    - Untimed measure (e.g., time to event)
- For each timepoint, record the following elements as applicable:
    - Specify actual timing of outcome (in months)
    - Group: Arm 1, Arm 2, Arm 3, Arm 4
    - N Analyzed (enter UNK if unknown)
    - Unadjusted Result
        - Mean

        - Median
        - Mean within group change
        - Mean between group change
        - Number of patients with outcome
        - % of patients with outcome
        - Events/denominator
        - Odds ratio
        - Hazard ratio
        - Relative risk
        - Other (specify)
    - Unadjusted Result Variability
        - Standard Error (SE)
        - Standard Deviation (SD)
        - IQR
        - 95% CI
        - Other % CI (specify)
        - Other (specify)
    - Unadjusted Result, p-value between groups
    - Unadjusted Result, Reference group (for comparison between groups)
    - Adjusted Result
        - Mean
        - Median
        - Mean within group change
        - Mean between group change
        - Number of patients with outcome
        - % of patients with outcome
        - Events/denominator
        - Odds ratio
        - Hazard ratio
        - Relative risk
        - Other (specify)
    - Adjusted Result Variability
        - Standard Error (SE)
        - Standard Deviation (SD)
        - IQR
        - 95% CI
        - Other % CI (specify)
        - Other (specify)
    - Adjusted Result, p-value between groups
    - Adjusted Result, Reference group (for comparison between groups)
    - If adjusted data is recorded, indicate the adjustments applied
- Does the study report any subgroup analyses for this outcome? (Yes/No)
    - If Yes, describe the subgroup analyses and summarize results
- Comments

Adverse Events

- Are adverse events reported? (Yes/No)
- Record the Number of patients, % of patients, and exact p-value for the Total Population, Arm 1, Arm 2, Arm 3, and Arm 4 (as applicable) for the following:
  - Infection
  - Heart block
  - Esophageal fistula
  - Tamponade
  - Dyspepsia
- Does the study report any AE subgroup analyses? (Yes/No)
  - If Yes, describe the subgroup analyses and summarize results
- Comments

KQ1/2 Diagnostic Efficacy

- Type of risk being evaluated
  - Thromboembolic risk
  - Intracerebral hemorrhage bleeding risk
- Tool or individual risk factor being tested
  - $CHADS_2$ score
  - CHA_2DS_2-VASc score
  - ABC stroke risk score
  - Transthoracic echo (TTE)
  - Transesophageal echo (TEE)
  - CT scan
  - Cardiac MRI
  - $HEMORR_2HAGES$
  - HAS-BLED
  - ATRIA
  - Framingham score
  - Bleeding Risk Index
  - Patient age
  - Prior stroke
  - Type of AF (paroxysmal, persistent, permanent)
  - International normalized ratio (INR)
  - Dementia/cognitive impairment
  - Falls risk
  - INR level
  - Duration and frequency of AF
  - Presence of heart disease
  - Presence and severity of CKD
  - DM
  - Sex
  - Race/ethnicity
  - Cancer
  - HIV
- Additional details describing risk being evaluated

- Outcomes reported on this form for this tool or risk factor (Select all that apply): Diagnostic Accuracy; Diagnostic Thinking/Therapeutic Efficacy; Patient Outcome Efficacy
  - If Diagnostic Accuracy:
    - Timing of the outcome data reported
    - Total Population, Group 1, Group 2, Group 3, Group 4, Group 5, Group 6
      - N and %
      - C statistic
      - C statistic CI (Lower – Upper bound)
        - 95% CI
        - Other % (specify)
      - Hazard Ratio
      - Hazard Ratio (Lower – Upper bound)
        - 95% CI
        - Other % (specify)
      - Event rate (define)
      - Event rate (Lower – Upper bound)
        - 95% CI
        - Other % (specify)
      - True positive (# patients)
      - True negative (# patients)
      - False positive (# patients)
      - False negative (# patients)
      - Indeterminate/inadequate results (# patients)
      - Sensitivity (%)
      - Sensitivity (SD)
      - Sensitivity CI (Lower – Upper bound)
        - 95% CI
        - Other % (specify)
      - Specificity (%)
      - Specificity (SD)
      - Specificity CI (Lower – Upper bound)
        - 95% CI
        - Other % (specify)
      - Positive predictive value (%)
      - Positive predictive value (Std dev)
      - Positive predictive value (Lower – Upper bound)
        - 95% CI
        - Other % (specify)
      - Negative predictive value (%)
      - Negative predictive value (SD)
      - Negative predictive value (Lower – Upper bound)
        - 95% CI
        - Other % (specify)
      - Positive likelihood ratio

        - Negative likelihood ratio
        - Other (specify)
    - If Diagnostic Thinking/Therapeutic Efficacy: Describe
    - If Patient Outcome Efficacy: Describe
- Does the study report any subgroup analyses for this tool/ outcome? (Yes/No)
    - If Yes, describe the subgroup analyses and summarize results
- QUADAS 2 Tool for Quality Assessment of Study of Diagnostic Accuracy. (2017 and 2013 Studies) Indicate Yes, No, or Unclear for the following:
    - Signaling questions
        - Patient Selection
            - Was a consecutive or random sample of patients enrolled?
            - Was a case-control design avoided?
            - Did the study avoid inappropriate exclusions?
        - Index Test
            - Were the index test results interpreted without knowledge of the results of the reference standard?
            - If a threshold was used, was it pre-specified?
        - Reference Standard
            - Is the reference standard likely to correctly classify the target condition?
            - Were the reference standard results interpreted without knowledge of the results of the index test?
        - Flow & Timing
            - Was there an appropriate interval between index test(s) and reference standard?
            - Did all patients receive a reference standard?
            - Did all patients receive the same reference standard?
            - Were all patients included in the analysis?
    - Risk of bias
        - Patient Selection
            - Could the selection of patients have introduced bias?
        - Index Test
            - Could the conduct or interpretation of the index test have introduced bias?
        - Reference Standard
            - Could the reference standard, its conduct or its interpretation have introduced bias?
        - Flow & Timing
            - Could the patient flow have introduced bias?
    - Concerns regarding applicability
        - Patient Selection
            - Are there concerns that the included patients do not match the review question?
        - Index Test
            - Are there concerns that the index test, its conduct, or interpretation differ from the review question?
        - Reference Standard

        - Are there concerns that the target condition as defined by the reference standard does not match the review question?
- Overall study rating
    - High risk of bias/ Low risk of bias/ Unclear
- Comments

- ROBINS-I (The Risk of Bias in Non-Randomized Studies—of Interventions). (2017 Studies Only) Indicate Yes, No, or Unclear for the following:
    - Bias due to confounding
        - Was there any bias arising in the randomization process or due to confounding?
    - Bias in selection of participants into the study
        - Was there any bias in selecting participants into the study?
    - Bias in classification of interventions
        - Was there any bias in classifying interventions?
    - Bias due to deviations from intended intervention
        - Was there any bias due to departures from intended interventions?
    - Bias due to missing data
        - Was there any bias due to missing data?
    - Bias in measurement of outcomes
        - Was there any bias in the measurement of outcomes?
    - Bias in selection of the reported result
        - Was there any bias in reporting results selectively?
- Overall Bias
    - Risk of Bias Judgment:
        - Low/Moderate/High
- Overall ROB outcome-specific quality rating
    - Do you think that any of the outcomes abstracted for this study should be assigned a quality rating DIFFERENT from the overall study rating?
        - No/Yes
    - Comments

- Cochrane Quality Tool (2017 Studies Only). Select Low/High/Unclear risk of bias for each of the following questions:
    - Random sequence generation
        - Low risk/High risk/Unclear risk
        - Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups
    - Allocation concealment
        - Low risk/High risk/Unclear risk
        - Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen before or during enrollment
    - Blinding of participants and personnel
        - Low risk/High risk/Unclear risk

        - Describe all measures used, if any, to blind trial participants and researchers from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective
    - Blinding of outcome assessment
        - Low risk/High risk/Unclear risk
        - Describe all measures used, if any, to blind outcome assessment from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective
    - Incomplete Outcome Data
        - Low risk/High risk/Unclear risk
        - Describe the completeness of the outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition or exclusions where reported, and any reinclusions in analyses for the review
    - Selective Reporting
        - Low risk/High risk/Unclear risk
        - State how selective outcome reporting was examined and what was found
    - Other Bias
        - Low risk/High risk/Unclear risk
        - State any important concerns about bias not covered in the other domains in the tool
- Overall Study Quality Rating
    - Good/Fair/Poor
- Overall ROB Quality Rating
    - Do you think that any of the outcomes abstracted for this study should be assigned a quality rating DIFFERENT from the overall study rating?
        - No/Yes
    - Comments

Quality (2013 Studies Only)

- Study Type (select one): RCT, Cohort, Case-control, Cross-sectional
- If RCT, select Yes/No/Unclear for each of the following questions:
  - Selection Bias
    - Was the allocation sequence generated adequately (e.g., random number table, computer-generated randomization)?
    - Was the allocation of treatment adequately concealed (e.g., pharmacy-controlled randomization or use of sequentially numbered sealed envelopes)?
    - Were participants analyzed within the groups they were originally assigned to?
    - Does the design or analysis control account for important confounding and modifying variables through matching, stratification, multivariable analysis, or other approaches?
  - Performance Bias
    - Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results?
    - Did the study maintain fidelity to the intervention protocol?
  - Attrition Bias
    - If attrition (overall or differential nonresponse, dropout, loss to follow-up, or exclusion of participants) was a concern, were missing data handled appropriately (e.g., intention-to-treat analysis and imputation)?
  - Detection Bias
    - In prospective studies, was the length of follow-up different between the groups, or in case-control studies, was the time period between the intervention/exposure and outcome different for cases and controls?
    - Were the outcome assessors blinded to the intervention or exposure status of participants?
    - Were interventions/exposures assessed/defined using valid and reliable measures, implemented consistently across all study participants?
    - Were outcomes assessed/defined using valid and reliable measures, implemented consistently across all study participants?
  - Reporting Bias
    - Were the potential outcomes prespecified by the researchers? Are all prespecified outcomes reported?
- If Cohort, select Yes/No/Unclear for each of the following questions:
  - Selection Bias
    - Were participants analyzed within the groups they were originally assigned to?
    - Did the study apply inclusion/exclusion criteria uniformly to all comparison groups?
    - Did the strategy for recruiting participants into the study differ across study groups?
    - Does the design or analysis control account for important confounding and modifying variables through matching, stratification, multivariable analysis, or other approaches?
  - Performance Bias
    - Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results?

        - Did the study maintain fidelity to the intervention protocol?
    - Attrition Bias
        - If attrition (overall or differential nonresponse, dropout, loss to follow-up, or exclusion of participants) was a concern, were missing data handled appropriately (e.g., intention-to-treat analysis and imputation)?
    - Detection Bias
        - In prospective studies, was the length of follow-up different between the groups, or in case-control studies, was the time period between the intervention/exposure and outcome different for cases and controls?
        - Were the outcome assessors blinded to the intervention or exposure status of participants?
        - Were interventions/exposures assessed/defined using valid and reliable measures, implemented consistently across all study participants?
        - Were outcomes assessed/defined using valid and reliable measures, implemented consistently across all study participants?
        - Were confounding variables assessed using valid and reliable measures, implemented consistently across all study participants?
    - Reporting Bias
        - Were the potential outcomes prespecified by the researchers? Are all prespecified outcomes reported?
- If Case-Control, select Yes/No/Unclear for each of the following questions:
    - Selection Bias
        - Were cases and controls selected appropriately (e.g., appropriate diagnostic criteria or definitions, equal application of exclusion criteria to case and controls, sampling not influenced by exposure status) (Yes/No/Unclear)
        - Does the design or analysis control account for important confounding and modifying variables through matching, stratification, multivariable analysis, or other approaches?
    - Performance Bias
        - Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results?
        - Did the study maintain fidelity to the intervention protocol?
    - Attrition Bias
        - If attrition (overall or differential nonresponse, dropout, loss to follow-up, or exclusion of participants) was a concern, were missing data handled appropriately (e.g., intention-to-treat analysis and imputation)?
    - Detection Bias
        - In prospective studies, was the length of follow-up different between the groups, or in case-control studies, was the time period between the intervention/exposure and outcome different for cases and controls?
        - Were the outcome assessors blinded to the intervention or exposure status of participants?
        - Were interventions/exposures assessed/defined using valid and reliable measures, implemented consistently across all study participants?
        - Were outcomes assessed/defined using valid and reliable measures, implemented consistently across all study participants?

        - Were confounding variables assessed using valid and reliable measures, implemented consistently across all study participants?
    - Reporting Bias
        - Were the potential outcomes prespecified by the researchers? Are all prespecified outcomes reported?
- If Cross-sectional, select Yes/No/Unclear for each of the following questions:
    - Selection Bias
        - Did the study apply inclusion/exclusion criteria uniformly to all comparison groups?
        - Does the design or analysis control account for important confounding and modifying variables through matching, stratification, multivariable analysis, or other approaches?
    - Performance Bias
        - Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results?
    - Attrition Bias
        - If attrition (overall or differential nonresponse, dropout, loss to follow-up, or exclusion of participants) was a concern, were missing data handled appropriately (e.g., intention-to-treat analysis and imputation)?
    - Detection Bias
        - Were the outcome assessors blinded to the intervention or exposure status of participants?
        - Were interventions/exposures assessed/defined using valid and reliable measures, implemented consistently across all study participants?
        - Were outcomes assessed/defined using valid and reliable measures, implemented consistently across all study participants?
        - Were confounding variables assessed using valid and reliable measures, implemented consistently across all study participants?
    - Reporting Bias
        - Were the potential outcomes prespecified by the researchers? Are all prespecified outcomes reported?
- Other Bias
    - If applicable, describe any other concerns that may impact risk of bias
- Overall Study Rating (Good/Fair/Poor)
    - **Good** (low risk of bias). These studies have the least bias, and the results are considered valid. These studies adhere to the commonly held concepts of high quality, including the following: a clear description of the population, setting, approaches, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytical methods and reporting; no reporting errors; a low dropout rate; and clear reporting of dropouts.
    - **Fair**. These studies are susceptible to some bias, but not enough to invalidate the results. They do not meet all the criteria required for a rating of good quality because they have some deficiencies, but no flaw is likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems.

- **Poor** (high risk of bias). These studies have significant flaws that may have invalidated the results. They have serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.
- **If the study is rated as "Fair" or "Poor," provide rationale.**

Applicability – Use the PICOS format to identify specific issues, if any, that may limit the applicability of the study to this review.

- Population (P)
  - Narrow eligibility criteria and exclusion of those with comorbidities
  - Large differences between demographics of study population and community patients
  - Narrow or unrepresentative severity, stage of illness, or comorbidities
  - Run-in period with high-exclusion rate for nonadherence or side effects
  - Event rates much higher or lower than observed in population-based studies
- Intervention (I)
  - Doses or schedules not reflected in current practice
  - Monitoring practices or visit frequency not used in typical practice
  - Older versions of an intervention no longer in common use
  - Cointerventions that are likely to modify effectiveness of therapy
  - Highly selected intervention team or level of training/proficiency not widely available
- Comparator (C)
  - Inadequate comparison therapy
  - Use of substandard alternative therapy
- Outcomes (O)
  - Composite outcomes that mix outcomes of different significance
  - Short-term or surrogate outcomes
- Setting (S)
  - Standards of care differ markedly from setting of interest
  - Specialty population or level of care differs from that seen in community
- Comments

Appendix C. List of Included Studies

**Denotes 2017 update*

*Abraham JM, Larson J, Chung MK, et al. Does CHA2DS2-VASc improve stroke risk stratification in postmenopausal women with atrial fibrillation?. Am J Med 2013;126(12):1143.e1-8. PMID: 24139523.

*Abraham NS, Noseworthy PA, Yao X, et al. Gastrointestinal Safety of Direct Oral Anticoagulants: A Large Population-Based Study. Gastroenterology 2017;152(5):1014-1022.e1. PMID: 28043907.

*Abraham NS, Singh S, Alexander GC, et al. Comparative risk of gastrointestinal bleeding with dabigatran, rivaroxaban, and warfarin: population based cohort study. Bmj 2015;350:h1857. PMID: 25910928.

*Abumuaileq RR, Abu-Assi E, Lopez-Lopez A, et al. Comparison between CHA2DS2-VASc and the new R2CHADS2 and ATRIA scores at predicting thromboembolic event in non-anticoagulated and anticoagulated patients with non-valvular atrial fibrillation. BMC Cardiovasc Disord 2015;15:156. PMID: 26584938.

Ad N, Henry L, Schlauch K, et al. The CHADS score role in managing anticoagulation after surgical ablation for atrial fibrillation. Ann Thorac Surg. 2010;90(4):1257-62. PMID: 20868824.

*Adeboyeje G, Sylwestrzak G, Barron JJ, et al. Major Bleeding Risk During Anticoagulation with Warfarin, Dabigatran, Apixaban, or Rivaroxaban in Patients with Nonvalvular Atrial Fibrillation. J Manag Care Spec Pharm 2017;23(9):968-978. Digital Object Identifier: 10.18553/jmcp.2017.23.9.968. PMID: 28854073.

*Alexander JH, Andersson U, Lopes RD, et al. Apixaban 5 mg Twice Daily and Clinical Outcomes in Patients With Atrial Fibrillation and Advanced Age, Low Body Weight, or High Creatinine: A Secondary Analysis of a Randomized Clinical Trial. JAMA Cardiol 2016;1(6):673-81. PMID: 27463942.

*Alexander JH, Lopes RD, Thomas L, et al. Apixaban vs. warfarin with concomitant aspirin in patients with atrial fibrillation: insights from the ARISTOTLE trial. Eur Heart J 2014;35(4):224-32. PMID: 24144788.

*Al-Khatib SM, Thomas L, Wallentin L, et al. Outcomes of apixaban vs. warfarin by type and duration of atrial fibrillation: results from the ARISTOTLE trial. Eur Heart J 2013;34(31):2464-71. PMID: 23594592.

*Allan V, Banerjee A, Shah AD, et al. Net clinical benefit of warfarin in individuals with atrial fibrillation across stroke risk and across primary and secondary care. Heart 2017;103(3):210-218. PMID: 27580623.

*Alli O, Doshi S, Kar S, et al. Quality of life assessment in the randomized PROTECT AF (Percutaneous Closure of the Left Atrial Appendage Versus Warfarin Therapy for Prevention of Stroke in Patients With Atrial Fibrillation) trial of patients at risk for stroke with nonvalvular atrial fibrillation. J Am Coll Cardiol 2013;61(17):1790-8. PMID: 23500276.

*Amin A, Keshishian A, Trocio J, et al. Risk of stroke/systemic embolism, major bleeding and associated costs in non-valvular atrial fibrillation patients who initiated apixaban, dabigatran or rivaroxaban compared with warfarin in the United States Medicare population. Current Medical Research and Opinion 2017;33(9):1595-1604. Digital Object Identifier: 10.1080/03007995.2017.1345729.

*Amin A, Keshishian A, Vo L, et al. Real-world comparison of all-cause hospitalizations, hospitalizations due to stroke and major bleeding, and costs for non-valvular atrial fibrillation patients prescribed oral anticoagulants in a US health plan. J Med Econ 2017;1-10. Digital Object Identifier: 10.1080/13696998.2017.1394866. PMID: 29047304.

*An J, Niu F, Zheng C, et al. Warfarin Management and Outcomes in Patients with Nonvalvular Atrial Fibrillation Within an Integrated Health Care System. J Manag Care Spec Pharm 2017;23(6):700-712. PMID: 28530526.

*Apostolakis S, Guo Y, Lane DA, et al. Renal function and outcomes in anticoagulated patients with non-valvular atrial fibrillation: the AMADEUS trial. Eur Heart J 2013;34(46):3572-9. PMID: 23966309.

*Apostolakis S, Lane DA, Buller H, et al. Comparison of the CHADS2, CHA2DS2-VASc and HAS-BLED scores for the prediction of clinically relevant bleeding in anticoagulated patients with atrial fibrillation: the AMADEUS trial. Thromb Haemost 2013;110(5):1074-9. PMID: 24048467.

Apostolakis S, Lane DA, Guo Y, et al. Performance of the HEMORR(2)HAGES, ATRIA, and HAS-BLED Bleeding Risk-Prediction Scores in Patients With Atrial Fibrillation Undergoing Anticoagulation: The AMADEUS (Evaluating the Use of SR34006 Compared to Warfarin or Acenocoumarol in Patients With Atrial Fibrillation) Study. J Am Coll Cardiol. 2012:60(9):861-7. PMID: 22858389.

*Ashburner JM, Go AS, Chang Y, et al. Effect of Diabetes and Glycemic Control on Ischemic Stroke Risk in AF Patients: ATRIA Study. J Am Coll Cardiol 2016;67(3):239-47. PMID: 26796386.

Aspinall SL, DeSanzo BE, Trilli LE, et al. Bleeding Risk Index in an anticoagulation clinic. Assessment by indication and implications for care. J Gen Intern Med. 2005;20(11):1008-13. PMID: 16307625.

*Avezum A, Lopes RD, Schulte PJ, et al. Apixaban in Comparison With Warfarin in Patients With Atrial Fibrillation and Valvular Heart Disease: Findings From the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) Trial. Circulation 2015;132(8):624-32. PMID: 26106009.

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Appendix D. List of Excluded Studies

All studies listed below were reviewed in their full-text version and excluded for the reasons cited. Reasons for exclusion signify only the usefulness of the articles for this study and are not intended as criticisms of the articles. Not all of the same exclusion reasons were used for the 2017 update as were used for the 2012 report. The 2017 excluded studies are all listed before the 2012 excluded studies.

Not a full publication, publication retracted/withdrawn, full text not obtainable, or full text not obtainable in English--2017

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Does not meet tool/intervention or comparator requirements--2017

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Appendix E. Key to Included Primary and Companion Articles

*Companion articles marked with an asterisk did not individually meet criteria for inclusion but were considered for supplemental information (e.g., methods data pertinent to an included study).

Study Designation	Primary Abstracted Article	Companion Articles*
ACE (Anticoagulation in Cardioversion Using Enoxaparin)	Stellbrink, 2004[1]	Stellbrink, 2002[2]*
ACTIVE-A (The Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events - A)	Connolly, 2009[3]	Connolly, 2006[4]* Perera, 2017[5]
ACTIVE-W (The Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events - W)	Connolly, 2006[6]	Connolly, 2006[4]* Flaker, 2010[7] Healey, 2008[8] Hohnloser, 2007[9]
AMADEUS (Evaluating the Use of SR34006 Compared to Warfarin or Acenocoumarol in Patients With Atrial Fibrillation)	Bousser, 2008[10]	Apostolakis, 2012[11] Apostolakis, 2013[12] Apostolakis, 2013[13] Lane, 2011[14] Senoo, 2016[15]
ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation)	Granger, 2011[16]	Alexander, 2014[17] Alexander, 2016[18] Al-Khatib, 2013[19] Avezum, 2015[20] Bahit, 2017[21], Cowper, 2017[22] De Caterina, 2016[23] Durheim, 2016[24] Easton, 2012[25] Ezekowitz, 2015[26] Guimaraes, 2017[27] Halvorsen, 2014[28] Held, 2015[29] Hijazi, 2016[30], HIjazi, 2017[31] Hohnloser, 2012[32] Hu, 2017[33] Hylek, 2014[34] Lopes, 2010[35]* Lopes, 2012[36] Lopes, 2017[37] McMurray, 2013[38] Melloni, 2017[39] Rao, 2017[40] Vinereanu, 2015[41] Vinereanu, 2017[42] Wallentin, 2013[43] Westenbrink, 2017[44]

Study Designation	Primary Abstracted Article	Companion Articles*
ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation)	Fang, 2011[45]	None
	Fang, 2008[46]	None
	Hylek, 2003[47]	Go, 1999[48]*
AVERROES (Apixaban Versus Acetylsalicylic Acid [ASA] to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment)	Connolly, 2011[49]	Diener, 2012[50] Eikelboom, 2012[51] Eikelboom, 2010[52]* O'Donnell, 2016[53] Ng, 2016[54] Lip, 2014[55] Coppens, 2014[56] Lip, 2013[57] Flaker, 2012[58]
BAFTA (Birmingham Atrial Fibrillation Treatment of the Aged Study)	Mant, 2007[59]	Hobbs, 2011[60] Mant, 2003[61]* Mavaddat, 2014[62]
Danish National Patient Registry	Bonde, 2016[63]	None
	Gorst-Rasmussen, 2016[64]	None
	Lamberts, 2017[65]	None
	Larsen, 2016[66]	None
	Lee, 2017[67]	None
	Lip, 2015[68]	None
	Lip, 2015[69]	None
	Lip, 2017[70]	None
	Nielsen, 2016[71]	None
	Nielsen, 2017[72]	None
	Olesen, 2012[73]	None
	Staerk, 2015[74]	None
	Staerk, 2017[75]	
	Staerk, 2017[76]	
ENGAGE-AF-TIMI 48 (The Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48)	Giugliano, 2013[77]	Bohula, 2016[78] Eisen, 2016[79] Fanola, 2017[80] Geller, 2015[81] Giugliano, 2014[82] Gupta, 2016[83] Link, 2017[84] Magnani, 2016[85] O'Donoghue, 2015[86] Rost, 2016[87] Ruff, 2014[88] Ruff, 2015[89] Ruff, 2016[90] Steffel, 2016[91] Xu, 2016[92] Yamashita, 2016[93]
Euro Heart Survey for AF	Lip, 2010[94]	None
	Pisters, 2010[95]	Nieuwlaat, 2008[96]* Nieuwlaat, 2005[97]*
Framingham Heart Study WASPO (Warfarin Versus Aspirin for Stroke Prevention in	Sam, 2004[98]	None
	Wang, 2003[99]	None
	Rash, 2007[100]	None

Study Designation	Primary Abstracted Article	Companion Articles*
Octogenarians with Atrial Fibrillation)	Ad, 2010[101]	None
GARFIELD-AF (The Global Anticoagulant Registry in the FIELD-Atrial Fibrillation)	Haas, 2016[102]	Bassand, 2016[103] Bassand, 2018[104] Camm, 2017[105]
Loire Valley Atrial Fibrillation Project	Lip, 2012[106]	Banerjee, 2013[107] Banerjee, 2014[108] Fauchier, 2016[109] Olesen, 2012[110] Philippart, 2016[111]
Murcia-AF Project	Rivera-Caravaca, 2017[112]	Esteve-Pastor, 2017[113] Rivera-Caravaca, 2017[114] Rivera-Caravaca, 2018[115]
NRAF (National Registry of Atrial Fibrillation)	Gage, 2006[116]	None
	Gage, 2001[117]	None
ORBIT-AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation)	O'Brien, 2015[118]	Inohara, 2017[119]
PROTECT-AF (Percutaneous Closure of the Left Atrial Appendage Versus Warfarin Therapy for Prevention of Stroke in Patients With Atrial Fibrillation)	Holmes, 2009[120]	Alli, 2013[121] Fountain, 2006[122]* Reddy, 2013[123] Reddy, 2014[124] Reddy, 2017[125] Viles-Gonzalez, 2012[126]
RAF-NOACs Study (Early Recurrence and Major Bleeding in Patients With Acute Ischemic Stroke and Atrial Fibrillation Treated With Non–Vitamin K Oral Anticoagulants)	Paciaroni, 2017[127]	None
RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy)	Connolly, 2009[128]	Brambatti, 2015[129] Connolly, 2013[130] Diener, 2010[131] Eikelboom, 2011[132] Ezekowitz, 2009[133]* Hart, 2012[134] Healey, 2012[135] Hijazi, 2014[136] Hijazi, 2018[137] Hilkens, 2017[138] Hohnloser, 2012[139] Lauw, 2017[140] Marijon, 2013[141] Monz, 2013[142] Nagarakanti, 2011[143] Oldgren, 2011[144] Oldgren, 2016[145] Proietti, 2017[146] Verdecchia, 2017[147]

Study Designation	Primary Abstracted Article	Companion Articles*
ROCKET-AF (Rivaroxaban Once-daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation)	Patel, 2011[148]	Anonymous, 2010[149]* Bansilal, 2015[150] Breithardt, 2014[151] Breithardt, 2016[152] DeVore, 2016[153] Fordyce, 2016[154] Fox, 2011[155] Goodman, 2014[156] Halperin, 2014[157] Hankey, 2012[158] Hankey, 2014[159] Kochar, 2018[160] Mahaffey, 2013[161] Mahaffey, 2014[162] Orgel, 2017[163] Patel, 2013[164] Piccini, 2014[165] Pokorney, 2016[166] Shah, 2016[167] Sherwood, 2015[168] Sherwood, 2016[169] van Diepen, 2013[170] Vemulapalli, 2016[171]
SPORTIF (Stroke Prevention using an ORal Thrombin Inhibitor in atrial Fibrillation)	Baruch, 2007[172]	Halperin, 2003[173]* Lip, 2010[174] Lip, 2011[175] Olsson, 2003[176]* Proietti, 2016[177] Proietti, 2016[178]
Swedish Atrial Fibrillation cohort study	Friberg, 2012[179]	Friberg, 2015[180]
	Sjogren, 2017[181]	None
None	Hansen, 2010[182]	Hansen, 2008[183]*
None	Inoue, 2006[184]	Nozawa, 2004[185]*
None	Poli, 2009[186]	Poli, 2009[187]
None	Rietbrock, 2008[188]	Rietbrock, 2009[189]
None	Sadanaga, 2010[190]	Sadanaga, 2010[191]*

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Appendix F. Characteristics of Included Studies

Appendix Table F-1. Study characteristics—KQ 1

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Tools Assessed	Total N	Follow-up period	Age	Special Population
Abraham, 2013[1]	Prospective cohort; Unclear/NR; US; Unclear/NR; Low risk of bias	**Clinical:** CHADS2 score CHADS2-VASc score	Patients on Warfarin: 5,981	Total: 11.8 years (IQR 8.0-13.6)	Total: 65.85 (SD: 7.18)	Age; Sex

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Tools Assessed	Total N	Follow-up period	Age	Special Population
Abumuail, 2015[2]	Retrospective cohort; Emergency Room; Europe; Unclear/NR; Low risk of bias	**Clinical:** CHADS2-VASc score **Individual risk factors:** Presence and severity of CKD	Non-anticoagulated: 154 Anticoagulated: 911	Non-anticoagulated: 11 months (SD: 2.7) Anticoagulated: 10 months (SD: 3)	Non-anticoagulated: 74 (SD: 12) Anticoagulated: 73 (SD: 11)	None
Ad, 2010[3]	Prospective cohort; Outpatient; US; Unclear/NR; Low risk of bias	**Clinical:** $CHADS_2$ score	Total: 347	Total: 32.77 months (SD: 16.33)	Total: 64.5 (SD: 11.6)	None
Allan, 2017[4]	Prospective cohort; Inpatient, Outpatient; UK Government, Non-govt, Non-industry; Moderate risk of bias	**Clinical:** CHADS2-VASc score	Total: 70,206	Total: 2.20 years (IQR 0.02-12.2)	Total: 77.9 (IQR 18.0-108.7)	None
An, 2017[5]	Retrospective cohort; Inpatient, Outpatient; US; Industry; Low risk of bias	**Clinical:** N/A **Individual risk factors include:** INR level	Total: 32,207	Total median: 3.8 years	Total: 72.2 (SD: 10.7)	None

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Tools Assessed	Total N	Follow-up period	Age	Special Population
Ashburner, 2016[6] ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation)	Retrospective cohort; Unclear/NR; US; Government, Non-govt, Non-industry; Low risk of bias	**Individual risk factors include:** Diabetes and glycemic control	Total: 2,101	Non Diabetics: 3.09 years (SD: 2.48) Diabetes: 2.48 years (SD: 2.23)	Non Diabetics: 71.8 (SD: 12.7) Diabetes broken down by duration: 0 to 3 years: 69.0 (SD: 11) 3 years: 71.7 (SD: 8.9) HbA1c values: <7.0: 71.5 (SD: 9.6) 7.0 – 8.9: 70.5 (SD: 9.7) >9.0 67.9(SD: 9.8)	None
Baruch, 2007[7] SPORTIF Companions: Proietti, 2016[8] Proietti, 2016[9] Proietti, 2018[10]	RCT; Outpatient; Unclear/NR; Industry; Low risk of bias	**Clinical:** HAS-BLED $CHADS_2$ score CHA_2DS_2-VASc score **Individual risk factors:** TTR for warfarin-treated patients	Total: 7,329	Total: 1.5 years Proietti, 2016[8]: Median follow-up 566 days (IQR 495-653)	Arm 1: 73.9 (SD: 8.6) Arm 2: 70.9 (SD: 8.9) Proietti, 2016[8]: Median 61 (IQR 56-64)	None
Beinart, 2011[11]	Retrospective cohort; Inpatient, Outpatient; US; Non-govt, Non-industry; High risk of bias	**Individual risk factors:** Cardiac MRI	Total: 144	Unclear/NR	Total: 54.5 (SD: 9.9)	None

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Tools Assessed	Total N	Follow-up period	Age	Special Population
Bonde, 2014[12]	Retrospective cohort; Inpatient, Outpatient; Europe; Industry, Non-govt, Non-industry; Low risk of bias	**Clinical:** CHADS2-VASc score HAS-BLED **Individual risk factors:** Presence and severity of CKD	Total: 12,856	Non-CKD patients: 1,179 days (IQR 397-2,412) Non-end-stage CKD patients: 312 days (IQR 48 to 952) RRT patients: 603 days (IQR 225-1,300)	Non-CKD: 73.57 (SD: 13.06) Non-end-stage CKD: 76.80 (SD: 11.11) RRT: 66.77 (SD: 12.03)	None
Bonde, 2016[13] Danish Patient Registry	Retrospective cohort; Inpatient; Europe; Government; Moderate risk of bias	**Clinical:** CHADS2-VASc score HAS-BLED **Individual risk factors:** eGFR	Total: 17,349	Total: 4.1 years	Total: 73 (IQR 64-81)	Presence of heart disease; Type of AF
Bouillon, 2015[14] SNIIRAM	Retrospective cohort; Unclear/NR; Europe; Unclear/NR; Low risk of bias	**Clinical:** HAS-BLED score	Total: 17,410	Total: 10 months (IQR 9.8-10)	Non- Switchers median: 75 (IQR 67–82) Switchers median: 75 (IQR 67–82)	None
Bousser, 2008[15] Paper for KQ 1: Apostolakis, 2013[16] AMADEUS	RCT; Unclear/NR; US, Canada, UK, Europe, Australia/NZ; Industry; Low risk of bias	**Clinical:** CHADS2 score CHADS2-VASc score HEMORR2HAGES HAS-BLED ATRIA	Total: 2,293 Apostolakis, 2013[16]: 4,554	Total: 429 days (SD: 118) Apostolakis, 2013[16]: 325 days (SD: 164)	Total: 70.2 (SD: 9.1) Apostolakis, 2013[16]: Total: 70 (SD: 9)	None

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Tools Assessed	Total N	Follow-up period	Age	Special Population
Connolly, 2009[17] Papers designated as KQ 1 for 2017: Oldgren, 2016[18], Marijon, 2013[19] RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy)	RCT; Outpatient; US, Canada, UK, Europe, S. America, C. America, Asia, Africa, Australia/NZ; Industry; Low risk of bias	**Clinical:** $CHADS_2$ score	Total: 18,113	Total median: 2.0 years	Total Median: 71	None
Connolly, 2011[20] Paper for KQ 1: Lip, 2013[21] AVERROES	RCT; Outpatient; Unclear/NR; Industry; Low risk of bias	**Clinical:** CHADS2 score CHADS2-VASc score by ASA and Apixaban use	Total: 5,599 ASA: 2,791 Apixaban: 2,808	Total: 1.1 years	Total: 69.9 (SD: 9.6) years ASA: 70.0 (SD: 9.7) years Apixaban: 69.7 (SD: 9.4) years	None
Crandall, 2009[22]	Retrospective cohort; Unclear/NR; US; Non-govt, Non-industry; High risk of bias	**Clinical:** $CHADS_2$ score	Total: 343	AF patients: 9.1 years (SD: 1.8)	AF patients: 69 (SD: 10)	None
Fang, 2008[23] ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation)	Retrospective cohort; Outpatient; US; Government, Non-govt, Non-industry; Low risk of bias	**Clinical:** CHADS2 score Framingham score	Total: 10,932	Total median: 6.0 years (IQR 3.1 – 6.7)	Total mean: 72	None

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Tools Assessed	Total N	Follow-up period	Age	Special Population
Flaker, 2010[24] ACTIVE-W Primary: Connolly, 2006[25] Companions: Healey, 2008[26] Hohnloser, 2007[27]	RCT; Outpatient; US, Canada, UK, Europe, S. America, C. America, Asia, Africa, Australia/NZ; Industry, Non-govt, Non-industry; Low risk of bias	**Individual risk factors:** INR level (TTR) Cognitive impairment	Total: 3,371	Total: 1.3 years	Total: 70.9 (SD: 9.5)	None
Forslund, 2014[28]	Retrospective cohort; Inpatient, Outpatient; Europe; Government, Non-govt, Non-industry; Low risk of bias	**Clinical:** CHADS2 score CHADS2-VASc score **Individual risk factors:** Age Sex Hypertension	Total: 41,810	Total: 1 year	Total mean: 73.2	None
Friberg, 2012[29] Swedish Atrial Fibrillation cohort study Companions: Friberg, 2015[30]	Prospective cohort; Inpatient, Outpatient; Europe; Government, Non-govt, Non-industry; Low risk of bias	**Clinical:** $CHADS_2$ score CHA_2DS_2-VASc score Framingham score HAS-BLED $HEMORR_2HAGES$ **Individual risk factors:** Presence and severity of CKD	Total: 283,969 Friberg, 2015[30]: Renal failure: 13,435 No Renal failure: 270,534	Total median: 1.4 years (IQR 1.8) Friberg, 2015[30]: Median: 2.1 years	Total: 76.2 Friberg, 2015[30]: Renal failure: 78.4 (SD: 10.3) No renal failure: 74.8 (SD: 12.5)	None
Gage, 2001[31] NRAF (National Registry of Atrial Fibrillation)	Retrospective cohort; Outpatient; US; Government; Low risk of bias	**Clinical:** $CHADS_2$ score	Total: 1,733	Total: 1.2 years	Total: 81	None

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Tools Assessed	Total N	Follow-up period	Age	Special Population
Giugliano, 2013[32] Papers for KQ 1: Fanola, 2017[33]; Gupta, 2016[34]; Link, 2017[35]; Ruff, 2016[36] ENGAGE-AF	RCT; Unclear/NR; US; Industry; Low risk of bias	**Clinical:** CHADS2 score CHADS2-VASc score **Individual risk factors:** Gupta, 2016[34]: TTE elements Link, 2017[35]: **Individual risk factors:** paroxysmal (<7 days duration), persistent (≥7 days but <1 year), or permanent (≥1 year or failed cardioversion) AF patterns	Total: 21,105 Fanola, 2017[33]: 2,898 VKA naïve patients Gupta, 2016[34]: 971 Ruff, 2016[36]: 4,880 with biomarker available	Total median: 2.8 years Fanola, 2017[33]: 7,272.7 PY follow-up Gupta, 2016[34]: 2.5 years Link, 2017[35]: Median 2.8 years	Total: 72 (IQR 64-78) Fanola, 2017[33]: Median: 71 (IQR 63-77) Link, 2017[35]: Paroxysmal: 70.5 (SD: 9.5); Persistent: 70.2 (SD: 9.7); Permanent: 70.8 (SD: 9.2) Ruff, 2016[36]: Median 71 years (IQR 64-77)	None Fanola, 2017[33]: VKA naïve patients
Granger, 2011[37] Papers listed as KQ 1: McMurray, 2013[38]; Vinereanu, 2017[39]; HIjazi, 2017[40] ARISTOTLE	RCT; Unclear/NR; US, Canada, Europe, Asia, Australia/NZ; Industry; Low risk of bias	**Individual risk factors:** LVD <=40% HF symptoms	Total: 18,201 McMurray, 2013[38]: Out of the 18,201 HF and LVD status: 14671 No HF and EF >40%: 8,728 LVD status: 2,736 HF-PEF: 3,207	Granger, 2011[37]: Total: ~2 years McMurray, 2013[38]: Median: 18 months	Granger, 2011[37]: Arm 1 median: 70 (IQR 63 to 76) Arm 2 median: 70 (IQR 63 to 76) McMurray, 2013[38]: No LVD/no HF LVD Median: 71 (IQR 64-76) LVD Median: 68 (IQR 60-74) HF-PEF Median: 69 (IQR 61-75)	None

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Tools Assessed	Total N	Follow-up period	Age	Special Population
Haas, 2016[41] GARFIELD-AF Companions: Camm, 2017[42]; Bassand, 2016[43]; Bassand, 2018[44]	Retrospective cohort; Inpatient, Outpatient; US, Canada, UK, Europe, S. America, C. America, Asia, Africa, Australia/NZ; Industry; Low risk of bias	**Individual risk factors:** INR level (TTR) Sex Treatment with and without OAC	Total: 28,624	Outcomes only reported out to 1 year	Haas, 2016[41]: 70.7 (SD: 10.6) years for TTR <65% 71.9 (SD: 9.7) years for TTR =>65% Camm, 2017[42]: Women: 72.4 (SD: 10.4) Men: 67.6 (SD: 11.7) Bassand, 2016[43]: 69.8 (SD: 11.4)	Camm, 2017[42]: Newly diagnoses (<= 6 weeks duration)
Hijazi, 2016[45] Created from ARISTOTLE (derivation) and STABILITY (for external validity)	RCT; Unclear/NR; US, Canada, UK, Europe, Australia/NZ; Government, Industry; Low risk of bias	**Clinical:** CHADS2 score ABC stroke risk score	Derivation cohort: 14,701 External validation cohort: 1,400	Derivation cohort: 27,929 PY of follow-up External Validation cohort: 4,751 PY of follow-up	Derivation cohort Total median: 70.0 (IQR 19-97) External validation cohort Total median: 69.0 (IQR 37-88)	None
Hylek, 2003[46] ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation)	Retrospective cohort; Outpatient; US; Government; Low risk of bias	**Individual risk factors:** INR level	Total: 596	Unclear/NR	Arm 1: 79 Arm 2: 80 Arm 3: 76	Patients with ischemic stroke
Jun, 2017[47]	Retrospective cohort; Inpatient, Outpatient, Emergency Room; Canada; Government; Low risk of bias	**Clinical:** HAS-BLED score **Individual risk factors include:** Presence and severity of CKD	Total: 14,892	Total: 1-year	Total: 78.1 (SD: 6.8)	Age Comorbid conditions (such as advanced CDK (eGFR<60), dementia)

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Tools Assessed	Total N	Follow-up period	Age	Special Population
Larsen, 2012[48]	Prospective cohort; Unclear/NR; Europe; Government; Low risk of bias	**Clinical:** CHADS2 score CHADS2-VASc score	Total: 1,603	Mean follow up period Total: 5.4 (SD: 3.7)	Unclear/NR	None
Lind, 2012[49]	Retrospective cohort; Outpatient; Europe; Unclear/NR; High risk of bias	**Individual risk factors:** INR	Total: 19,180	Unclear/NR	Unclear/NR	None
Lip, 2010[50] Euro Heart Survey for AF	Retrospective cohort; Outpatient; UK, Europe; Industry, Non-govt, Non-industry; Low risk of bias	**Clinical:** $CHADS_2$ score Framingham score CHA_2DS_2-VASc score	Total: 1,084	Total: 1 years	Total: 66 (SD: 14)	None
Lip, 2012[51] Loire Valley AF Project Companions: Olesen, 2012[52]; Banerjee, 2014[53]; Banerjee, 2013[54]; Fauchier, 2016[55]; Philippart, 2016[56]	Retrospective cohort; Inpatient; Europe; Unclear/NR; Moderate risk of bias	**Clinical:** CHADS2 score CHADS2-VASc score	Total: 7,156 Banerjee, 2014[53]: 3,607 Banerjee, 2013[54]: 5,912	Arm 1: 1.65 years (SD: 2.44) Arm 2: 2.45 years (SD: 3.56) Banerjee, 2014[53]: 1.65 years (SD: 2.44) Banerjee, 2013[54]: 2.45 years (SD: 3.56)	Arm 1: 77.7 (SD: 8.2) Arm 2: 73.8 (SD: 11.6) Arm 3: 49.0 (SD: 13.1) Banerjee, 2014[53]: Stroke/Bleeds No CKD- 69.7 (SD: 12.6) CKD – 72.7 (SD: 11.7) Stroke/TE No CKD- 69.8 (SD: 12.5) CKD – 73.6 (SD: 12.0)	None

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Tools Assessed	Total N	Follow-up period	Age	Special Population
McAlister, 2017[57]	Retrospective cohort; Inpatient, Outpatient, Emergency Room; Canada; Government; Low risk of bias	**Clinical:** CHADS2 score CHADS2-VASc score	Total: 58,451	Total median: 31 months (IQR 13-59)	Total: 66 years	None
Mikkelsen, 2012[58]	Retrospective cohort; Inpatient, Outpatient; Europe; Unclear/NR; Low risk of bias	**Individual risk factors include:** Sex	Total: 87,202 Women: 44,744 Men: 42,458	Women: 795 days (IQR 231–1785) Men: 897 days (IQR 274–1990)	Women: 78.2 (SD: 12.1) Men: 71.0 (SD: 14.3)	Sex
Morgan, 2009[59]	Retrospective cohort; Inpatient; UK; Industry; High risk of bias	**Clinical:** $CHADS_2$ score	Total: 5,513	Total: 1,025.1 days (SD: 714.8) Arm 1: 986.4 days (SD: 722)	Arm 1: 72.5 (SD: 10.4) Arm 2: 77.8 (SD: 12.1)	None
Nair, 2009[60]	Prospective cohort; Unclear/NR; US; Unclear/NR; Low risk of bias	**Individual risk factors:** TEE	Total: 226	Arm 1: 13 months (SD: 17) Arm 2: 93 months (SD: 173)	Arm 1: 72 (SD: 11) Arm 2: 70 (SD: 12)	None
Nielsen, 2016[61] Danish Patient Registry	Retrospective; Inpatient, Outpatient; Europe; Non-govt, Non-industry; Moderate risk of bias	**Clinical**: CHADS2-VASc score	Total: 198,697	Total: 2.9 years	Total: 75	None

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Tools Assessed	Total N	Follow-up period	Age	Special Population
Olesen, 2011[62]	Retrospective cohort; Inpatient; Europe; Unclear/NR; High risk of bias	**Clinical:** $CHADS_2$ score CHA_2DS_2-VASc score	Total: 132,372	Total: Max 12 years	Arm 1: 72.8 (SD: 14.4) Arm 2: 70.6 (SD: 11.1) Arm 3: 78.1 (SD: 11.2) Arm 4: 73.1 (SD: 9.6)	None
Olesen, 2011[63]	Retrospective cohort; Outpatient; Europe; Unclear/NR; Low risk of bias	**Clinical:** $CHADS_2$ score CHA_2DS_2-VASc score	Total: 73,538	Unclear/NR	Unclear/NR	None
Olesen, 2012[64]	Retrospective cohort; Outpatient; Europe; Unclear/NR; Low risk of bias	**Clinical:** $CHADS_2$ score CHA_2DS_2-VASc score	Total: 47,576	Total: 12 years Arm 1: 12 years Arm 2: 12 years	Total: 69.4 (SD: 14.7)	None
Olesen, 2012[65] Danish National Patient Registry	Retrospective cohort; Inpatient; Europe; Unclear/NR; Low risk of bias	**Clinical:** $CHADS_2$ score	Total: 87,202	Unclear/NR	Arm 1: 74.2 (SD: 14.2) Arm 2: 76.9 (SD: 10.3)	None
Orkaby, 2017[66] VARIA	Retrospective cohort; Inpatient, Outpatient; US; Government; Moderate risk of bias	**Individual risk factors include:** Cognitive impairment	Total: 2,572	Total: 2.2 PY following diagnosis of dementia	Total: 79.5 (SD: 6.0)	Patients with newly diagnosed dementia; Older Adults
Phelps, 2018[67]	Retrospective cohort; Outpatient; US; Industry, Non govt, non industry; Moderate risk of bias	**Individual risk factors include:** Time in therapeutic range (TTR)	Total: 8,405	Unclear/NR	Total: 74.3 (SD: 10.3)	None

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Tools Assessed	Total N	Follow-up period	Age	Special Population
Philippart, 2016[56]	Retrospective cohort; Inpatient; Europe; Unclear/NR; Moderate risk of bias	**Clinical:** CHADS2 score CHADS2-VASc score	Total: 8,602	Total Mean: 876 days (SD: 1048)	Non-valvular AF: 71 (SD: 15) Valvular AF: 75 (SD: 8) Valvular AF, with aortic bioprosthesis: 76 (SD: 8) Other AF: 73 (SD: 8)	None
Poli, 2009[68]	Prospective cohort; Inpatient, Outpatient; Europe; Unclear/NR; Low risk of bias	**Clinical:** $CHADS_2$ score	Total: 662	Total median: 3.1 years	Total: 75	None
Poli, 2011[69]	Prospective cohort; Unclear/NR; Europe; None; Low risk of bias	**Clinical:** $CHADS_2$ score Bleeding Risk Index	Total: 3,302	Total median: 2.3 years (IQR 0.8 - 4.4)	Total median: 74 (IQR 68-80)	None
Poli, 2011[70]	Prospective cohort; Outpatient; Europe; Unclear/NR; Low risk of bias	**Clinical:** $CHADS_2$ score CHA_2DS_2-VASc score	Total: 662	Total: 3.6 years (SD: 2.7) Arm 1: 3.6 years (SD: 2.7) Arm 2: 3.6 years (SD: 2.7)	Total: 74 (SD: 7.7)	None
Potpara, 2012[71] Belgrade Atrial Fibrillation Study	Prospective cohort; Unclear/NR; Europe; Government; Moderate risk of bias	**Clinical:** $CHADS_2$ score CHA_2DS_2-VASc score	Total: 345	Total: 12.1 years (SD: 7.3)	Total: 43.2 (SD: 9.9)	None

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Tools Assessed	Total N	Follow-up period	Age	Special Population
Renoux, 2017[72]	Retrospective cohort; Inpatient, Outpatient; Canada; Industry; Non-govt, Non-industry; Low risk of bias	**Clinical:** HAS-BLED **Individual risk factors include:** Age Sex Prior stroke *Duration and frequency of AF Presence and severity of CKD	Total: 147,622	Total: 2.9 years	Total: 75.5 (SD: 11.4)	None
Rietbrock, 2008[73]	Retrospective cohort; Outpatient; UK; Industry; Low risk of bias	**Clinical:** $CHADS_2$ score	Total: 51,807	Total median: 2.5 years	Total: 76.01 (SD: 10.13)	None
Rivera-Caravaca, 2017[74] Companions marked as KQ 1: Rivera-Caravaca, 2018[75]; Rivera-Caravaca, 2017[76] Murcia AF Project	Retrospective cohort; Inpatient; Europe; Government, Non govt, non industry; Low risk of bias	**Clinical:** CHA_2DS_2-VASc score HAS-BLED **Individual risk factors include:** Age Sex Prior stroke	Total: 1,361	Total median: 214 days (IQR 213−214)	Total median: 76 years (IQR 71-81)	None
Ruiz Ortiz, 2008[77]	Prospective cohort; Outpatient; Europe; Non-govt, Non-industry; Low risk of bias	**Clinical:** $CHADS_2$ score	Total: 296	Total: 21 months (SD: 17) Arm 1: 21 months (SD: 17)	Total: 75 (SD: 9)	Permanent AF

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Tools Assessed	Total N	Follow-up period	Age	Special Population
Ruiz Ortiz, 2010[78]	Prospective cohort; Outpatient; Europe; Non-govt, Non-industry; Low risk of bias	**Clinical:** $CHADS_2$ score	Total: 796	Total: 2.4 years (SD: 1.9)	Total: 73 (SD: 8)	Permanent AF
Ruiz-Nodar, 2011[79]	Retrospective cohort; Outpatient; Europe; Unclear/NR; Low risk of bias	**Clinical:** $CHADS_2$ score	Total: 604	Total: 642 days (SD: 503) Arm 1: 642 days (SD: 503) Arm 2: 642 days (SD: 503)	Total: 71.8 (SD: 8.4)	None
Ruiz-Nodar, 2012[80]	Retrospective cohort; Unclear/NR; Europe; Unclear/NR; High risk of bias	**Clinical:** HAS-BLED CHA_2DS_2-VASc score	Total: 590	Total: ~12 months	Total: 72.2 (SD: 8.1)	None
Singer, 2013[81] ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation)	Retrospective cohort; Outpatient, US; Government; Low risk of bias	**Clinical:** CHADS2 score CHADS2-VASc score	Total: 10,927	Total: 32,609	Unclear/NR	None
Stoddard, 2003[82]	Prospective cohort; Outpatient; US; Unclear/NR; Low risk of bias	**Individual risk factors:** TEE	Total: 272	Total: 30.3 months (SD: 20.6) Arm 1: 28.3 months (SD: 23.3) Arm 2: 30.9 months (SD: 20)	Total: 66 (SD: 11)	None

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Tools Assessed	Total N	Follow-up period	Age	Special Population
Stollberger, 2004[83] ELAT (Embolism in Left Atrial Thrombi)	Prospective cohort; Outpatient; Europe; Unclear/NR; Low risk of bias	**Individual risk factors:** TTE TEE	Total: 409	Total: 101 months (SD: 2)	Total: 62 (IQR 61 - 64)	None
Thambidorai, 2005[84] ACUTE	RCT; Outpatient; US; Non-govt, Non-industry	**Imaging:** Transesophageal echo (TEE)	Total: 571	Unclear/NR	Thromboembolism: 62.2 (SD: 14.1) No-Thromboembolism: 65.0 (SD: 13)	None
van den Ham, 2015[85]	Retrospective cohort; Outpatient; UK; Unclear/NR; Low risk of bias	**Clinical:** CHADS2 score CHA2DS2-VASc score ATRIA	Total: 60,594	Total: 2.81 years	Total Mean Age: 74.4	None
Van Staa, 2011[86]	Retrospective cohort; Outpatient; UK; Unclear/NR; High risk of bias	**Clinical:** $CHADS_2$ score CHA_2DS_2-VASc score Framingham score	Total: 79,844	Total: 4.0 years	Total: 73.3 (SD: 12.5)	None
Wang, 2003[87] Framingham Heart Study	Prospective cohort; Outpatient; US; Government, Non-govt, Non-industry; Low risk of bias	**Clinical:** Framingham score	Total: 705	Total: 4.0 years	Total: 75 (SD: 9)	None
Yarmohammadi, 2013[88]	Retrospective cohort, Outpatient; US; Unclear/NR; Low risk of bias	**Imaging:** Transesophageal echo (TEE)	Total: 2,369	Total: 37 months (SD: 35)	Total Mean Age: 66 (SD: 13)	None

Abbreviations: AF=atrial fibrillation; IQR=interquartile range; N=number of patients; NR=not reported; PY=patient years; RCT=randomized controlled trial; SD=standard deviation

Appendix Table F-2. Study characteristics—KQ 2

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Tools Assessed	Total N	Follow-up period	Age	Special Population
An, 2017[5]	Retrospective cohort; Inpatient, Outpatient; US; Industry; Low risk of bias	**Individual risk factors include:** INR level	Total: 32,074	Total: 5 years	Total: 72.2 (10.7)	None
Aspinall, 2005[89]	Retrospective cohort; Outpatient; US; Unclear/NR; Low risk of bias	**Clinical:** Bleeding Risk Index	Total: 1,269	Unclear/NR	Total: 67.9 (SD: 11.4)	None
Barnes, 2014[90] MAQI	Prospective cohort; Outpatient; US; Industry; Low risk of bias	**Clinical:** HAS-BLED score HEMORR2HAGES score ATRIA score	Total: 2,600	Total: 1.0 years (SD: 0.8)	Total: 70.1 (SD: 12.8)	None
Baruch, 2007[7] SPORTIF Companions: Proietti, 2016[8] Proietti, 2016[9]	RCT; Outpatient; Unclear/NR; Industry; Low risk of bias	**Clinical:** HAS-BLED CHADS2 score CHA2DS2-VASc score Proietti, 2016[9] **Clinical:** HAS-BLED score HEMORR2HAGES score ATRIA score	Total: 7,329 Proietti, 2016[9] 3,551	Total: 1.5 years Proietti, 2016[9] Median:1.6 years (IQR=1.3-1.8)	Arm 1: 73.9 (SD: 8.6) Arm 2: 70.9 (SD: 8.9) Proietti, 2016[9] Median: 72 (IQR 66-77)	None

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Tools Assessed	Total N	Follow-up period	Age	Special Population
Beinart, 2011[11]	Retrospective cohort; Inpatient, Outpatient; Europe; Government; Moderate risk of bias	**Clinical** HAS-BLED score **Individual risk factors include:** Presence and severity of CKD	Total: 17,349	Median follow-up was 4.0 (IQR, 1.4–7.8), 4.9 (IQR, 2.0–8.1), 3.5 (IQR 1.3–6.7), 1.3 (IQR, 0.3–3.5), and 0.5 (IQR, 0.1–1.4) years in patients with eGFR ≥ 90, 60 to 89, 30 to 59, 15 to 29, and <15 mL/min per 1.73 m 2 at baseline, respectively.	Total: 73 (IQR 64–81)	None
Bouillon, 2015[14] SNIIRAM	Retrospective cohort; Unclear/NR; Europe; Unclear/NR; Low risk of bias	**Clinical:** HAS-BLED score	Total: 17,410	Total median: 10 months (IQR 9.8-10)	Non- Switchers median: 75 (IQR 67–82) Switchers median: 75 (IQR 67–82)	None
Bousser, 2008[15] Papers for KQ 2: Apostolakis, 2013[16]; Senoo,2016 [91] AMADEUS	RCT; Unclear/NR; US, Canada, UK, Europe, Australia/NZ; Industry; Low risk of bias	**Clinical:** HEMORR2HAGES HAS-BLED ATRIA Apostolakis, 2013[16]: **Clinical:** HAS-BLED score Senoo,2016 [91]: **Clinical:** HAS-BLED score ATRIA Bleeding Risk Index	Total: 2,293	Total: 429 days (SD: 118)	Total: 70.2 (SD: 9.1)	None

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Tools Assessed	Total N	Follow-up period	Age	Special Population
Connolly, 2009[17] Paper for KQ 2: Marijon, 2013[19]; Proietti, 2017[92]; Hilkens, 2017[93] RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy)	RCT; Outpatient; US, Canada, UK, Europe, S. America, C. America, Asia, Africa, Australia/NZ; Industry; Low risk of bias	**Clinical:** CHADS2 score Proietti, 2017, Hilkens, 2017 [92,93] HAS-BLED score ATRIA Bleeding Risk Index HEMORR2HAGES ORBIT	Total: 18,113 Hilkens, 2017[93]: 3,623	Total median: 2.0 years	Total: 71	None
Esteve-Pastor, 2016[94] FANTASIIA Registry	Prospective cohort; Inpatient; Europe; Industry, Government; Low risk of bias	**Clinical:** HAS-BLED score ORBIT	ECV cohort: 406 FANTASIIA: 1,276	ECV= median follow-up of 1,005 days (IQR 619–1,489) FANTASIIA = follow-up of 1 years	ECV = 66.9 (SD: 10.9) FANTASIIA = 73.9 (9.4)	Persistent nonvalvular AF who underwent one or more programmed ECV procedures
Fang, 2011[95] ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation)	Retrospective cohort; Outpatient; US; Government, Industry, Non-govt, Non-industry; Low risk of bias	**Clinical:** ATRIA $HEMORR_2HAGES$ Bleeding Risk Index	Total: 9,186	Total median: 3.5 years (IQR 1.2-6.0)	Unclear/NR	None

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Tools Assessed	Total N	Follow-up period	Age	Special Population
Friberg, 2012[29] Swedish Atrial Fibrillation cohort study Companions: Friberg, 2015[30]; Friberg, 2012[29]	Prospective cohort; Inpatient, Outpatient; Europe; Government, Non-govt, Non-industry; Low risk of bias	**Clinical:** CHADS2 score CHA2DS2-VASc score Framingham score HAS-BLED HEMORR2HAGES Friberg, 2015[30]: **Clinical**: HAS-BLED score **Individual risk factors:** Presence and severity of CKD Friberg, 2012[29]: **Clinical:** HAS-BLED HEMORR2HAGES **Individual risk factors:** Age Prior stroke Presence of heart disease Presence and severity of CKD DM Sex Cancer	Total: 170,291 Friberg, 2015[30]: 283,969 Friberg, 2012[29]: 182,678	Total median: 1.4 years Friberg, 2015[30]: Total median: 2.1 years	Total: 76.2 Friberg, 2015[30]: Total: Renal Failure group: 78.4 (SD: 10,3) No renal failure group: 74.8 (SD: 12.5)	None
Gage, 2006[96] NRAF (National Registry of Atrial Fibrillation)	Retrospective cohort; Outpatient; US; Government, Non-govt, Non industry; Low risk of bias	**Clinical:** $HEMORR_2HAGES$ Bleeding Risk Index	Total: 3,791	Total: 0.82 years (3138 PY / 3791 PY)	Total: 80.2	None

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Tools Assessed	Total N	Follow-up period	Age	Special Population
Gallego, 2012[97]	Retrospective cohort; Outpatient; Europe; Government; Moderate risk of bias	**Clinical:** HAS-BLED	Total: 965	Total median: 861 days	Total median: 76 (IQR 70-81)	Patients in the therapeutic range
Granger, 2011[37] Paper listed as KQ 2: McMurray, 2013[38] ARISTOTLE	RCT; Unclear/NR; US, Canada, Europe, Asia, Australia/NZ; Industry; Low risk of bias	**Individual risk factors:** Presence of heart disease (ISTH/ GUSTO/ TIMI)	Total: 18,201 McMurray, 2013[38]: 14,671	Total: ~2 years McMurray, 2013[38]: Total median: 18 months	Arm 1 median: 70 (IQR 63-76) Arm 2 median: 70 (IQR 63-76) McMurray, 2013[38]: LVSD: group median: 68 (IQR 60-74) HF-PEF group median: 69 (IQR 61-75) No LVSD/No HF median: 71 (IQR 64-76)	None
Giugliano, 2013[32] Paper for KQ 2: Fanola, 2017[33] ENGAGE-AF	RCT; Outpatient; US; Industry; Low risk of bias	**Clinical:** Developed a clinical tool **Individual risk factors include:** Age Prior stroke Presence of heart disease DM Sex *Race/ethnicity	Total: 2,898	Total: 3 years	Total: 71 (IQR 63-77)	VKA naïve patients only

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Tools Assessed	Total N	Follow-up period	Age	Special Population
Haas, 2016[41] GARFIELD-AF Companions: Camm, 2017[42]; Bassand, 2016[43]; Bassand, 2018[44]	Prospective cohort; Unclear/NR; US, Canada, UK, Europe, S. America, C. America, Asia, Africa, Australia/NZ; Industry; Low risk of bias	**Clinical:** None **Individual risk factors include:** INR level Bassand, 2018[44]: **Individual risk factors include:** Age Sex Race, Diabetes Stroke Cardiovascular disease Renal Disease	Total: 9,934 Bassand, 2018[44] N=28,628	Total: 1 years Bassand, 2018[44] 2-years	Total: 71.2 (SD: 10.2) Bassand, 2018[44] Total: Median 71.0 IQR:63.0-78.0	None
Hijazi, 2016[98]	RCT; Outpatient; US, Canada, UK, Europe, S. America, C. America, Asia; Industry; Low risk of bias	**Clinical:** HAS-BLED score ABC Bleeding Risk score **Individual risk factors include:** None	ARISTOTLE: 14,537 RE-LY: 8,461	ARISTOTLE Median follow up 1.2 years RE-LY Median follow-up 1.9 years	ARISTOTLE Median 70 (IQR 19-97) RE-LY Median 72 (IQR 22-95)	None
Hylek, 2003[46] ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation)	Retrospective cohort; Outpatient; US; Government; Low risk of bias	INR	Total: 596	Unclear/NR	Arm 1: 79 Arm 2: 80 Arm 3: 76	Patients with prior stroke

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Tools Assessed	Total N	Follow-up period	Age	Special Population
Jaspers, 2016[99]	Prospective cohort; Outpatient; Europe; Unclear/NR; Low risk of bias	**Clinical:** HAS-BLED score HEMORR2HAGES score ATRIA score **Individual risk factors include:** None	Total: 1,157	Total: 30 months (SD: 10)	Total median: 84 (IQR 82-87)	Age (Very Elderly)
Jun, 2017[47]	Retrospective cohort; Inpatient, Outpatient, Emergency Room; Canada; Government; Low risk of bias	**Clinical:** HAS-BLED score **Individual risk factors include:** Presence and severity of CKD	Total: 14,892	Total: 1 year	Total: 78.1 (SD: 6.8)	Age; Comorbid conditions (such as advanced CDK (eGFR<60), dementia)
Lind, 2011[49]	Retrospective cohort; Outpatient; Europe; Unclear/NR; High risk of bias	**Individual risk factors include:** INR	Total: 19,180	Unclear/NR	Unclear/NR	None

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Tools Assessed	Total N	Follow-up period	Age	Special Population
Lip, 2012[51] Loire Valley AF Project Companions: Olesen, 2012[52]; Banerjee, 2014[53]; Banerjee, 2013[54]; Fauchier, 2016[55]; Philippart, 2016[56]	Retrospective cohort; Inpatient; Europe; Unclear/NR; Moderate risk of bias	**Clinical:** HAS-BLED HEMORR2HAGES ATRIA Bleeding Risk Index Fauchier, 2016, Philippart, 2016:[55,56] **Clinical:** CHA_2DS_2-VASc score	Total: 7,156 Banerjee, 2013[54]: 5,912 Banerjee, 2014[53]: 36077,156 Fauchier, 2016[55]; N=2208 Philippart, 2016[56] N=8,053 without bioprosthesis N=549 with bioprosthesis	Unclear/NR Banerjee, 2013[54]: Total: 1 year. Cohort follow-up mean 2.45 years (SD: 3.56) Banerjee, 2014[53]: Arm 1: 1.65 (2.44) Fauchier, 2016[55]; Median 495 days IQR: 5-1882 Philippart, 2016[56] Median 400 days IQR=12-1483	Arm 1: 77.7 (SD: 8.2) Arm 2: 73.8 (SD: 11.6) Arm 3: 49.0 (SD: 13.1) Fauchier, 2016[55]; Mean 55 years (SD=14) Philippart, 2016[56] Mean 71 years (SD=15)	None Banerjee, 2013[54]: Presence and severity of CKD None Fauchier, 2016[55]; Non-gender related risk factors
Lip, 2017[100]	Retrospective cohort; Inpatient; Outpatient Europe; Government; Low risk of bias	**Clinical:** HAS-BLED ATRIA ORBIT Bleeding Score	Total: 57,930	1-year follow-up	Total: 73.5 (SD: 11.4)	None
McAlister, 2017[57]	Retrospective cohort; Inpatient, Outpatient, Emergency Room; Canada; Government, Industry, Non-govt, Non-industry; Low risk of bias	**Clinical:** HAS-BLED score HEMORR2HAGES score ATRIA score **Individual risk factors include:** Presence and severity of CKD	Total: 58,451	Total median: 31 months (IQR 13-59)	Total: 66	Comorbid conditions (such as advanced CDK (eGFR<60))

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Tools Assessed	Total N	Follow-up period	Age	Special Population
O'Brien, 2015[101] ORBIT-AF Companion: Inohara, 2017[102]	Prospective cohort; Outpatient; US; Government, Industry; Low risk of bias	**Clinical:** HAS-BLED score ATRIA score (ORBIT –AF) **Individual risk factors:** Age Presence and severity of CKD	Total: 7411 Inohara, 2017[102] N=9,749	Total median: 2 years (IQR 1.6-2.5)	Total median: 75 (IQR 68–82)	None
Olesen, 2011[62]	Retrospective cohort; Inpatient; Europe; Unclear/NR; High risk of bias	**Clinical:** $CHADS_2$ score CHA_2DS_2-VASc score	Total: 132,372	Total: Max 12	Arm 1: 72.8 (SD: 14.4) Arm 2: 70.6 (SD: 11.1) Arm 3: 78.1 (SD: 11.2) Arm 4: 73.1 (SD: 9.6)	None
Olesen, 2011[103]	Retrospective cohort; Inpatient; Europe; Unclear/NR; Low risk of bias	**Clinical:** HAS-BLED $HEMORR_2HAGES$	Total: 118,584	Total: 10	Arm 1: 78.6 (SD: 10.6) Arm 2: 74.7 (SD: 13.6) Arm 3: 74.6 (SD: 9.2) Arm 4: 71.2 (SD: 10.7)	None
Orkaby, 2017[66] VARIA	Retrospective cohort; Inpatient, Outpatient; US; Government; Moderate risk of bias	**Clinical:** N/A **Individual risk factors include:** Cognitive impairment	Total: 2,572	Total: 2.2 PY following diagnosis of dementia	Total: 79.5 (SD: 6.0)	Patients with newly diagnosed dementia; Older Adults

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Tools Assessed	Total N	Follow-up period	Age	Special Population
Patel, 2011[104] Companions marked as KQ 2: Sherwood, 2015[105]; Hankey, 2014[106]; Goodman, 2014[107] ROCKET-AF	RCT; Outpatient; US, Canada, UK, Europe, S. America, Asia, Africa, Australia/NZ; Industry; Low risk of bias Hankey, 2014[106]; Moderate risk of bias	Sherwood, 2015[105]: **Clinical:** HAS-BLED score **Individual risk factors:** Age INR level Presence and severity of CKD Sex Hankey, 2014[106]: **Individual risk factors:** Age Prior stroke Presence of heart disease Race/ethnicity Goodman, 2014[107]: **Clinical:** HAS-BLED score ATRIA	Total: 14,264 Arm 1. 7,131 Arm 2. 7,133	Total median: 707 days Hankey, 2014[106]: Total median: 1.94 years (IQR 1.42-2.41)	Total median: 73 Arm 1 median: 73 (IQR 65-78) Arm 2 median: 73 (IQR 65-78)	None
Peacock, 2017[108]	Retrospective cohort; Inpatient, Outpatient, Emergency Room; US; Industry, Non-govt, Non-industry; Low risk of bias	**Individual risk factors include:** Age Prior stroke *Type of AF Presence of heart disease DM Sex	Total: 44,793	Total: 2.5 years	Total: 78.7 (SD: 7.9)	Military Personnel or Veterans

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Tools Assessed	Total N	Follow-up period	Age	Special Population
Phelps, 2018[67]	Retrospective cohort; Outpatient; US; Industry, Non govt, non industry; Moderate risk of bias	**Individual risk factors include:** Time in therapeutic range (TTR)	Total: 8,405	Unclear/NR	Total: 74.3 (SD: 10.3)	None
Pisters, 2010[109] Euro Heart Survey for AF	Prospective cohort; Inpatient, Outpatient; Europe; Industry; Low risk of bias	**Clinical:** HAS-BLED HEMORR2HAGES **Individual risk factors:** Age Prior stroke Presence of heart disease Presence and severity of CKD	Total: 3,456	Total: ~1 years	Total: 66.8 (SD: 12.8)	None
Poli, 2011[69]	Prospective cohort; Unclear/NR; Europe; None; Low risk of bias	**Clinical:** $CHADS_2$ score Bleeding Risk Index	Total: 3,302	Total median: 2.3 (IQR 0.8- 4.4)	Total median: 74 (IQR 68-80)	None
Renoux, 2017[72]	Retrospective cohort; Inpatient, Outpatient; Canada; Industry, Non-govt, Non-industry; Low risk of bias	**Clinical:** HAS-BLED **Individual risk factors include:** Age Sex Prior stroke *Duration and frequency of AF Presence and severity of CKD	Total: 147,622	Total: 2.9 years	Total: 75.5 (SD: 11.4)	None

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Tools Assessed	Total N	Follow-up period	Age	Special Population
Rivera-Caravaca, 2017[74] Companions marked as KQ 2: Rivera-Caravaca, 2018[75]; Esteve-Pastor, 2017[110] Murcia AF Project	Retrospective cohort; Inpatient; Europe; Government, Non govt, non industry; Low risk of bias	**Clinical:** CHA_2DS_2-VASc score HAS-BLED ATRIA HEMORR2HAGES **Individual risk factors include:** Age Sex Prior stroke	Total: 1,361	Total median: 6.5 years (IQR 4.3–7.9)	Total median: 76 years (IQR 71-81)	None
Roldan, 2012[111]	Retrospective cohort; Outpatient; Europe; Unclear/NR; Moderate risk of bias	**Clinical:** ATRIA HAS-BLED	Total: 937	Total median: 952 days (IQR 785-1074)	Total median: 76 (IQR 70-81)	Patients in the therapeutic range
Ruiz-Nodar, 2012[80]	Retrospective cohort; Unclear/NR; Europe; Unclear/NR; High risk of bias	**Clinical:** HAS-BLED CHA_2DS_2-VASc score	Total: 590	Total: ~12 months	Total: 72.2 (SD: 8.1)	None
Shireman, 2006[112]	Retrospective cohort; Outpatient; US; Government; Low risk of bias	**Clinical:** Bleeding Risk Index	Total: 26,345	Unclear/NR	Unclear/NR	None
Yao, 2017[113]	Retrospective cohort; Patient Database; US; Unclear/NR; Low risk of bias	**Clinical:** ATRIA $CHADS_2$ score CHA_2DS_2-VASc score HAS-BLED ORBIT	Total: 39,539	Total: 0.6 years (SD: 0.7)	Total median: 71 (IQR 63–79)	None

Abbreviations: AF = atrial fibrillation; IQR = interquartile range; N = number of patients; NR = not reported; PY = patient years; RCT = randomized controlled trial; SD = standard deviation

Appendix Table F-3. Study characteristics—KQ 3

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Intervention or Tool and Comparators	Total N Interventions (N)	Follow-up period	Age	Special Population	Outcomes Assessed
Abraham, 2015[114]	Retrospective cohort; Inpatient, Outpatient, Emergency Room; US; Non-govt, Non-industry; Low risk of bias	Arm 1: Warfarin Arm 2: Dabigatran Arm 3: Rivaroxaban	Arm 1: 22,787 (full) Arm 2: 7846 (matched 7749 per arm W & D) Arm 3: 5434 (matched 5166 per arm W & R)	Unclear/NR	Arm 1: 72.2 (SD: 9.9) Arm 2: 67.0 (SD: 11.3) Arm 3: 68.4 (SD: 11.1)	None	Major bleeding events; GI bleeding
Abraham, 2017[115] OptumLabs Data Warehouse	Retrospective cohort; Inpatient; Outpatient; US; Non-govt, Non-industry; Low risk of bias	Sub-Study 1: Arm 1. Apixaban Arm 2. Dabigatran Sub-Study 2: Arm 1: Apixaban Arm 2: Rivaroxaban Sub-Study 3: Arm 1. Rivaroxaban Arm 2. Dabigatran	Total: 43,303; Sub-Study 1: 13,084 (6542 per arm) Sub-Study 2: 13,130 (6565 per arm) Sub-Study 3: 31,574 (15,787 per arm)	Sub-Study 1: Arm 1. 89 days (IQR 30-194) Arm 2. 120 days (IQR 30-338) Sub-Study 2: Arm 1. 89 days (IQR 30-194) Arm 2. 106 days (IQR 30-260) Sub-Study 1: Arm 1. 113 days (IQR 30-271) Arm 2. 120 days (IQR 30-340)	Sub-Study 1: Arm 1. 72.2 (SD: 11.1) Arm 2. 72.1 (SD: 10.5) Sub-Study 2: Arm 1. 72.3 (SD: 11.1) Arm 2. 72.1 (SD: 11.2) Sub-Study 3: Arm 1. 69.2 (SD: 11.6) Arm 2. 69.7 (SD: 11.2)	None	GI bleeding

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Intervention or Tool and Comparators	Total N Interventions (N)	Follow-up period	Age	Special Population	Outcomes Assessed
Adeboyeje, 2017[116] HealthCore Integrated Research Environment (HIRE)	Retrospective cohort; Claims Database; US; Industry; Low risk of bias	Arm 1: Warfarin Arm 2: Dabigatran Arm 3: Apixaban Arm 4: Rivaroxaban	Arm 1: 23,431 Arm 2: 8,539 Arm 3: 3,689 Arm 4: 8,398	Major bleeding events: 36,636 person-years of follow-up	Arm 1: 70 (SD: 12.2) Arm 2: 70 (SD: 12.3) Arm 3: 70 (SD: 12.6) Arm 4: 70 (SD: 12.3)	None	Major bleeding events; GI bleeding; Intracranial bleeding
Amin, 2017[117] OptumInsight Research Database	Retrospective cohort; Claims Database US Industry; Low risk of bias	Sub-Study 1: Arm 1. Apixaban Arm 2. Warfarin Sub-Study 2: Arm 1. Apixaban Arm 2. Dabigatran Sub-Study 3: Arm 1. Apixaban Arm 2. Rivaroxaban	Total: 47,634; Sub-Study 1: Arm 1. 8,328 Arm 2. 8,328 Sub-Study 2: Arm 1. 3,557 Arm 2. 3,557 Sub-Study 3: Arm 1. 8,440 Arm 2. 8,440	Unclear/NR	Sub-Study 1: Arm 1. 73.54 (SD: 10.72) Arm 2. 73.37 (SD: 10.42) Sub-Study 2: Arm 1. 70.92 (SD: 11.41) Arm 2. 70.68 (SD: 11.19) Sub-Study 3: Arm 1. 72.84 (SD: 11.06) Arm 2. 72.53 (SD: 10.79)	Insurance type subgroup analyses	All-cause hospitalization; Hospitalization due to stroke/SE; Hospitalization due to major bleeding events; healthcare-related costs

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Intervention or Tool and Comparators	Total N Interventions (N)	Follow-up period	Age	Special Population	Outcomes Assessed
Amin, 2017[118]	Retrospective cohort; Claims Database; US; Industry; Low risk of bias	Sub-Study 1: Arm 1. Warfarin Arm 2. Dabigatran Sub-Study 2: Arm 1: Warfarin Arm 2: Rivaroxaban Sub-Study 3: Arm 1. Warfarin Arm 2. Apixaban	Total: 186,132; Sub-Study 1. 16,731 per arm Sub-Study 2. 52,476 per arm Sub-Study 3. 20,803 per arm	(In days) Sub-Study 1: Arm 1. 199.3 (SD: 185.2) Arm 2. 196.1 (SD: 192.3) Sub-Study 2: Arm 1. 197.1 (SD: 185.2) Arm 2: 203.8 (SD: 192.4) Sub-Study 3: Arm 1. 196.2 (SD: 184.1) Arm 2. 171.2 (SD: 153.4)	Sub-Study 1: Arm 1. 77.1 (SD: 7.3) Arm 2. 77.2 (SD: 7.0) Sub-Study 2: Arm 1. 77.8 (SD: 7.2) Arm 2. 77.7 (SD: 7.2) Sub-Study 3: Arm 1. 78.1 (7.5) Arm 2. 78.4 (SD: 7.4)	None	Major bleeding events; GI bleeding; Intracranial bleeding; Stroke/SE
Avgil, 2015[119]	Prospective cohort; Inpatient, Prescription databases; Canada; Government; Low risk of bias	Arm 1. Warfarin Arm 2. Dabigatran 110mg Arm 3. Dabigatran 150mg doses	Arm 1: 47,192 Men (22,978) Women (24,214) Arm 2: 8926 Men (4019) Women (4907) Arm 3: 6992 Men (4327) Women (2665)	Total median: 1.3 years (IQR 0–3.2)	Total: Men: 76.3 (SD: 9.3) Women: 80.3 (SD: 8.8)	Men and Women subgroups	Ischemic Stroke/TIA; Bleeding events; MI

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Intervention or Tool and Comparators	Total N Interventions (N)	Follow-up period	Age	Special Population	Outcomes Assessed
Azoulay, 2012[120]	Case-control; Outpatient; UK; Industry; Fair	Arm 1: No therapy Arm 2: VKA (warfarin) Arm 3: Aspirin	Total: 70,766	Total: 3.9 years (SD: 3.3)	Total: 74.1 (SD: 11.8)	None	Ischemic stroke Intracerebral hemorrhage Composite outcome (CV infarction/stroke, Intracerebral hemorrhage)
Bengtson, 2017[121] Truven Health MarketScan	Retrospective cohort; Inpatient, Outpatient; US Government, Non-Industry, Non-govt; Low risk of bias	Sub-Study 1: Arm 1. Dabigatran Arm 2. Warfarin Sub-Study 2: Arm 1. Rivaroxaban Arm 2. Warfarin	Sub-Study 1: Arm 1. 18,981 Arm 2. 37,707 Sub-Study 2: Arm 1. 3301 (new and switchers) Arm 2 (8280)	Dabigatran (new users) Median 15 months Rivaroxaban user (new and switchers) Median 8 months	Dabigatran (new users) 68.5 (SD: 12.3) Matched warfarin user 70.8 (SD: 12.1) Rivaroxaban user (new and switchers) 70.4 (SD: 12.0) Matched warfarin user 72.5 (SD: 12.2)	None	Intracranial bleed Ischemic stroke Myocardial infarction Gastrointestinal bleed
Berge, 2000[122] HAEST	RCT; Inpatient; Europe; Non-govt, Non-industry; Good	Arm 1: LMWH (Dalteparin) Arm 2: Aspirin	Total: 449; Arm 1. 224 Arm 2. 225	Total: 14 days	Arm 1: Median 80 (IQR 55-96) Arm 2: Median 80 (IQR 44-98)	Patients with prior stroke	Ischemic stroke Intracerebral hemorrhage All-cause mortality

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Intervention or Tool and Comparators	Total N Interventions (N)	Follow-up period	Age	Special Population	Outcomes Assessed
Beyer-Westendorf, 2016[123]	Retrospective cohort; Primary Care; Germany; Industry High risk of bias	Arm 1. VKA Arm 2. Dabigatran Arm 3. Rivaroxaban	Total: 8,607; Arm 1. VKA at 180 days 5,127; VKA at 360 days 2,978 Arm 2. Dabigatran at 180 days 821; Dabigatran at 360 days 374 Arm 3. Rivaroxaban at 180 days 1,317; Rivaroxaban at 360 days 433	Follow-up period of 180 days and 360 days	Arm 1. 74.7 (SD: 9.8); 74.6 (SD: 9.7) Arm 2. 73.9 (10.1); 74.0 (9.8) Arm 3. 74.8 (10.4); 74.3 (10.0)	None	Long-term adherence/ persistence to therapy
Bjorck, 2016[124] Swedish National Patient Register (NPR) and Swedish Prescribed Drug Register	Retrospective cohort; Inpatient, Outpatient; Sweden; Government; High risk of bias	Arm 1. Warfarin with additional anti-platelet therapy Arm 2. Warfarin and aspirin	Total: 40,449; Arm 1. 34,851 Arm 2. 4,311	Unclear/NR	Total: 72.5 (SD: 10.1)	None	Thromboembolism • Arterial • Myocardial infarction • Venous Major bleeding • Gastrointestinal • Intracranial • Other All-cause mortality
Borne, 2017[125]	Retrospective cohort; Inpatient, Outpatient; US; Unclear/NR; Moderate risk of bias	Arm 1. Dabigatran Arm 2. Rivaroxaban Arm 3. Apixaban	Total: 2,882; Arm 1. 2,096 Arm 2. 571 Arm 3. 215	Total: 667.2 days (SD: 432.2)	Arm 1. 66.9 (SD: 9.3) Arm 2. 67.3 (SD: 9.7) Arm 3. 73.1 (SD: 8.8)	None	Long-term adherence/ persistence to therapy

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Intervention or Tool and Comparators	Total N Interventions (N)	Follow-up period	Age	Special Population	Outcomes Assessed
Bouillon, 2015 [14] SNIIRAM	Retrospective cohort; Inpatient; Europe (France); Unclear/NR; Low risk of bias	Arm 1: VKA switched to NOAC (rivaroxaban, dabigatran) Arm 2: stayed on VKA therapy (fluindione, warfarin or acenocoumarol)	Total: 17,410; Arm 1 (6,705) Arm 2 (10,705)	Total: 10.0 months (IQR 9.8-10.0)	Total: 75 (IQR 67-82)	None	Intracranial bleeding GIB Ischemic CVA Systemic embolism Death First/recurrent MI Composite: bleeding (any bleeding); ischemic CVA + systemic embolism; Any event of the above
Bousser, 2008[15] AMADEUS	RCT; Unclear/NR; US, Canada, UK, Europe, Australia/NZ; Industry; Good	Arm 1: Factor Xa Inhibitors (idraparinux) Arm 2: VKA (Warfarin or acenocoumarol)	Total: 4,576; Arm 1 (2,283) Arm 2 (2,293)	Arm 1: 311 (SD: 161) Arm 2: 339 (SD: 165)	Total: 70.1 (SD: 9.1) Arm 1: 70.1 (SD: 9.0) Arm 2: 70.2 (SD: 9.1)	None	Time in therapeutic range Ischemic stroke Intracerebral hemorrhage Myocardial infarction Systemic embolism Major bleed All-cause mortality Composite outcome: Cerebral infarction, Systemic embolism Composite outcome: Intracerebral hemorrhage, Subdural hematoma, Major bleed, Minor bleed Diagnostic Accuracy
Brown, 2016[126] Truven Health Analytics MarketScan database	Prospective cohort; Inpatient, Outpatient; US; Government, Non-govt, Non-industry; High risk of bias	Arm 1. Rivaroxaban Arm 2. Dabigatran Arm 3. Apixaban	Total: 5,223 Arm 1. 3,455 Arm 2. 1,264 Arm 3. 504	Follow-up period at 3, 6, 9 months	Arm 1. 68.1 (SD: 12.4) Arm 2. 66.5 (SD: 12.3) Arm 3. 70.3 (SD: 12.2)	None	Long-term adherence to therapy

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Intervention or Tool and Comparators	Total N Interventions (N)	Follow-up period	Age	Special Population	Outcomes Assessed
Brown, 2017[127] Truven Health Analytics MarketScan database	Retrospective cohort; Inpatient, Outpatient; US; Government; Moderate risk of bias	Arm 1. Rivaroxaban Arm 2. Dabigatran Arm 3. Apixaban	Total: 15,341 Arm 1. 9,817 Arm 2. 2,751 Arm 3. 2,773	Follow-up period at 3, 6, 9 months	Arm 1. 70.5 (SD: 11.8) Arm 2. 67.9 (SD: 12.5) Arm 3. 73.9 (SD: 10.6)	None	Adherence to therapy
Chrischilles, 2018[128]	Prospective cohort; Claims Database; US; Government; Low risk of bias	Arm 1. Rivaroxaban Arm 2. Warfarin	Arm 1. 36,173 Arm 2. 79,520	Arm 1. 85 days Arm 2. 71 days	Arm 1. 71.1 (SD: 10.4) Arm 2. 71.1 (SD: 10.7)	None	Intracranial bleeding, GI bleeding; Ischemic stroke
Chun, 2013[129]	Prospective cohort; Inpatient; Europe; Unclear/NR; High risk of bias	Arm 1: Watchman Arm 2: ACP device	Total: 80	Total: 6-week follow-up	Total: 76 (SD: 9)	None	Thromboembolic events (Thrombus) Cardiac tamponade Safety Duration of follow-up Long-term adherence to therapy
Coleman, 2016[130] US Truven Health MarketScan	Retrospective; Inpatient, Outpatient; US; Industry, Non-govt, Non-industry; Low risk of bias	Arm 1: Rivaroxaban Arm 2: Dabigatran Arm 3: Warfarin	Total: 32,634	Arm 1: 329 days Arm 2: 482 days Arm 3: 454 days	Arm 1: 71.3 (SD: 11.1) Arm 2: 70.9 (SD: 10.8) Arm 3: 71.5 (SD: 11.3	None	Medication persistence (defined as absent refill gap > 60 days)

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Intervention or Tool and Comparators	Total N Interventions (N)	Follow-up period	Age	Special Population	Outcomes Assessed
Coleman, 2016[131] REVISIT-US	Retrospective cohort; Inpatient, Outpatient; US; Industry, Non-govt, Non-industry; Low risk of bias	Sub-Study 1: Arm 1. Rivaroxaban Arm 2. Warfarin Sub-Study 2: Arm 1. Apixaban Arm 2. Warfarin	Total: 30,988; Sub-Study 1: 11,411 per arm Sub-Study 2: 4083 per arm	Not available.	Sub-Study 1: Arm 1: 70.66 (SD: 10.99) Arm 2. 70.72 (SD: 11.35) Sub-Study 2: Arm 1: 71.00 (SD: 11.25) Arm 2: 71.15 (SD:11.32)	None	Intracranial hemorrhage Ischemic CVA Composite: Ischemic CVA + Intracranial hemorrhage
Coleman, 2016[132] RELIEF	Retrospective cohort; Outpatient; Europe; Industry; Low risk of bias	Arm 1: Rivaroxaban Arm 2: VKA	Total: 2,078	1 year	Arm 1: 74.0 (SD: 10.7) Arm 2: 74.4 (SD: 9.9)	None	
Coleman, 2017[133] IMS Disease Analyzer data	Retrospective; Outpatient; Europe; Industry, Non-govt; Low risk of bias	Arm 1: Apixaban Arm 2: VKA	Total: 1,670; Arm 1. 835 Arm 2. 835	Follow-up in person years Arm 1.809 Arm 2.814	Arm 1. 75.3 (SD: 10.6) Arm 2. 74.8 (SD: 9.2)	None	CVA TIA MI Intracerebral hemorrhage Other non-traumatic intracranial hemorrhage

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Intervention or Tool and Comparators	Total N Interventions (N)	Follow-up period	Age	Special Population	Outcomes Assessed
Coleman, 2017[134] US Truven Health MarketScan	Retrospective cohort; Claims Database; US; Industry; Low risk of bias	Sub-Study 1: Arm 1. Apixaban Arm 2. Warfarin Sub-Study 2: Arm 1. Dabigatran Arm 2. Warfarin Sub-Study 3: Arm 1. Rivaroxaban Arm 2. Warfarin	Total: 9,684; Sub-Study 1: 1,257 per arm Sub-Study 2: 981 per arm Sub-Study 3: 2,604 per arm	Sub-Study 1: 0.5 years (SD: 0.5) Sub-Study 2: 0.6 years (SD: 0.6) Sub-Study 3: 0.6 years (SD: 0.6)	Sub-Study 1: Arm 1. 74 (IQR 63-82) Arm 2. 74 (IQR 63-82) Sub-Study 2: Arm 1. 73 (IQR 63-80) Arm 2. 73 (64-82) Sub-Study 3: Arm 1. 72 (IQR 63-81) Arm 2. 73 (IQR 63-82)	None	Intracranial hemorrhage; Ischemic stroke; Major bleeding
Coleman, 2017[135] US Truven Health MarketScan; IMS RWD Adjudicated Claims database	Retrospective cohort; Inpatient, Outpatient; US; Industry; Low risk of bias	Sub-Study 1 (IMS database): Arm 1. Rivaroxaban Arm 2. Apixaban Sub-Study 2 (Truven Health): Arm 1. Rivaroxaban Arm 2. Apixaban	Sub-Study 1: Arm 1. 26,635 Arm 2. 10,441 Sub-Study 2: Arm 1. 47,666 Arm 2. 21,485	Sub-Study 1: Arm 1. 26,635 Arm 2. 10,441 Sub-Study 2: Arm 1. 47,666 Arm 2. 21,485	Sub-Study 1: Arm 1. 61.95 (SD: 10.5) Arm 2. 62.90 (SD: 10.4) Sub-Study 2: Arm 1. 68.18 (SD: 12.4) Arm 2. 69.99 (SD: 12.5)	None	

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Intervention or Tool and Comparators	Total N Interventions (N)	Follow-up period	Age	Special Population	Outcomes Assessed
Collings, 2018[136]	Retrospective cohort; Outpatient; Europe; Industry; Moderate risk of bias	Arm 1: Apixaban Arm 2: Rivaroxaban Arm 3: Dabigatran Arm 4: VKA	Total: 4,111; Arm 1. 744 Arm 2. 1,257 Arm 3. 400 Arm 4. 1,710	Total: 8.6 years (IQR 4.8-13.7)	Total: 76 (IQR 67-83) Arm 1. 75 (IQR 68-81) Arm 2. 74 (IQR 66-80) Arm 3. 74 (66-81) Arm 4. 78 (70-84)	None	Medication persistence
Connolly, 2006[25] ACTIVE-W Companions: Flaker, 2010[24] Healey, 2008[26] Hohnloser, 2007[27]	RCT; Unclear/NR; US, Canada, UK, Europe, S. America, Asia, Africa, Australia/NZ; Industry; Good	Arm 1: Clopidogrel+ Aspirin Arm 2: VKA (Unspecified)	Total: 6,706; Arm 1. 3,335 Arm 2. 3,371	Total: Median 1.28 years	Arm 1: 70.2 (SD: 9.4) Arm 2: 70.2 (SD: 9.5)	None	Systemic embolism Myocardial infarction CV infarction/stroke Ischemic stroke Intracerebral hemorrhage HRQOL/ Functional capacity All-cause mortality CV mortality Major bleed Minor bleed Composite outcome: Systemic embolism, CV infarction/stroke, Myocardial infarction, CV mortality

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Intervention or Tool and Comparators	Total N Interventions (N)	Follow-up period	Age	Special Population	Outcomes Assessed
Connolly, 2009[17] RE-LY Companions: Oldgren, 2011[137] Eikelboom, 2011[138] Diener, 2010[139] Hohnloser, 2012[140] Nagarakanti, 2011[141] Hart, 2012[142] Healey, 2012[143] Ezekowitz, 2009[144]* Verdecchia, 2017[145], Lauw, 2017[146], Brambatti, 2015[147], Hijazi, 2014[148], Marijon, 2013[19], Connolly, 2013[149], Monz, 2013[150], Eikelboom, 2013[151]; Hijazi, 2018[152]	RCT; Outpatient; US, Canada, UK, Europe, S. America, C. America, Asia, Africa, Australia/NZ; Industry; Good	Arm 1: Dabigatran (110 mg twice daily) Arm 2: Dabigatran (150 mg twice daily) Arm 3: VKA (Warfarin)	Total: 18,113	Total: Median 2.0 years	Arm 1: 71.4 (SD: 8.6) Arm 2: 71.5 (SD: 8.8) Arm 3: 71.6 (SD: 8.6)	None	Compiled all together for ease: Cerebrovascular infarction Systemic embolism DVT Hemorrhagic stroke Intracerebral hemorrhage Extracranial hemorrhage Major bleed Minor bleed Mortality All-cause mortality Cardiovascular mortality Myocardial infarction Health-related quality of life Composite outcomes (include combinations of the above)

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Intervention or Tool and Comparators	Total N Interventions (N)	Follow-up period	Age	Special Population	Outcomes Assessed
Connolly, 2009[153] ACTIVE-A Companion: Perera, 2017[154]	RCT; Outpatient; US, Canada, UK, Europe, S. America, C. America, Asia, Africa, Australia/NZ; Industry; Good	Arm 1: Clopidogrel; Aspirin Arm 2: Aspirin	Total: 7,554	Total: 3.6 years	Total: 71 Arm 1: 70.9 (SD: 10.2) Arm 2: 71.1 (SD: 10.2)	None	CV infarction/stroke Ischemic stroke Intracerebral hemorrhage Myocardial infarction Systemic embolism CV mortality All-cause mortality Major bleed Minor bleed Composite outcome: Systemic embolism, CV infarction/stroke, Myocardial infarction, CV mortality

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Intervention or Tool and Comparators	Total N Interventions (N)	Follow-up period	Age	Special Population	Outcomes Assessed
Connolly, 2011[20] AVERROES Companions: Lawrence, 2012[155] Eikelboom, 2012[156] Eikelboom, 2010[157] O'Donnell, 2016[158], Ng, 2016[159], Lip, 2014[160], Coppens, 2014[161], Flaker, 2012[162]	RCT; Outpatient; Unclear/NR; Industry; Good	Arm 1: Apixaban Arm 2: Aspirin	Total: 5,599	Total: 1.1 years	Arm 1: 70 (SD: 9) Arm 2: 70 (SD: 10)	None Lawrence, 2012[155]: Previous stroke or TIA; No prior CVA Eikelboom, 2012[156]: Stage III CKD O'Donnell, 2016[158]: Apixaban group MRIs Ng, 2016[159]: Age Coppens, 2014[161] Tried but failed VKA therapy	Intracerebral hemorrhage; Systemic embolism; Myocardial infarction; CV infarction/stroke; Subdural hematoma; Minor bleed; Major bleed; Ischemic stroke; All-cause mortality; Healthcare utilization - Hospital admissions Composite outcomes (include combinations of the above)

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Intervention or Tool and Comparators	Total N Interventions (N)	Follow-up period	Age	Special Population	Outcomes Assessed
Deambrosis, 2017[163]	Retrospective cohort; Inpatient, Outpatient; Italy; Unclear/NR; High risk of bias	Arm 1. N-VKA group (did not receive any VKA treatment) Arm 2. VKA group (received 6 months of treatment)	Total: 6,138 Arm 1. N-VKA. 3,114 Arm 2. VKA. 3,024	Total: 37.70 months (IQR 0–85.17) Arm 1. 23.47 months (IQR 0- 85.13) Arm 2. 48.73 months (IQR 6.70-85.17)	Total: 75.59 (SD: 11.51)	None	Stroke; Medication persistence
Deitelzweig, 2016[164] Premier Hospital database and the Cerner Database	Retrospective cohort; Inpatient; US; Industry; High risk of bias	Premier Database Arm 1. Apixaban Arm 2. Dabigatran Arm 3. Rivaroxaban Cerner Database Arm 1. Apixaban Arm 2. Dabigatran Arm 3. Rivaroxaban	Premier Total: 74,730 Cerner Total: 14,201	Unclear/NR	Premier: Total: 72.2 (SD: 11.8) Cerner: Total: 72.5 (SD: 12.3)	None	Health-related quality of life Health services utilization (e.g., hospital admissions, outpatient office visits, ER visits, prescription drug use)
Deitelzweig, 2017[165] Humana research database	Retrospective cohort; Claims Database US; Industry; Low risk of bias	Arm 1. Apixaban Arm 2. Warfarin	Arm 1. 7,107 Arm 2. 7,107	Arm 1. 6.7 months (SD: 5.3) Arm 2. 6.6 (SD: 5.4)	Arm 1. 78.2 (SD: 9.1) Arm 2. 78.1 (SD: 8.8)	Age (≥ 65 years old)	Health care resource utilization (HCRU); HCRU-associated costs

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Intervention or Tool and Comparators	Total N Interventions (N)	Follow-up period	Age	Special Population	Outcomes Assessed
Deitelzweig, 2017[166] Humana Research Database	Retrospective cohort; Claims Database; US; Industry; Low risk of bias	Sub-Study 1: Arm 1: Apixaban Arm 2: Rivaroxaban Sub-Study 2: Arm 1: Apixaban Arm 2: Dabigatran Sub-Study 3: Arm 1: Apixaban Arm 2: Warfarin	Sub-Study 1: Arm 1. 6,810 Arm 2. 6,810 Sub-Study 2: Arm 1. 2,327 Arm 2. 2,327 Sub-Study 3: Arm 1. 7,107 Arm 2. 7,107	Sub-Study 1: Arm 1. 6.5 months (SD: 5.1) Arm 2. 6.4 months (SD: 5.1) Sub-Study 2: Arm 1. 7.1 months (SD: 5.5) Arm 2. 7 months (SD: 5.5) Sub-Study 3: Arm 1. 6.7 months (SD: 5.3) Arm 2. 6.6 months (SD: 5.4)	Sub-Study 1: Arm 1. 77.1 (SD: 8.0) Arm 2. 77.0 (SD: 7.8) Sub-Study 2: Arm 1. 77.3 (SD: 9.0) Arm 2. 76.9 (SD: 8.3) Sub-Study 3: Arm 1. 78.2 (SD: 9.1) Arm 2. 78.1 (SD: 8.8)	age of ≥ 65 years	Stroke/Systemic embolism, any; Ischemic stroke; Hemorrhagic stroke; and SE; Major bleeding events, any; Intracranial hemorrhage; GI bleeding;
Denas, 2017[167]	Retrospective cohort; Patient Registry; Europe; Government; Low risk of bias	Arm 1. NOAC Arm 2. VKA	Arm 1. 6,740 Arm 2. 6,740	Total: ≥3 months Arm 1: 7645 patient years Arm 2: 47,428 patient years	Mean Arm 1. 75.2 Arm 2. 75.1	None	Myocardial infarction; All-cause mortality; Ischemic stroke; All bleeding events; Intracranial bleeding

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Intervention or Tool and Comparators	Total N Interventions (N)	Follow-up period	Age	Special Population	Outcomes Assessed
Douros, 2017[168] Canadian Province of Quebec's Health Insurance Database (RAMQ)	Retrospective cohort; Inpatient, Outpatient; Canada; Industry, Non-govt, Non-industry; Moderate risk of bias	Arm 1. Initiating NOAC Arm 2. Initiating VKA	Total: 32,431; Arm 1. 14,746 Arm 2. 17,685	Unclear/NR	Arm 1. 75.07 (SD: 9.18) Arm 2. 76.78 (SD: 9.07)	None	Treatment persistence
Ezekowitz, 2007[169] PETRO	RCT; Inpatient; US, Europe; Industry; Good	Arm 1: Dabigatran (50 mg twice daily) Arm 2: Dabigatran (150 mg twice daily) Arm 3: Dabigatran (300 mg twice daily) Arm 4: Warfarin	Total: 502	Total: 3 months	Arm 1: 70 (SD: 8.8) Arm 2: 70 (SD: 8.1) Arm 3: 69.5 (SD: 8.4) Arm 4: 69 (SD: 8.3)	None	Major bleed CV infarction/stroke Composite outcome: Major or clinically relevant bleed
Figini, 2017[170]	Retrospective cohort; Inpatient; Italy; Unclear/NR High risk of bias	Arm 1. Watchman Arm 2. Amplatzer Cardiac Plug (ACP)	Total: 165; Arm 1. 66 Arm 2. 99	Total: 448 days (IQR 167–793)	Total: 72 (SD: 9)	None	Thromboembolic stroke; Hemorrhagic stroke; Major bleeding Gastrointestinal bleeding Intracranial bleeding Other bleeding Minor bleed; Mortality
Fonseca, 2015[171] IMS Health's Charge Detail Master Database	Retrospective cohort; Inpatient, Outpatient; US; Industry; Low risk of bias	Arm 1: Warfarin Arm 2: Dabigatran	Arm 1: 1292; 488 for re-admission analysis Arm 2: 646; 244 for re-admission analysis	30 days	Arm 1: Warfarin= 72.1 (SD: 10.9) Arm 2: Dabigatran= 71.7 (SD: 11.4)	None	Health services utilization (e.g., hospital admissions; costs) Difference in average length of stay

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Intervention or Tool and Comparators	Total N Interventions (N)	Follow-up period	Age	Special Population	Outcomes Assessed
Forslund, 2016[172] Administrative health data register of the Stockholm Region	Prospective cohort; Inpatient, Outpatient; Europe; Government; High risk of bias	Arm 1. Warfarin Arm 2. Dabigatran Arm 3. Rivaroxaban Arm 4. Apixaban Arm 5. Aspirin	Total: 17,741 Arm 1. 9,969 Arm 2. 2,701 Arm 3. 2,074 Arm 4. 1,352 Arm 5. 4,540	Follow-up at 1 year and 2 years	Mean age Arm 1. 76.3 Arm 2. 73.8 Arm 3. 75.6 Arm 4. 76.1 Arm 5. 79.5	None	Long-term adherence to therapy
Forslund, 2017[173]	Retrospective cohort; Inpatient, Outpatient; Europe; Government, Non-govt, Non-industry; Low risk of bias	Arm 1: Warfarin Arm 2: NOAC (rivaroxaban, apixaban, dabigatran)	Total: 22,198; Arm 1. 12,919 Arm 2. 9,279	Arm 1: 1.61 years Arm 2: 1.07 years	Arm 1: 74.1 (SD: 11.0) Arm 2: 72.9 (SD: 11.1)	None	Ischemic CVA Death Hemorrhagic CVA GIB Hospitalized bleed Composite: TIA+Ischemic CVA+Stroke unspecified+ death; Any severe bleed (defined by: intracranial, GIB, hemothorax, hemipericardium, intraocular, anemia 2/2 to bleed, esophageal); TIA/Ischemic CVA+Stroke unspecified; Any intracranial bleed

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Intervention or Tool and Comparators	Total N Interventions (N)	Follow-up period	Age	Special Population	Outcomes Assessed
Fosbol, 2012[174]	Retrospective cohort; Inpatient, Outpatient; US; Industry, Non-govt, Non-industry; Good	Arm 1: Aspirin Arm 2: Aspirin; Clopidogrel Arm 3: VKA (Warfarin) Arm 4: Aspirin; VKA (Warfarin) Arm 5: Aspirin; Clopidogrel; VKA (Warfarin)	Total: 7,619; Arm 1. 2,213 Arm 2. 2,841 Arm 3. 563 Arm 4. 1,271 Arm 5. 731	Unclear/NR	Total: 80 (IQR 74-85) Arm 1 80 (IQR 74-86) Arm 2: 80 (IQR 74-86) Arm 3: 80 (IQR 74-85) Arm 4: 80 (IQR 74-85) Arm 5: 78 (IQR 73-82)	None	Major Bleed Composite outcome: CV infarction/stroke, Myocardial infarction, All-cause mortality
Frost, 2002[175]	Retrospective cohort; Inpatient, Outpatient; Europe; Government, Non-govt, Non-industry; Poor	Arm 1: VKA (Warfarin) Arm 2: No oral anticoagulation	Total: 5,124; Arm 1. 1,390 Arm 2. 3,734	Total: 2.31 years	Unclear/NR	None	CV infarction/stroke
Giner-Soriano, 2017[176] ESC-FA (Effectiveness, Safety and Costs in Atrial Fibrillation)	Retrospective cohort; Inpatient, Outpatient, Europe; Government, Non-govt/non-industry, High risk of bias	Arm 1. No antithrombotic Arm 2. Antiplatelets Arm 3. VKAs	Total: 22,205; Arm 1. 5,724 Arm 2. 7,424 Arm 3. 9,057	The total person-time during the follow-up was 44,370.2 PY	Total: 72.8 (SD: 13.1) Arm 1. 69.6 (SD: 16.4) Arm 2. 74.6 (SD: 12.9) Arm 3. 73.4 (SD: 10.3)	None	Cerebral Hemorrhage, Gastrointestinal Hemorrhage, All-cause mortality, Stroke

Giugliano 2013[32] ENGAGE AF-TIMI 48 Companions: Steffel, 2016[177], Rost, 2016[178], Bohula, 2016[179], Magnani, 2016[180], Gupta, 2016[34], Xu, 2016[181], Yamashita, 2016[182], Eisen, 2016[183], Geller, 2015[184], Ruff, 2015[185], O'Donoghue, 2015[186], Ruff, 2014[187], Giugliano, 2014[188]	RCT; Inpatient, Outpatient; US, Canada, UK, Europe, S. America, C. America, Asia, Africa, Australia/NZ; Industry; Low risk of bias	Arm 1: Warfarin (INR 2.0 – 3.0) Arm 2: Endoxaban (high dose) Arm 3: Endoxaban (low dose)	Total: 21,105; Arm 1. 7036 Arm 2. 7035 Arm 3. 7034	Median: 2.8 years	Arm1: 72 (IQR 64-78) Arm2: 72 (IQR 64-78) Arm 3: 72 (IQR 64-78)	None Subgroups: analyses: Patients at increased fall risk, Patients with prior cerebrovascular events, Varying degrees of renal function, heart failure, concomitant antiplatelet use, East Asia, FDA approved indication, subsets of systemic embolic events, subsets of cerebrovascular disease, dose reduction status, prior VKA use, post trial open label use.	Cerebrovascular infarction TIA Systemic embolism Hemorrhagic stroke Intracerebral hemorrhage Extracranial hemorrhage Major bleed Minor bleed Mortality All-cause mortality Cardiovascular mortality Myocardial infarction Infection Heart block Esophageal fistula Cardiac tamponade Dyspepsia Health-related quality of life Functional capacity Subset analyses: Magnani, 2016[180]: CV hospitalization Geller, 2015[184]: Fatal or nonfatal SEE Ruff, 2014[187]:30 day open label stroke, bleeding or death
Gloekler, 2015[189]	Prospective cohort; Outpatient; Europe; Unclear/NR;	Arm 1: Amplatzer cardiac plug Arm 2: Amulet	Total: 100; Arm 1: 50 Arm 2: 50	Arm 1: 127 (SD: 46) Arm 2: 105 (SD: 48)	Arm 1: 72.5 (SD: 11.5) Arm 2: 75.6 (SD: 9.7)	None	Procedural success Stroke All-cause mortality Cardiac tamponade

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Intervention or Tool and Comparators	Total N Interventions (N)	Follow-up period	Age	Special Population	Outcomes Assessed
	High risk of bias						Bailout by surgery
Go, 2017[190] The Sentinel program	Retrospective cohort; Claims Database US; Government; Low risk of bias	Arm 1. Dabigatran Arm 2. Warfarin	Total: 50,578; Arm 1. 25,289 Arm 2. 25,289	Arm 1: 123 days (SD: 149) Arm 2: 102 days (SD: 119)	Arm 1: 68.48 (SD: 10.91) Arm 2: 68.34 (SD: 11.11)	None	Ischemic stroke; Intracranial bleeding; All strokes; GI bleeding; Myocardial infarction
Gorst-Rasmussen, 2016[191] Danish National Patient Registry	Prospective cohort/registry; Inpatient, Outpatient; Europe, Unclear/NR; Low risk of bias	Arm1. Warfarin (any dose) Arm 2. Dabigatran 110mg Arm 3. Dabigatran 150mg bid Arm 4. Rivaroxaban 15mg Arm 5. Rivaroxaban 20mg qday	Total: 22,358; Arm 1. 11,045 Arm 2. 8,908 Arm 3. 8,908 Arm 4. 2,405 Arm 5. 2,405	Total: 1.08 years (IQR 0.52-1.72)	Arm 1. 72.6 (SD: 11.3) Arm 2. 80.8 (SD: 8.0) Arm 3. 66.0 (SD: 8.5) Arm 4. 82.8 (SD: 8.7) Arm 5. 72.8 (SD: 9.9)	None	ischemic stroke/systemic embolism (SE)/transient ischemic attack (TIA) any bleeding (intracranial bleeding, gastrointestinal, major bleeding events) all-cause death. intracranial bleeding gastrointestinal bleeding myocardial infarction venous thromboembolism

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Intervention or Tool and Comparators	Total N Interventions (N)	Follow-up period	Age	Special Population	Outcomes Assessed
Graham, 2015[192] Medicare database	Retrospective cohort; Inpatient, Outpatient; US; Government; Low risk of bias	Arm 1. Warfarin Arm 2. Dabigatran	Arm 1. 67,207 Arm 2. 67,207	Unclear/NR	Arm 1. Warfarin: 65–74 years 41% 75–84 43% ≥85 16% Arm 2. Dabigatran: 65–74 years 42% 75–84 43% ≥85 16%	Age ≥ 65 years old	Ischemic stroke, Major bleeding with specific focus on intracranial and gastrointestinal bleeding AMI All hospitalized bleeding events Mortality
Graham, 2016[193]	Prospective cohort; Unclear/NR, US; Government; Low risk of bias	Arm 1. Dabigatran 150 mg twice daily Arm 2. Rivaroxaban 20 mg once daily.	Arm 1: 52,240 Arm 2: 66,651	Arm 1. Dabigatran mean 108 days (0-969) Arm 2. Rivaroxaban mean 111 days (0-923)	65-74: 50% 75-84: 40% ≥85: 9%	Age ≥ 65 with Medicare	Thromboembolic stroke Intracranial hemorrhage Major gastrointestinal bleeding Death Acute myocardial infarction

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Intervention or Tool and Comparators	Total N Interventions (N)	Follow-up period	Age	Special Population	Outcomes Assessed
Granger, 2011[37] ARISTOTLE Companions: Easton, 2012[194]; Hohnloser, 2012[195]; Lopes, 2012[196]; Lopes, 2010[197]* 2017 Includes KQ3 Papers: Lopes, 2017[198]; Cowper, 2017[199]; Westenbrink, 2017[200]; Hu 2017[201]; Guimaraes, 2017[202]; Bahit, 2017[203]; Alexander, 2016[204]; Hijazi, 2016[205]; De Caterina, 2016[206]; Durheim, 2016[207]; Vinereanu, 2015[208]; Avezum, 2015[209]; Ezekowitz, 2015[210]; Held, 2015[211]; Hylek, 2014[212]; Halvorsen, 2014[213]; Alexander, 2014[214]; Wallentin, 2013[215]; Al-Khatib, 2013[216]; Rao, 2017[217]; Vinereanu, 2017[39]; Melloni, 2017[218]	RCT; Unclear/NR; US, Canada, Europe, Asia, Australia/NZ; Industry; Good	Arm 1: Apixaban Arm 2: VKA (Warfarin) Alexander, 2014[214]: Arm 1: Aspirin Arm 2: No aspirin	Total: 18,201 Alexander, 2014[214]: Arm 1. 4,434 Arm 2. 13,699	Total: ~2 years	Arm 1: 70 (IQR 63-76) Arm 2: 70 (IQR 63-76)	None Avezum,2015[209]: h/o moderate to severe valve disease or previous valve surgery	Ischemic stroke CV infarction/stroke Intracerebral hemorrhage Systemic embolism All-cause mortality Myocardial infarction Major bleed Clinically relevant nonmajor bleeding Intracranial bleeding Subdural bleeding Hemorrhagic stroke Cerebrovascular infarction CV mortality Composite outcomes (includes a combination of outcomes above)

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Intervention or Tool and Comparators	Total N Interventions (N)	Follow-up period	Age	Special Population	Outcomes Assessed
Halvorsen, 2017[219] Norwegian Patient Registry (NPR) and the Norwegian Prescription Database	Prospective cohort/registry,; Inpatient, Outpatient, Norway; Industry; High risk of bias	Arm 1. Warfarin Arm 2. Dabigatran Arm 3. Rivaroxaban Arm 4. Apixaban	Total: 32,675; Arm 1. 11,427 Arm 2. 7,925 Arm 3. 6,817 Arm 4. 3,579	Total: 173 days (IQR 84–340)	Total: 73.6 Arm 1. 74.6 (SD: 11.9) Arm 2. 70.8 (SD: 11.3) Arm 3. 74.7 (SD: 10.7) Arm 4. 74.5 (SD: 11.1)	None	Gastrointestinal bleeding Renal bleeding Intracranial bleeding Non-major bleeding (minor)
Hansen, 2010[220]	Retrospective cohort; Outpatient; Europe; Industry; Good	Arm 1: VKA (Warfarin) Arm 2: Aspirin Arm 3: Clopidogrel Arm 4: Clopidogrel; Aspirin Arm 5: VKA (Warfarin); Aspirin Arm 6: VKA (Warfarin); Clopidogrel Arm 7: VKA (Warfarin); Clopidogrel; Aspirin	Total: 118,606; Arm 1. 50,919 Arm 2. 47,541 Arm 3. 3,717 Arm 4. 2,859 Arm 5. 18,345 Arm 6. 1,430 Arm 7. 1,261	Total: 3.3 years (SD: 2.6)	Total: 73.7 (SD: 12.3)	None	Major bleed

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Intervention or Tool and Comparators	Total N Interventions (N)	Follow-up period	Age	Special Population	Outcomes Assessed
Hart, 2008[221] CHARISMA	RCT; Unclear/NR; US; Industry; Good	Arm 1: Clopidogrel; Aspirin Arm 2: Aspirin	Total: 583; Arm 1 (298) Arm 2 (285)	Total: 2.3 years	Total: 70	None	Ischemic stroke Intracerebral hemorrhage Myocardial infarction CV mortality All-cause mortality Healthcare utilization - Hospital admissions Composite outcome: Intracerebral hemorrhage, Ischemic stroke Composite outcome: Myocardial infarction, CV mortality, Ischemic stroke Composite outcome: Cerebrovascular infarction, Intracerebral hemorrhage, Myocardial infarction, CV mortality, Healthcare utilization – Hospital admissions

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Intervention or Tool and Comparators	Total N Interventions (N)	Follow-up period	Age	Special Population	Outcomes Assessed
Hernandez, 2017[222] US Medicare claims data	Retrospective cohort; Claims Database; US; Government, Industry; Moderate risk of bias	Arm 1. Apixaban Arm 2. Dabigatran Arm 3. Rivaroxaban Arm 4. Warfarin Arm 5. No oral anticoagulant	Total: 41,366 Arm 1: 2358 Arm 2: 1415 Arm 3: 5139 Arm 4: 12,353 Arm 5: 20,101	Arm 1. 185 days (SD: 140) Arm 2. 294 days (SD: 192) Arm 3. 255 days (SD: 181) Arm 4. 274 days (SD: 187) Arm 5. 274 days (SD: 226)	Arm 1. 77.4 (SD: 8.6) Arm 2. 74.9 (SD: 8.7) Arm 3. 76.4 (SD: 8.6) Arm 4. 76.0 (SD: 10.3) Arm 5. 78.0 (SD: 11.0)	None	Stroke, SE, death; Ischemic stroke; all-cause mortality; Any bleeding event; intracranial bleeding; GI bleeding
Hohnloser, 2017[223] CARBOS study	Retrospective cohort; Unclear/NR; Europe; Industry, Non-govt, Non-industry; Low risk of bias	Arm 1. VKA Arm 2. Apixaban Arm 3. Dabigatran Arm 4. Rivaroxaban	Total: 35,013; Arm 1. 16,179 Arm 2. 3,633 Arm 3. 3,138 Arm 4. 12,063	Arm 1. 280 days Arm 2. 218 days Arm 3. 261 days Arm 4. 258 days	Arm 1. 76.1 (SD:9.1) Arm 2. 75.5 (SD: 10.8) Arm 3. 72.6 (SD: 11.2) Arm 4. 73.4 (SD: 11.3)	None	Major bleeding (ED admission) GIB Any bleeding Composite: ischemic CVA + systemic embolism +major bleeding
Hohnloser, 2018[224]	Retrospective cohort; outpatient; Europe; Industry; Low risk of bias	Arm 1. Phenprocoumon Arm 2. Apixaban Arm 3. Dabigatran Arm 4. Rivaroxaban	Total: 74,764; Arm 1. 23,823 Arm 2. 10,117 Arm 3. 5,122 Arm 4. 22,143	Arm 1. 362 days (SD:275) Arm 2. 306 days (SD: 239) Arm 3. 339 days (SD: 317) Arm 4. 340 days (SD: 284)	Arm 1. 75.2 (SD: 9.5) Arm 2. 74.5 (SD: 11.4) Arm 3. 71.7 (SD: 11.6) Arm 4. 72.1 (SD: 11.8)	None	Composite: Stroke (ischemic or hemorrhagic), Stroke/SE, Ischemic stroke, Hemorrhagic stroke, All-cause mortality, major bleeding events, intracranial bleeding, GI bleeding, Any bleeding

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Intervention or Tool and Comparators	Total N Interventions (N)	Follow-up period	Age	Special Population	Outcomes Assessed
Holmes, 2009[225] PROTECT-AF Companions: Viles-Gonzalez, 2012[226] Fountain, 2006[227]* Reddy, 2014[228], Alli, 2013[229], Reddy, 2013[230]; Reddy, 2017[231]	RCT; Inpatient; US, Europe; Industry; Good	Arm 1: Transcatheter: WATCHMAN Arm 2: VKA (Warfarin)	Total: 707; Arm 1. 463 Arm 2. 244	Arm 1: 18 months (SD: 10) Arm 2: 18 months (SD: 10)	Arm 1: 71.7 (SD: 8.8) Arm 2: 72.7 (SD: 9.2)	None	Ischemic stroke CV mortality Intracerebral hemorrhage All-cause mortality Composite outcome: Systemic embolism, CV infarction/stroke, Intracerebral hemorrhage, CV mortality Composite outcome: Major bleed, Minor bleed
Holmes, 2014[232] PREVAIL	RCT; Outpatient; US; Industry; Fair	Arm 1: WATCHMAN device Arm 2: Warfarin (Control)	Total: 407	Total: 11.8 months (SD: 5.8)	Arm 1: 74 (SD: 7.4) Arm 2: 74.9 (SD: 7.2)	None	Composite outcome: Hemorrhagic or ischemic stroke, SE, and cardiovascular/ unexplained Death Composite outcome: Ischemic stroke or SE Composite outcome: All-cause death, ischemic stroke, SE, or device-procedure-related events
Hylek, 2003[46] ATRIA	Retrospective cohort; Outpatient; US; Government; Good	Arm 1: No antithrombotic therapy Arm 2: Aspirin Arm 3: VKA (Warfarin)	Total: 596; Arm 1. 248 Arm 2. 160 Arm 3. 188	Unclear/NR	Arm 1: 79 Arm 2: 80 Arm 3: 76	Patients with prior stroke	All-cause mortality

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Intervention or Tool and Comparators	Total N Interventions (N)	Follow-up period	Age	Special Population	Outcomes Assessed
Jain, 2018[233] HealthCore Integrated Research Database (HIRD)	Retrospective cohort; Inpatient, Outpatient; US; Industry; Low risk of bias	Arm 1. Dabigatran Arm 2. Warfarin	Arm 1. 824 Arm 2. 824	Total: 12 months	Arm 1. 64 (SD: 11.6) Arm 2. 64 (SD: 11.9)	None	Health care resource utilization (HCRU); HCRU-associated costs
Johnson, 2016[234] Clinical Practice Research Datalink (CPRD)	Retrospective cohort; Primary Care; U.K. Industry; High risk of bias	Arm 1. Apixaban Arm 2. Rivaroxaban Arm 3. Dabigatran Arm 4. VKA	Total: 13,089; Arm 1. 541 Arm 2. 1,589 Arm 3. 741 Arm 4. 10,218	Arm 1. 4 months (IQR 2.1-7.3) Arm 2. 5.8 months (IQR 2.6-11.0) Arm 3. 9.4 months (IQR 4.2-15.6) Arm 4. 10.3 months (IQR 5.0-15.9)	Total: 75.0 (IQR 68.0–82.0)	None	Bleeding outcomes; Long-term adherence to therapy (Persistence)
Laliberte, 2014[235]	Retrospective cohort; inpatient, outpatient; US; Industry, Non-govt, Non-industry; Low risk of bias	Arm 1: Rivaroxaban Arm 2: Warfarin	Total: 18,270; Arm 1. 3,654 Arm 2. 14,616	Arm 1: 83 Days (SD: 58) Arm 2. 113 days (SD: 70)	Arm 1. 73.3 (SD: 8.4) Arm 2. 73.7 (SD: 8.3)	None	Medication persistence (gap < 60D) Intracranial hemorrhage GI bleeding Ischemic CVA Hemorrhagic CVA Systemic embolism Composite: major bleed; CVA + systemic embolism

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Intervention or Tool and Comparators	Total N Interventions (N)	Follow-up period	Age	Special Population	Outcomes Assessed
Laliberte, 2015[236] Humana database	Retrospective cohort; Inpatient, Outpatient, Emergency Room; US; Industry; Low risk of bias	Arm 1. Warfarin Arm 2. Rivaroxaban	Arm 1. 2,253 Arm 2. 2,253	Arm 1. Warfarin 123.7 days (SD: 91.4) Arm 2. Rivaroxaban 114.0 days (SD: 93.9)	Arm 1. Warfarin 74.5 (SD: 8.7) Arm 2. Rivaroxaban 74.2 (SD: 9.0)	None	Total number of hospitalization days All-cause and AF related: Hospitalizations ED visits Outpatient visits
Lamberts, 2017[237] Danish Patient Registry	Retrospective cohort/Registry; Unclear/NR; Denmark; Industry High risk of bias	Arm 1. Apixaban Arm 2. Rivaroxaban Arm 3. Dabigatran Arm 4. Warfarin	Total: 54,321; Arm 1. 7,963 Arm 2. 6,715 Arm 3. 15,413 Arm 4. 24,230	Total patient-time at-risk 67,764 PY. per patient 403 days	Total: 73 (IQR, 66-81) Arm 1. 76 (68-84) Arm 2. 74 (67-83) Arm 3. 71 (65-79) Arm 4. 73 (65-80)	None	Gastrointestinal bleeding Renal bleeding Intracranial bleeding
Larsen, 2014[238]	Retrospective cohort; Inpatient; Europe; Unclear/NR; Low risk of bias	Sub-Study 1: VKA naïve Arm 1. Warfarin Arm 2. Dabigatran 110mg Arm 3. Dabigatran 150mg Sub-Study 2: VKA experienced Arm 1. Warfarin Arm 2. Dabigatran 110mg Arm 3. Dabigatran 150mg	Total: 6,141; Sub-Study 1: Arm 1. 1,825 Arm 2. 793 Arm 3. 646 Sub-Study 2: Arm 1. 1,918 Arm 2. 547 Arm 3. 412	Total: 12.6 months (SD: 4.5)	Sub-Study 1: Arm 1. 76 (IQR 69-82) Arm 2. 83 (IQR 78-87) Arm 3. 69 (IQR 64-74) Sub-Study 2: Arm 1. 75 (IQR 69-82) Arm 2. 82 (IQR 78-86) Arm 3. 70 (IQR 64-74)	None	CVA TIA Composite: CVA + TIA

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Intervention or Tool and Comparators	Total N Interventions (N)	Follow-up period	Age	Special Population	Outcomes Assessed
Larsen, 2014[239]	Retrospective cohort; Unclear/NR; Europe; Unclear/NR; High risk of bias	Sub-Study 1: VKA naïve stratum Arm 1. Dabigatran 110 mg Arm 2. Dabigatran 150 mg Arm 3. Warfarin Sub-Study 2: VKA experienced stratum: Arm 1. Dabigatran 110mg Arm 2. Debigatran 150 mg Arm 3. Warfarin	Sub-Study 1: Arm 1. 3,045 Arm 2. 4,018 Arm 3. 14,126 Sub-Study 2: Arm 1. 2,038 Arm 2. 2,214 Arm 3. 8,504	Total: 13.2 months (SD: 6.1)	Sub-Study 1 Arm 1. 82 Arm 2. 67 Arm 3. 73 Sub-Study 2: Arm 1. 82 Arm 2. 69 Arm 3. 74	None	Any bleeding Major bleeding Intracranial bleeding (including retinal bleeding and traumatic intracranial bleeding) Gastrointestinal bleeding Fatal bleeding
Larsen, 2016[240] Danish National Patient Registry	Prospective cohort/registry; Inpatient, Outpatient; Europe, Non-govt, Non-industry; Low risk of bias	Arm 1. Warfarin Arm 2. Dabigatran 150mg bid Arm 3. Rivaroxaban 20mg qday Arm 4. Apixaban 5mg bid	Total: 61,678; Arm 1. 35,436 Arm 2. 12,701 Arm 3. 7,192 Arm 4. 6,349	Total mean: 1.9 years Apixaban, mean: 0.9 years	Total: 70.9 (IQR 64.3-77.7) Arm 1. 72.4 (IQR 64.7-79.8) Arm 2. 67.6 (IQR 62.0-72.4) Arm 3. 71.8 (IQR 65.7-78.9) Arm 4. 71.3 (IQR 65.8-77.2)	None	Ischaemic stroke or systemic embolism Ischaemic stroke All cause mortality Ischaemic stroke, systemic embolism, or death Any bleeding Major bleeding Intracranial bleeding

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Intervention or Tool and Comparators	Total N Interventions (N)	Follow-up period	Age	Special Population	Outcomes Assessed
Larsen, 2014[241] Danish National Patient Registry	Prospective cohort/registry; Inpatient, Outpatient; Europe, Non-govt, Non-industry; Low risk of bias	Sub-Study 1: VKA naïve Arm 1. Dabigatran 110mg Arm 2. Dabigatran 150mg Arm 3. Warfarin Sub-Study 2: VKA experienced Arm 1. Dabigatran 110mg Arm 2. Dabigatran 150mg Arm 3. Warfarin	Sub-Study 1: Arm 1. 2,124 Arm 2. 2,694 Arm 3. 8,133 Sub-Study 2: Arm 1. 1,554 Arm 2. 1,825 Arm 3. 49,868	Total: 16 months (SD: 4.6)	Sub-Study 1: Arm 1. 82 (IQR 76-86) Arm 2. 68 (IQR 63-72) Arm 3. 72 (IQR 65-80) Sub-Study 2: Arm 1. 82 (IQR 77-86) Arm 2. 69 (IQR 64-74) Arm 3. 75 (IQR 68-81)	None	Myocardial ischemic events: MI, Unstable angina, Cardiac arrest Composite: Myocardial ischemic events, Fatal myocardial ischemic events
Lauffenburger, 2015[242] Truven Health MarketScan Commercial Claims and Encounters and Medicare supplement databases	Retrospective cohort; Inpatient, Outpatient; US Government, Non-govt, Non-industry; Low risk of bias	Arm 1. Warfarin Arm 2. Dabigatran	Arm 1. 43,865 Arm 2. 64,935	Total: 358 days (SD: 224)	Total: 69.9 (SD: 12.4)	None	Composite of the occurrence of ischemic stroke, TIA, and other thromboembolic events; Composite of intracranial hemorrhage or hemorrhagic stroke, gastrointestinal (GI) hemorrhage, or other bleeding; MI.
Lee, 2016[243]	RCT; Inpatient, US; Unclear/NR; Poor	Arm 1: Internal ligation Arm 2: Stapled excision Arm 3: Surgical excision	Total: 28	Total: 0.4 years (SD: 0.1)	Arm 1: 69 (SD: 7.0) Arm 2: 67.9 (SD: 8.9) Arm 3: 66.9 (SD: 7.3)	None	Systemic embolism (excludes PE and DVT) Hemorrhagic stroke Major bleed Mortality

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Intervention or Tool and Comparators	Total N Interventions (N)	Follow-up period	Age	Special Population	Outcomes Assessed
Lee, 2017[244] Danish Patient Registry	Prospective cohort/registry; Unclear/NR Europe; Unclear/NR High risk of bias	Arm 1. VKA Arm 2. ASA Arm 3. VKA + ASA	Total: 71,959; Arm 1. 37,539 Arm 2. 25,458 Arm 3. 8,962	Total median: 4.1 years	Total median: 75 years	All Danish residents hospitalized with first-time AF and without a history of CAD	Myocardial Infarction Stroke Bleeding
Leef, 2015[245]	Retrospective cohort; Inpatient, Outpatient; US; Unclear/NR; Low risk of bias	Arm 1. Warfarin Arm 2. NOAC (includes Dabigatran, Rivaroxaban, and Apixaban	Arm 1: 554 Arm 2: 554 (Dabigatran, n=475 Rivaroxaban, n=123 Apixaban, n=8)	Total median: 42.5 months	Arm 1. Warfarin: 63.6 (SD: 12.1) Arm 2. NOAC: 64.3 (SD: 11.4)	None	All-cause mortality; Stroke (combined ischemic, hemorrhagic, and unspecified)
Li, 2017[246] Truven MarketScan®; IMS PharMetrics Plus; Optum Clinformatics™; Humana Research Database	Retrospective cohort; Inpatient, Outpatient, Emergency Room; US, Unclear/NR; Low risk of bias	Arm 1. Apixaban Arm 2. Warfarin	Arm 1: 38,470 Arm 2: 38,470	Restricted to 1 year follow-up	Arm 1. Apixaban 70.9 (SD: 12.0) Arm 2. Warfarin 70.9 (SD: 11.9)	None	Stroke/SE Hemorrhagic stroke Ischemic stroke SE Major bleeding ICH GI bleeding Other bleeding

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Intervention or Tool and Comparators	Total N Interventions (N)	Follow-up period	Age	Special Population	Outcomes Assessed
Li, 2018[247]	Retrospective cohort; Claims Database; US; Industry; Low risk of bias	Sub-Study 1: Arm 1. Apixaban 5 mg Arm 2. Warfarin Sub-Study 2: Arm 1. Apixaban 2.5 mg Arm 2. Warfarin	Total: 115,186 Sub-Study 1: Arm 1. 31,827 Arm 2. 31,827 Sub-Study 2: Arm 1. 6,600 Arm 2. 6,600	Sub-Study 1: Arm 1. 179.4 days (SD: 163.2 Arm 2. 199.5 days (SD: 194.8) Sub-Study 2: Arm 1. 179.1 days (SD: 163.1) Arm 2. 204.4 days (SD: 192.6)	Sub-Study 1: Arm 1. 68.6 (SD: 11.0) Arm 2. 69.2 (SD: 11.7) Sub-Study 2: Arm 1. 82.5 (SD: 9.5) Arm 2. 80.1 (SD: 8.5)	None	Stroke/SE; Ischemic stroke, hemorrhagic stroke, Systemic embolism; Major bleeding events; GI bleeding, intracranial hemorrhage
Lin, 2017[248] IMS Pharmetrics Plus database.	Retrospective cohort; Inpatient, Outpatient; US; Industry, Non-govt, Non-industry; Low risk of bias	Sub-Study 1: Arm 1: Apixaban Arm 2: Rivaroxaban Sub-Study 2: Arm 1: Apixaban Arm 2: Dabigatran Sub-Study 3: Arm 1: Apixaban Arm 2: Warfarin	Total: 23,186; Sub-Study 1: 8,124 Sub-Study 2: 5,368 Sub-Study 3: 9,694	Sub-Study 1 Arm 1. 4.5 months (SD:4.3) Arm 2. 4.5 months (SD: 4.5) Sub-Study 2 Arm 1. 5.2 months (SD: 5.1) Arm 2. 5.0 months (SD: 5.2) Sub-Study 3 Arm 1. 4.9 months (SD: 4.9) Arm 2. 4.8 months (SD: 4.8)	Sub-Study 1 Arm 1. 62.0 (SD: 8.5) Arm 2. 62.0 (SD: 8.4) Sub-Study 2 Arm 1. 63.0 (SD: 9.2) Arm 2. 63.0 (SD: 9.3) Sub-Study 3 Arm 1. 63.9 (SD: 9.5) Arm 32. 64.0 (SD: 9.4)	None	Inpatient hospitalization Outpatient office visit Outpatient prescription claims Major bleed (includes GI, intracranial hemorrhage and other major bleeds)

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Intervention or Tool and Comparators	Total N Interventions (N)	Follow-up period	Age	Special Population	Outcomes Assessed
Lip, 2015[249] Danish Patient Registry	Retrospective cohort; Inpatient, Outpatient; Europe; Non-govt, Non-industry; High risk of bias	Arm 1: No treatment Arm 2: Aspirin Arm 3: Warfarin	Total: 49,916; Arm 1: 43,092 Arm 2: 3,006 Arm 3: 3,818	Total: 5.68 (SD: 4.48) Arm 1: 5.77 (SD: 4.47) Arm 2: 5.69 (SD: 4.44) Arm 3: 4.72 (SD: 4.51)	Total: 60 (IQR 53-67) Arm 1: 60 (IQR 52-66) Arm 2: 62 (IQR 57-68) Arm 3: 62 (IQR 57-68)	Patients with none or one risk factor only	Ischemic stroke Intracerebral hemorrhage Major bleeding Myocardial infarction All cause mortality
Lip, 2015[250] Danish Patient Registry	Retrospective cohort; Inpatient, Outpatient; Europe; Non-govt, Non-industry; High risk of bias	Arm 1: Warfarin Arm 2: Aspirin Arm 3: No Treatment	Total: 39.400	Total: 5.9 years	Total: 59 (51-65)	None	Stroke Ischemic stroke Intracranial bleeding All-cause mortality
Lip, 2016[251] Truven Health Analytics MarketScan database	Retrospective cohort; Inpatient; U.S.; Industry; High risk of bias	Arm 1. Apixaban Arm 2. Dabigatran Arm 3. Rivaroxaban Arm 4. Warfarin	Total: 29,338; Arm 1. 2,402 Arm 2. 4,173 Arm 3. 10,050 Arm 4. 12,713	Arm 1. 90.37 days (SD: 72.06) Arm 2. 126.74 days (SD: 102.54) Arm 3. 117.71 days (SD: 97.17) Arm 4. 127.55 days (SD: 102.09)	Arm 1. 69.34 (SD: 12.33) Arm 2. 66.83 (SD: 12.17) Arm 3. 67.33 (SD: 12.25) Arm 4. 72.53 (SD: 11.88)	None	Ischemic stroke; Major bleed

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Intervention or Tool and Comparators	Total N Interventions (N)	Follow-up period	Age	Special Population	Outcomes Assessed
Lip, 2016[252]	Retrospective cohort; Unclear/NR; US; Unclear/NR; Low risk of bias	Sub-Study 1 Arm 1. Warfarin Arm 2. Apixaban Sub-Study 2: Arm 1. Warfarin Arm 2. Dabigatran Sub-Study 3: Arm 1. Warfarin Arm 2. Rivaroxaban Sub-Study 4: Arm 1. Apixaban Arm 2. Dabigatran Sub-Study 5: Arm 1. Apixaban Arm 2. Rivaroxaban Sub-Study 6: Arm 1. Dabigatran Arm 2. Rivaroxaban	Sub-Study 1: 13,928 (6,964 per arm) Sub-Study 2: 9,030 (4,515 per arm) Sub-Study 3: 25,250 (12,625 per arm) Sub-Study 4: 8,814 (4,407 per arm) Sub-Study 5: 14,798 (7,399 per arm) Sub-Study 6: 9,314 (4,657 per arm)	In days. Sub-Study 1: Arm 1. 161.6 (SD: 159.0) Arm 2. 14.8.1 (SD: 138.0) Sub-Study 2: Arm 1. 160.5 (SD: 159.7) Arm 2. 178.1 (SD: 179.3) Sub-Study 3: Arm 1. 162.7 (SD: 160.8) Arm 2. 177.9 (SD: 171.5) Sub-Study 4 Arm 1. 145.6 (SD: 136.5) Arm 2. 179.0 (SD: 179.1) Sub-Study 5: Arm 1. 147.6 (SD: 137.6) Arm 2. 182.1 (SD: 174.9) Sub-Study 6: Arm 1. 177.3 (SD: 178.7) Arm 2. 172.5 (SD: 169.5)	Sub-Study 1: Arm 1. 69 (SD: 12.3) Arm 2. 69.1 (SD: 12.3) Sub-Study 2: Arm 1. 67.5 (SD: 12.3) Arm 2. 66.9 (SD: 12.2) Sub-Study 3: Arm 1. 70.1 (SD: 12.0) Arm 2. 69.7 (SD: 11.9) Sub-Study 4: Arm 1. 67.0 (SD: 12.3) Arm 2. 66.9 (SD: 12.2) Sub-Study 5: Arm 1. 68.4 (SD: 12.4) Arm 2. 68.3 (SD: 12.2) Sub-Study 6: Arm 1. 66.5 (SD: 12.4) Arm 2. 66.3 (SD; 12.3)	None	Major bleeding (definition: requiring hospitalization)

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Intervention or Tool and Comparators	Total N Interventions (N)	Follow-up period	Age	Special Population	Outcomes Assessed
Lip, 2017[253] Danish National Prescription Registry	Prospective cohort/registry; Unclear/NR Europe; Unclear/NR; Low risk of bias	Arm 1. Apixaban 5mg bid Arm 2. Dabigatran 150mg bid Arm 3. Rivaroxaban 20mg day Arm 4. Warfarin	Total: 14,020; Arm 1. 1,470 Arm 2. 3,272 Arm 3. 1,604 Arm 4. 7,674	Total: 2.6 years (SD: 1.6)	Total: 66.5 (IQR 61.1-70.4) Arm 1. 67.4 (IQR 62.5-70.9) Arm 2. 66.2 (IQR 61.3-69.8) Arm 3. 67.2 (IQR 62.4-70.7) Arm 4. 66.2 (IQR 60.5-70.4)	Patients with 1 nonsex-related stroke risk factor that was assigned 1 point in the CHA2DS2-VASc score	Ischemic stroke/SE All-cause death Any bleeding
Loo, 2018[254] Clinical Practice Research Datalink (CPRD)	Retrospective cohort; outpatient; UK; Government, Non-govt, Non-industry; Low risk of bias	Sub-Study 1: All patients with NVAF: Arm 1. NOAC Arm 2. VKAs Sub-Study 2: Patients with NVAF + CKD: Arm 1. NOAC Arm 2. VKAs	Total: 18,666; Sub-Study 1: 6,731 per arm Sub-Study 2: 2,596 per arm	Unclear/NR	All patients with NVAF: NOAC: 74.91 (SD: 10.29) VKAs: 74.91 (SD: 10.29) Patients with NVAF + CKD: NOAC: 77.62 (SD: 8.49) VKAs: 77.62 (SD: 8.49)	Patients with NVAF + CKD are stratified	Composite outcome: Ischemic stroke/SE; Major bleeding event; GI bleeding, Intracranial bleeding; Myocardial infarction; All-cause mortality
Lorenzoni, 2004[255] CLAAF	RCT; Outpatient; Europe; Industry; Fair	Arm 1: VKA (Warfarin) Arm 2: Clopidogrel; Aspirin	Total: 30; Arm 1. 14 Arm 2. 16	Arm 1: 3 months Arm 2: 3 months	Arm 1: Median 72 Arm 2: Median 68	None	Composite outcome: Major bleed, minor bleed

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Intervention or Tool and Comparators	Total N Interventions (N)	Follow-up period	Age	Special Population	Outcomes Assessed
Mant, 2007[256] BAFTA Companions: Hobbs, 2011[257] Mant, 2003[258]* Mavaddat, 2014[259]	RCT; Inpatient; UK; Non-govt, Non-industry; Good	Arm 1: VKA (Warfarin) Arm 2: Aspirin	Total: 973; Arm 1. 488 Arm 2. 485	Total: 2.7 years (SD: 1.2)	Arm 1: 81.5 (SD: 4.3) Arm 2: 81.5 (SD: 4.2)	None	Ischemic stroke Intracerebral hemorrhage Systemic embolism Major bleed All-cause mortality Composite outcomes (includes a combination of the above outcomes)
Mar Contreras Muruaga, 2017[260] ALADIN	Cross-sectional; Unclear/NR; Europe; Industry; Low risk of bias	Arm 1: VKA Arm 2: DOAC (Rivaroxaban, Apixaban, Dabigatran)	Total: 1,337; Arm 1. 750 Arm 2. 587	Total: 36.7 months (SD: 48.5) Arm 1. 52.28 months Arm 2. 17.07 months	Total: 75.0 (SD: 8.9) Arm 1. 75.3 (SD: 9.2) Arm 2. 76.1 (SD: 8.5)	None	Health related quality of life.
Martinez, 2016[261] Clinical Practice Research Datalink (CPRD)	Prospective cohort; Outpatient, UK; Unclear/NR; Low risk of bias	Arm 1. VKAs: includes acenocoumarol, phenindione or warfarin Arm 2. NOACs: includes apixaban, dabigatran or rivaroxaban	Arm 1: 12,307 Arm 2: 914	Unclear/NR	Arm 1. VKAs: 74.4 (SD: 10.4) Arm 2. NOACs: 74.5 (SD: 11.3)	None, but results also stratified by risk score	Persistence with OAC, was estimated using competing risk survival analyses accounting for switching of type of OAC and mortality as competing risks
McHorney, 2016[262]	Retrospective cohort; Inpatient; Outpatient; US; Industry; Low risk of bias	(Matched cohorts) Arm 1. Rivaroxaban Arm 2. Apixaban	Arm 1. 2,992 Arm 2. 2,992	Arm 1. 271.8 days (SD: 63.9) Arm 2. 271.5 days (SD: 63.4)	Arm 1. 71.55 (SD: 11.5) Arm 2. 71.84 (SD: 11.5)	None	Long-term adherence to therapy

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Intervention or Tool and Comparators	Total N Interventions (N)	Follow-up period	Age	Special Population	Outcomes Assessed
Monaco, 2017[263] VigiBase	Retrospective cohort; Patient data; Europe; Unclear/NR; High risk of bias	Arm 1: DOACs ROR Arm 2: Rivaroxaban Arm 3: Apixaban Arm 4: Dabigatran	Total: 32,972	Unclear/NR	Total: 75.6 (SD: 10.1)	None	Cerebrovascular infarction Stroke Gastrointestinal hemorrhage Intracerebral hemorrhage Muscular weakness Renal impairment
Mueller, 2017[264]	Retrospective cohort; Inpatient; Europe; Government, Non-govt, Non-industry; Moderate risk of bias	Arm 1: Dabigatran Arm 2: Rivaroxaban Arm 3: Apixaban	Total: 5,398	Total: 228 days (IQR 105-425)	Total: 74.4 (SD: 11.3) Arm 1. 71.6 (SD: 11.8) Arm 2. 75.3 (SD: 10.9) Arm 3. 74.3 (SD: 11.5)	None	Medication persistence
Nelson, 2014[265] Truven Health MarketScan Research Databases	Retrospective cohort; Inpatient, Outpatient; US; Industry, Non-govt, Non-industry; Low risk of bias	Arm 1. Rivaroxaban Arm 2. Warfarin	Total: 14,518; Arm 1. 7,259 Arm 2. 7,259	Arm 1. 184 days Arm 2. 408 days	Arm 1. 71.6 (SD: 11.8) Arm 2. 71.6 (SD: 11.7)	None	Medication persistence (defined as absent refill gap > 60 days)
Nelson, 2015[266]	Retrospective cohort; Inpatient; Outpatient; US; Industry; Low risk of bias	Arm 1. Rivaroxaban Arm 2. Dabigatran	Arm 1. 7,259 Arm 2. 7,259	Arm 1. Mean 184 days Arm 2. Mean 447 days	Arm 1. Mean 71.6 Arm 2. Mean 71.5	None	Medication persistence

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Intervention or Tool and Comparators	Total N Interventions (N)	Follow-up period	Age	Special Population	Outcomes Assessed
Nielsen, 2017[267] Danish National Patient Registry,Other : Danish national prescription registry; Danish civil registration system	Prospective cohort/registry; Inpatient, Outpatient; Europe; Non-govt, Non-industry; Low risk of bias	Arm 1. Warfarin Arm 2. Dabigatran 110mg bid Arm 3. Rivaroxaban 15mg qday Arm 4. Apixaban 2.5mg bid	Total: 55,644; Arm 1. 38,893 Arm 2. 8,875 Arm 3. 3,476 Arm 4. 4,400	Total mean: 2.3 years Apixaban mean: 1 year	Total: 73.9 (SD: 12.7) Arm 1. 71.0 (SD: 12.6) Arm 2. 79.9 (SD: 9.0) Arm 3. 77.9 (SD: 13.5) Arm 4. 83.9 (SD: 8.2)	None, but more older age and renal disease given reduced dosing	Ischaemic stroke/systemic embolism Ischaemic stroke All cause mortality Any bleeding Major bleeding Haemorrhagic stroke
Norby, 2017[268] Truven Health MarketScan® Commercial Claims and Encounters Database and the Medicare Supplemental and Coordination of Benefits Database	Retrospective cohort; Claims Database; US; Government, Non-govt, Non-industry; Low risk of bias	Sub-Study 1 (New users warfarin): Arm 1. Rivaroxaban Arm 2. Warfarin Sub-Study 2 (Switchers): Arm 1. Rivaroxaban Arm 2. Warfarin Sub-Study 3 (New users dabigatran): Arm 1. Rivaroxaban Arm 2. Dabigatran	New users warfarin: Arm 1. 32,495 Arm 2. 45,496 Switchers: Arm 1. 11,845 Arm 2. 43,904 New users dabigatran: Arm 1. 16,957 Arm 2. 16,957	Total: mean of 12 months (median 10.5 months)	New users warfarin: Arm 1. 69.3 (SD: 12.2) Arm 2. 71.1 (SD: 12.5) Switchers: Arm 1. 71.2 (SD: 12.1) Arm 2. 71.4 (SD: 12.0) New users dabigatran: Arm 1. 67.2 (SD: 12.1) Arm 2. 67.2 (SD: 12.1)	None	Ischemic stroke; Intracranial bleeding, GI bleeding; Myocardial infarction

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Intervention or Tool and Comparators	Total N Interventions (N)	Follow-up period	Age	Special Population	Outcomes Assessed
Noseworthy, 2016[269] Optum Labs Data Warehouse	Retrospective cohort; Inpatient, Outpatient; US; Non-govt, Non-industry; Low risk of bias	Sub-Study 1: Arm 1. Rivaroxaban Arm 2. Dabigatran Sub-Study 2: Arm 1. Apixaban Arm 2. Dabigatran Sub-Study 3: Arm 1. Apixaban Arm 2. Rivaroxaban	Total: 57,788; Sub-Study 1: 31,574 (15,787 per arm) Sub-Study 2: 13,084 (6,543 per arm) Sub-Study 3. 13,130 (6565 per arm)	Not available	Sub-Study 1: Arm 1. 70 (IQR 62-78) Arm 2. 71 (IQR 62-78) Sub-Study 2: Arm 1. 73 (IQR 65-81) Arm 2. 73 (IQR 65-81) Sub-Study 3: Arm 1. 73 (IQR 65-81) Arm 2. 73 (IQR 65-81)	None	Ischemic CVA Hemorrhagic CVA Intracranial bleed Major bleed (GI bleed, intracranial, other) Composite: stroke + systemic embolism
Olesen, 2011[62]	Retrospective cohort; Inpatient; Europe; Unclear/NR; Poor	Arm 1: Placebo Arm 2: VKA (unspecified) Arm 3: Aspirin Arm 4: VKA (unspecified); Aspirin	Total: 132,372; Arm 1. 58,883 Arm 2. 37,425 Arm 3. 24,984 Arm 4. 11,080	Total: Max 12 years	Arm 1: 72.8 (SD: 14.4) Arm 2: 70.6 (SD: 11.1) Arm 3: 78.1 (SD: 11.2) Arm 4: 73.1 (SD: 9.6)	None	Diagnostic Accuracy

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Intervention or Tool and Comparators	Total N Interventions (N)	Follow-up period	Age	Special Population	Outcomes Assessed
Paciaroni, 2017[270] RAF-NOACs Study	Prospective cohort; Inpatient, Outpatient, US, UK, Europe, Asia; Industry, Non-govt, Non-industry; Moderate risk of bias	Arm 1: Dabigatran Arm 2: Apixaban Arm 3: Rivaroxaban	Total: 1127; Arm 1: 381 Arm 2: 380 Arm 3: 366	Total: 90 days	Total: 75.6 (SD: 9.9)	None	Combined endpoint: symptomatic hemorrhagic transformation, ischemic stroke, transient ischemic attack (TIA), systemic embolism and severe extracranial bleeding: Stroke, TIA, systemic embolism; Symptomatic hemorrhagic transformation, severe extracranial bleeding; ischemic stroke; TIA; SE; serious extracranial bleeding

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Intervention or Tool and Comparators	Total N Interventions (N)	Follow-up period	Age	Special Population	Outcomes Assessed
Patel, 2011[104] ROCKET-AF Companions: Hankey, 2012[271]; Fox, 2011[272]; Anonymous, 2010[273]*; Orgel, 2017[274]; Shah, 2016[275]; Sherwood, 2016[276]; Vemulapalli, 2016[277]; Fordyce, 2015[278]; DeVore, 2016[279]; Pokorney, 2016[280]; Breithardt, 2016[281]; Sherwood, 2015[105]; Bansilal, 2015[282]; Breithardt, 2014[283]; Halperin, 2014[284]; Piccini, 2014[285]; Hankey, 2014[106]; Goodman, 2014[107]; Mahaffey, 2014[286]; Mahaffey, 2013[287]; van Diepen, 2013[288]; Patel, 2013[289]; Kochar, 2018[290]	RCT; Outpatient; US, Canada, UK, Europe, S. America, Asia, Africa, Australia/NZ; Industry; Good	Arm 1: Rivaroxaban Arm 2: VKA (Warfarin)	Total: 14,264; Arm 1. 7,131 Arm 2. 7,133	Total median: 707 days	Total median: 73	None	Major bleeding; Ischemic stroke; CV infarction/stroke; Systemic embolism; All cause death; CV death; Myocardial infarction; Nonmajor clinically relevant bleeding Composite outcome (includes combinations of multiple outcomes including the above)
Pillarisetti, 2015[291]	Prospective cohort; Inpatient, Outpatient; US; Industry, Non-govt, Non-industry; High risk of bias	Arm 1: Lariat Arm 2: Watchman	Arm 1: 219 Arm 2: 259	Total: 1 year	Arm 1: 74 (SD: 6) Arm 2: 68 (SD: 11)	None	Procedural complications Cardiac tamponade Groin hematoma Hemorrhagic stroke Thromboembolic events

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Intervention or Tool and Comparators	Total N Interventions (N)	Follow-up period	Age	Special Population	Outcomes Assessed
Proietti, 2018[10] SPORTIF III/V	RCT (secondary analysis); Outpatient; US, Canda, UK, Europe, Australia, Asia; Industry; Low risk of bias	Arm 1. ASA non-users (TTR ≥ 65%) Arm 2. ASA users (TTR ≥ 65%) Arm 3. ASA non-users with poor TTR (<65%) Arm 4. ASA users (poor TTR)	Total: 3,624	Total median: 568 days (IQR 493–652)	Total median: 72 (IQR 66–77)	None	Stroke/SE; Major bleeding
Rash, 2007[292] WASPO	RCT; Outpatient; UK; Unclear/NR; Good	Arm 1: VKA (Warfarin) Arm 2: Aspirin	Total: 75; Arm 1. 36 Arm 2. 39	Total: 12 months	Total: 83 (IQR 80-90) Arm 1: 83.5 (IQR 80-90) Arm 2: 82.6 (IQR 80-90)	Permanent AF	All-cause mortality TIA Composite outcome: TIA, Major bleed, Ischemic stroke
Reynolds, 2017[293]	Retrospective cohort; Inpatient, Outpatient, Emergency Room; US; Industry; Low risk of bias	Arm 1. Dabigatran Arm 2. Warfarin	Arm 1. 1,110 Arm 2. 1,110	Total: 12 months	Arm 1. 75.1 (SD: 6.9) Arm 2. 75.0 (SD: 7.0)	None	Healthcare utilization
Schmid, 2013[294]	Prospective cohort; Inpatient; Europe Industry, Non-govt, Non-industry; High risk of bias	Arm 1: Amplatzer NDA Arm 2: ACP device	Total: 64	Total: 7.2 months (SD: 2.7)	Total: 66 (SD: 9)	None	Major bleeding Thrombus Mortality Procedural complications Device embolisation Stroke

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Intervention or Tool and Comparators	Total N Interventions (N)	Follow-up period	Age	Special Population	Outcomes Assessed
Seeger, 2015[295] Two commercial health insurance databases (MarketScan, Truven and Clinformatics, Optum)	Retrospective cohort; Inpatient, Outpatient; US ; Industry; Low risk of bias	Arm 1. Warfarin Arm 2. Dabigatran	Arm 1: 19,189 Arm 2: 19,189	Arm 1. Mean 0.34 years Arm 2. Mean 0.42 years	Arm 1. 68.33 (SD: 12.2) Arm 2. 68.73 (SD: 12.0)	None but entire cohort and by sub-groups by age, gender, and comorbidities	Hospitalization for Haemorrhagic or Ischaemic stroke; major bleeding, Stroke or embolism, Systemic embolism, Ischemic stroke, Hemorrhagic stroke, MI, Major intracranial bleeding, GI bleeding
Seeger, 2017[296] Truven MarketScan	Retrospective cohort; Inpatient, Outpatient; US; Industry, Non-govt, Non-industry; Low risk of bias	Sub-Study 1: Matched in MarketScan Arm 1: Dabigatran Arm 2: Warfarin Sub-Study 2: Matched in Clinformatics Arm 1: Dabigatran Arm 2: Warfarin	Total: 38,378; Sub-Study 1 Arm 1. 15,529 Arm 2. 15,529 Sub-Study 2 Arm 1. 3,660 Arm 2. 3,660	Unclear/NR	Sub-Study 1: Arm 1. 68.7 (SD: 12.0) Arm 2. 68.3 (SD: 12.2) Sub-Study 2: Arm 1. 63.4 (SD: 10.9) Arm 2. 63.1 (SD: 10.9)	None	CVA (hemorrhagic or ischemic) Major bleeding (including intracranial or extracranial)

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Intervention or Tool and Comparators	Total N Interventions (N)	Follow-up period	Age	Special Population	Outcomes Assessed
Shah, 2018[297] Truven Health MarketScan Commercial Claims and Encounters Database and the Medicare supplemental and Coordination of Benefits Database	Retrospective cohort; Claims Database; US; Government, Non-govt, Non-industry; Low risk of bias	Sub-Study1: Arm 1. Rivaroxaban Arm 2. Warfarin Sub-Study 2: Arm 1. Dabigatran Arm 2. Warfarin Sub-Study 3: Arm 1. Apixaban Arm 2. Warfarin Sub-Study 4: Arm 1. Dabigatran Arm 2. Rivaroxaban Sub-Study 5: Arm 1. Rivaroxaban Arm 2. Apixaban	Total: 16,096	Total: 12 months	Rivaroxaban. 73.8 (SD: 10.2) Dabigatran. 74.0 (SD: 10.3) Apixaban. 74.9 (SD: 10.3) Warfarin. 75.4 (SD: 10.1)	Patients with cancer	Ischemic stroke; severe bleeding; other bleeding; VTE
Shireman, 2004[298] Medicaid National Stroke Project	Retrospective cohort; Inpatient; US; Non-govt, Non-industry; Fair	Arm 1: VKA (Warfarin) Arm 2: VKA (Warfarin); Clopidogrel or Aspirin or Ticlopidine	Total: 10,093; Arm 1. 8,131 Arm 2. 1,962	Total: 90 days	Total: 77.2	None	Major bleeding Composite outcome: Intracerebral hemorrhage, Subdural hematoma

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Intervention or Tool and Comparators	Total N Interventions (N)	Follow-up period	Age	Special Population	Outcomes Assessed
Sjogren, 2017[299]	Retrospective cohort; Inpatient, Outpatient; Europe; Government, Non-govt, Non-industry; Low risk of bias	Arm 1. NOAC Arm 2. Warfarin matched and weighted	NOAC: 12,694 Warfarin matched: 12,694	(Mean) NOAC: 299 days (SD: 260) Warfarin matched: 283 days (SD: 257)	NOAC: 72.2 (SD: 10.3) Warfarin matched: 72.3 (SD: 10.3)	None	All-cause stroke/SE; All-cause mortality; Ischemic stroke; Hemorrhagic stroke; Myocardial infarction; Major bleeding events; Intracranial bleeding, GI bleeding, Other bleeding that was fatal or required hospital care.
Song, 2017[300]	Retrospective cohort; Claims Database; US; Industry; Low risk of bias	Arm 1. Dabigatran Arm 2. Warfarin	Arm 1. 18,980 Arm 2. 18,980	Total: 12 months	Arm 1. 67.8 (SD: 11.9) Arm 2. 68.1 (SD: 12.0)	None	All-cause hospitalization, stroke-specific, and bleed-specific Health care resource utilization (HCRU)
Staerk, 2015[301] Danish Patient Registry	Retrospective cohort; Inpatient, Outpatient; Europe; Non-govt, Non-industry; High risk of bias	Arm 1: OAC-naive warfarin Arm 2: OAC-naive dabigatran 110 Arm 3: OAC-naive dabigatran 150 Arm 4: OAC-experienced dabigatran 110 Arm 5: OAC-experienced dabigatran 150	Total: 10,437	Total: 244 days (IQR 105–377)	Total: 71.2 (SD: 11.0)	None	Dyspepsia; GI bleeding; Long-term adherence to therapy

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Intervention or Tool and Comparators	Total N Interventions (N)	Follow-up period	Age	Special Population	Outcomes Assessed
Staerk, 2017[302] Danish Patient Registry	Retropective cohort/registry; Inpatient, Outpatient; Europe; Non-govt, Non-industry; High risk of bias	Arm 1. VKA Arm 2. Dabigatran Arm 3. Rivaroxaban Arm 4. Apixaban	Total: 43,299; Arm 1. 18,094 Arm 2. 12,613 Arm 3. 5,693 Arm 4. 6,899	Arm 1. 252 days (IQR 129–575) Arm 2. 386 days (IQR 119–720) Arm 3. 208 days (IQR 79–491) Arm 4. 204 days (IQR 83–377)	Arm 1. 73 (IQR 65–80) Arm 2. 71 (IQR 65–80) Arm 3. 74 (IQR 67–83) Arm 4. 76 (IQR 68–84)	None	Ischemic stroke; Hemorrhagic stroke; Intracranial bleeding; Thromboembolism
Staerk, 2018[303] Danish Patient Registry	Retrospective cohort; Inpatient, Outpatient; Europe; Non-govt, Non-industry; Moderate risk of bias	Arm 1. Dabigatran 150 mg Arm 2. Dabigatran 150 mg Arm 3. Rivaroxaban 20mg Arm 4. Rivaroxaban 15mg Arm 5. Apixaban 5mg Arm 6. Apixaban 2.5 mg	Total: 31,522 Arm 1. 7,078 Arm 2. 4,414 Arm 3. 6,868 Arm 4. 2,098 Arm 5. 7,203 Arm 6. 3,861	Total: 2 years	Arm 1. 67 (IQR 61-71) Arm 2. 81 (IQR 76-85) Arm 3. 71 (IQR 65-78) Arm 4. 83 (IQR 76-88) Arm 5. 71 (IQR 65-77) Arm 6. 84 (IQR 80-89)	None	Stroke/TE; Ischemic stroke; Major bleeding events; Intracranial bleeding, GI bleeding
Stellbrink, 2004[304] ACE	RCT; Inpatient, Outpatient; Europe; Industry; Fair	Arm 1: LMWH (Enoxaparin) Arm 2: VKA (Phenprocoumon); UFH (IV Heparin)	Total: 496; Arm 1. 248 Arm 2. 248	Total: 28-49 days	Arm 1: 66 (SD: 11) Arm 2: 65 (SD: 11)	None	Systemic embolism Cerebrovascular infarction TIA All-cause mortality Major bleed Minor bleed CV mortality Composite outcome: Cerebrovascular infarction, TIA, Systemic embolism, Major bleed, All-cause mortality

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Intervention or Tool and Comparators	Total N Interventions (N)	Follow-up period	Age	Special Population	Outcomes Assessed
Vaughan Sarrazin, 2014[305]	Retrospective cohort; VA patient data; US; Government; High risk of bias	Arm 1: VKA (warfarin) Arm 2: Dabigatran	Arm 1: 83,950 Arm 2: 1,394	Unclear/NR	Arm 1: 74.4 (SD: 10.1) Arm 2: 69.7 (SD: 9.0)	None	Any bleeding Gastrointestinal hemorrhage Intracranial hemorrhage Hemorrhage – other site All cause mortality
Vemmos, 2006[306]	RCT; Outpatient; Europe; Unclear/NR; Fair	Arm 1: Aspirin Arm 2: VKA (Warfarin 1mg/day fixed dose) Arm 3: VKA (Warfarin adjusted dose)	Total: 45; Arm 1. 15 Arm 2. 14 Arm 3. 16	Total: 3.7 months (IQR 1-6)	Arm 1: 79.5 (SD: 2.9) Arm 2: 79.9 (SD: 1.7) Arm 3: 80.1 (SD: 2.5)	None	Ischemic stroke Systemic embolism All-cause mortality Myocardial infarction Major bleed
Villines, 2015[307] DoD database	Retrospective cohort; Inpatient, Outpatient; US; Industry; Low risk of bias	Arm 1. Warfarin Arm 2. Dabigatran	Arm 1: 12,793 Arm 2: 12,793	Arm 1. Warfarin 217.2 days (SD: 222.9) Arm 2. Dabigatran 297.3 days (258.1)	Arm 1. 74.0 (SD: 9.0) Arm 2. 73.8 (SD: 9.3)	None	Stroke Major bleeding Ischemic stroke Hemorrhagic stroke Major intracranial bleeding Major GI bleeding MI Death
Wang, 2018[308]	Retrospective cohort; Claims Database; US; Government; Moderate risk of bias	Sub-Study 1: Optum Clinformatics Arm 1. Dabigatran Arm 2. Warfarin Sub-Study 2: MarketScan Arm 1. Dabigatran Arm 2. Warfarin	Sub-Study 1 Total: 13,624 Arm 1. 3,995 Arm 2. 9,629 Sub-Study 2 Total: 62,596 Arm 1. 17,256 Arm 2. 45,340	(Mean) Sub-Study 1: Arm 1. 5.6 months Arm 2. 4.7 months Sub-Study 2: Arm 1. 5.6 months Arm 2. 4.8 months	Sub-Study 1: Arm 1. 65 (SD: 10.6) Arm 2. 67 (SD: 11.9) Sub-Study 2: Arm 1. 70 (SD: 11.3) Arm 2. 73 (SD: 11.5)	Prior thromboembolism; renal disease	Thromboembolism; Major bleeding

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Intervention or Tool and Comparators	Total N Interventions (N)	Follow-up period	Age	Special Population	Outcomes Assessed
Weir, 2017[309] Optum's Integrated Claims-Clinical de-identified dataset	Retrospective cohort; Inpatient; Outpatient; ER; US; Industry; Non-govt, Non-industry; Low risk of bias	Sub-Study 1: (eCrCl < 50) Arm 1. Rivaroxaban Arm 2. Wafarin Sub-Study 2: (eCrCl 50-80) Arm 1. Rivaroxaban Arm 2. Warfarin Sub-Study 3: (eCrCl >80) Arm 1. Rivaroxaban Arm 2. Warfarin	Total: 3,756; Sub-Study 1: Arm 1. 427 Arm 2. 447 Sub-Study 2: Arm 1. 655 Arm 2. 720 Sub-Study 3: Arm 1. 713 Arm 2. 794	Sub-Study 1: Arm 1. 232 days (SD: 202) Arm 2. 275 (SD: 243) Sub-Study 2: Arm 1. 222 (SD: 215) Arm 2. 257 (SD: 230) Sub-Study 3: Arm 1. 231 (SD: 222) Arm 2. 223 (SD: 226)	Categorized into percentages in the following groups: <65, 65-75, >75	None	Ischemic CVA Major bleed (defined by Cunningham et al.) Composite: VTE+MI+CVA
Weitz, 2010[310]	RCT; Outpatient; Unclear/NR; Industry; Good	Arm 1: Edoxaban (30mg qd) Arm 2: Edoxaban (30mg bid) Arm 3: Edoxaban (60mg qd) Arm 4: Edoxaban (60mg bid) Arm 5: VKA (Warfarin)	Total: 1,143; Arm 1. 235 Arm 2. 244 Arm 3. 234 Arm 4. 180 Arm 5. 250	Total: 12 weeks	Arm 1: 65.2 (SD: 8.3) Arm 2: 64.8 (SD: 8.8) Arm 3: 64.9 (SD: 8.8) Arm 4: 64.7 (SD: 9.0) Arm 5: 66.0 (SD: 8.5)	Persistent AF	Major bleed Minor bleed Myocardial infarction CV mortality Composite outcome: Cerebrovascular infarction, TIA, Intracerebral hemorrhage, Ischemic stroke

Study Author Year Acronym	Study Design Setting Location Funding Source Quality	Intervention or Tool and Comparators	Total N Interventions (N)	Follow-up period	Age	Special Population	Outcomes Assessed
Yao, 2016 [311] OptumLabs Data Warehouse (OLDW),	Retrospective; Inpatient, Outpatient, US; Non-govt, Non-industry; Low risk of bias	Sub-Study 1: Arm 1. Apixaban Arm 2. Warfarin Sub-Study 2: Arm 1. Dabigatran Arm 2. Wafarin Sub-Study 3: Arm 1. Rivaroxaban Arm 2. Warfarin	Total: 76,354; Sub-Study 1: 15,390 (7,695 in each arm) Sub-Study 2: 28,614 (14,307 in each arm) Sub-Study 3: 32,350 (16,175 in each arm)	Sub-Study 1: 0.5 years (SD: 0.6) Sub-Study 2: 0.7 years (SD: 0.8) Sub-Study 3: 0.6 years (SD: 0.7)	Sub-Study 1: Arm 1. 73 (IQR 66-81) Arm 2. 73 (IQR 66-81) Sub-Study 2: Arm 1. 70 (IQR 62-78) Arm 2. 70 (IQR 61-78) Sub-Study 3: Arm 1. 72 (IQR 64-79) Arm 2. 72 (IQR 64-80)	None	Ischemic CVA Hemorrhagic CVA Intracranial bleed GI bleed Composite: CVA + systemic embolism; Major bleed (def: GI, intracranial and other sites)
Yigit, 2003[312]	RCT; Inpatient, Outpatient Turkey; Unclear/NR; Fair	Arm 1: TEE; VKA (Warfarin); LMWH (Dalteparin) Arm 2: TEE; VKA (Warfarin); UFH (IV Heparin)	Total: 170; Arm 1. 89 Arm 2. 81	Total: 6 months Arm 1: 4 weeks Arm 2: 4 weeks	Total: 62.6 (SD: 10.2) Arm 1: 63.4 (SD: 9.4) Arm 2: 61.9 (SD: 10.2)	Persistent AF	Systemic embolism

Abbreviations: AF=atrial fibrillation; DVT=deep vein thrombosis; GI=gastrointestinal; IQR=interquartile range; MI=myocardial infarction; N=number of patients; NR=not reported; PY=patient years; RCT=randomized controlled trial; SD=standard deviation; SE=systemic embolism; TIA=transient ischemic attack; VKA=vitamin K antagonist

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Appendix G. Outcomes for Specific Subgroups of Interest: Detailed Study Findings

Patients Not Eligible for Warfarin Use

Three studies have specifically looked at effectiveness of therapy in patients who were considered unsuitable for warfarin therapy.[1-3] The ACTIVE-A trial[1] was designed to determine whether the combination of clopidogrel (75mg daily) plus aspirin (75 to 100mg daily) was better than aspirin alone for prevention of stroke and cardiovascular events (non-CNS embolism, MI, or vascular death) in patients with AF and at least one additional risk factor for vascular events who were considered unsuitable for warfarin therapy. A total of 7,554 patients were enrolled in a double-blind fashion from 580 centers in 33 countries, and the median followup was 3.6 years. In the ITT analyses, the combination of clopidogrel plus aspirin compared with aspirin alone significantly reduced the primary outcome by 11 percent, primarily due to a 28 percent reduction in stroke (ischemic or unknown origin) (RR 0.72; 95% CI 0.62 to 0.83; p<0.001). MI occurred in 90 patients in the clopidogrel group (0.7% per year) and in 115 in the placebo group (0.9% per year; RR 0.78; 95% CI 0.59 to 1.03; p=0.08). Importantly, clopidogrel plus aspirin compared with aspirin alone significantly increased the rate of major bleeding, including intracranial and extracranial bleeding, from 1.3 percent to 2.0 percent per year (RR 1.57; 95% CI 1.29 to 1.92; p<0.001). The rates of bleeding in the clopidogrel plus aspirin group were very similar to those observed in the warfarin arm from the ACTIVE-W study. One should also keep in mind that among the reasons for enrolling in this trial, 50 percent of the time this was due to physician assessment that the patient was inappropriate for warfarin and therefore could be in the study, which is a subjective decision. On the other hand, it is known that this subjective decision from physicians is common in clinical practice, and the results of this trial might be applicable to daily practice. In summary, if we treat 1,000 AF patients that "cannot be put on warfarin" during 3 years, clopidogrel plus aspirin would prevent 28 strokes and 6 MIs, but it would cause 20 major bleeding events, 3 of them fatal. Thus, caution is warranted when considering clopidogrel plus aspirin for patients with AF for stroke prevention.

In the light of the ACTIVE-A results, another recent study deserves special attention. In patients with AF who failed, or were unsuitable for VKA treatment, apixaban (5mg orally twice daily) was compared with aspirin (81–324mg daily) in the AVERROES trial, a randomized, double-blind, and multicenter study.[3] In a prespecified analysis of the AVERROES trial, results were consistent in the subgroup of patients who tried but failed VKA therapy. Of 5599 patients, 2216 (40%) had previously failed VKA treatment [main reasons: poor international normalized ratio (INR) control 42%, refusal 37%, bleeding on VKA 8%]. Compared with those expected to be unsuitable for VKA therapy, those who had previously failed were older, more often male, had higher body mass index, more likely to have moderate renal impairment and a history of stroke and less likely to have heart failure or to be medically undertreated. The effects of apixaban compared with aspirin were consistent in those who previously failed and those who were expected to be unsuitable, for both SSE (p=0.13 for interaction) and major bleeding (p=0.74 for interaction) and were also consistent among different subgroups of patients who had previously failed VKA therapy defined by reasons for unsuitability, age, sex, renal function, CHADS2 score, aspirin dose, duration, indication, and quality of INR control of prior VKA use.

A subanalysis of the AVERROES trial explored the patterns of bleeding during treatment and defined bleeding risks based on stroke risk with aspirin versus apixaban in patients with

atrial fibrillation unsuitable for warfarin. The rate of a bleeding event was 3.8% per year with aspirin and 4.5% per year with apixaban (hazard ratio with apixaban, 1.18; 95% CI 0.92-1.51; P=0.19). The anatomic site of bleeding did not differ between therapies. Risk factors for bleeding common to apixaban and aspirin were use of non-study aspirin>50% of the time and a history of daily/occasional nosebleeds. The rates of both stroke and bleeding increased with higher CHADS2 scores but apixaban compared with aspirin was associated with a similar relative risk of bleeding (p=0.21 for interaction) and a reduced relative risk of stroke (p=0.37 for interaction) irrespective of CHADS2 category.

In a multicenter prospective, nonrandomized trial[2] the ASAP study evaluated left atrial appendage closure with the Watchman device in patients with a contraindication for oral anticoagulation. The purpose of this study was to assess the safety and efficacy of left atrial appendage (LAA) closure in nonvalvular atrial fibrillation patients ineligible for warfarin therapy. The mean CHADS score and CHADS-VASc (CHADS score plus 2 points for age ≥75 years and 1 point for vascular disease, age 65 to 74 years, or female sex) score were 2.8 ± 1.2 and 4.4 ± 1.7, respectively. History of hemorrhagic/bleeding tendencies (93%) was the most common reason for warfarin ineligibility. Mean duration of followup was 14.4 ± 8.6 months. Serious procedure- or device-related safety events occurred in 8.7% of patients (13 of 150 patients). All-cause stroke or systemic embolism occurred in 4 patients (2.3% per year): ischemic stroke in 3 patients (1.7% per year) and hemorrhagic stroke in 1 patient (0.6% per year). This ischemic stroke rate was less than that expected (7.3% per year) based on the CHADS scores of the patient cohort.

In summary, three studies, evaluating very different interventions, included patients with nonvalvular AF who were deemed unsuitable for oral anticoagulation with warfarin; these studies found that there are alternative treatments for prevention of ischemic events in this patient population. One study found that clopidogrel plus aspirin was superior to aspirin alone for stroke prevention, but was associated with a higher risk of bleeding. One study found that apixaban compared with aspirin was associated with a lower risk of stroke and no difference in risk of bleeding. One single arm study found that use of the Watchman device was associated with a lower risk of stroke compared to the risk predicted by the CHADS scores of the participants in the study.

Patients With AF and Renal Impairment

Seven substudies from five large RCTS evaluated stroke prevention treatment in patients with AF and renal impairment. One substudy[4] of the ROCKET AF study[5] analyzed the efficacy results using rivaroxaban compared with warfarin in patients with renal impairment. ITT analysis showed that both medications had similar results with similar rates of stroke or systemic embolism (HR 0.86; 95% CI 0.63 to 1.17). In the per-protocol population, there were 2,950 patients (20.7%) with renal impairment (creatinine clearance 30–49 mL/min) using rivaroxaban 15mg/d (n=1,434) or warfarin (n=1,462). Among those patients, the primary outcome of stroke or systemic embolism occurred in 2.32 per 100 patient-years using rivaroxaban versus 2.77 per 100 patient-years with warfarin (HR 0.84; 95% CI 0.57 to 1.23). Rates of the principal safety outcome in the safety population (major and clinically relevant non-major bleeding: 17.82 vs. 18.28 per 100 patient-years; p=0.76) and intracranial bleeding (0.71 vs. 0.88 per 100 patient-years; p=0.54) were similar with rivaroxaban or warfarin. Fatal bleeding (0.28 vs. 0.74% per 100 patient-years; p=0.047) occurred less often with rivaroxaban. This study suggested that patients with AF and moderate renal insufficiency have higher rates of stroke and bleeding than those

with normal renal function. Rivaroxaban preserved the benefit of warfarin in preventing stroke and systemic embolus and produced lower rates while on treatment. Bleeding rates with the reduced dose of rivaroxaban were similar to those on warfarin therapy, and there were fewer fatal bleeds with rivaroxaban.

Another substudy[6] of the ROCKET AF trial[5] evaluated outcomes in patients with worsening renal function (WRF), as defined as >20% decline in creatinine clearance (CrCl) measurement at any point in the study. Dose of rivaroxaban was determined based on CrCl during the initial screening visit and despite changes in renal function over time, dose was not changed unless patient had two consecutive measurements of CrCl <25 mL/min at which point the medication was discontinued. Overall, patients treated with Rivaroxaban had similar screening CrCl compared to those randomized to warfarin (68 mL/min (IQR 53 to 87) vs. 68 mL/min (IQR 53 to 88); p=0.36). Patients randomized to warfarin had a larger decline in mean CrCl compared to those taking rivaroxaban (-4.3 vs. -3.5; p<0.0001). Compared to patients with stable renal function (SRF), there was no difference in stroke or systemic embolism among patients with worsening renal function (Adj HR 1.25; 95% CI 0.89 to 1.75; p=0.19). However, patients with worsening renal function had higher rates of all-cause mortality (HR 1.49; 95% CI 1.12 to 1.98; p=0.0067) and the composite outcome of stroke/systemic embolism/vascular death/MI (HR 1.40; 95% CI 1.13-1.73; p=0.0023). Among patients with worsening renal function, those randomized to treatment with rivaroxaban were less likely to have stroke/systemic embolism (WRF HR 0.50; 95% CI 0.27 to 0.93; SRF HR 0.97; 95% CI 0.76 to 1.24; p value for interaction 0.05), more likely to have a hemoglobin decrease (WRF HR 1.98; 95% CI 1.11 to 3.55; SRF HR 1.06; 95% CI 0.85 to 1.32; p value for interaction 0.047) and had no difference in major or NMCR bleeding (HR WRF 1.06; 95% CI 0.80 to 1.39; HR SRF 0.98; 95% CI 0.89 to 1.08; p value for interaction 0.61).

One substudy[7] of the AVERROES trial[3] compared apixaban 5mg twice daily (2.5mg twice daily in selected patients) with aspirin 81–324mg daily in 1,697 patients with stage III chronic kidney disease (CKD). Apixaban significantly reduced primary events (stroke and systemic embolism) by 68 percent (5.6% per year on aspirin vs. 1.8% per year on apixaban; HR 0.32; 95% CI 0.18 to 0.55; p<001) for stage III CKD participants and by 43 percent (2.8% per year on aspirin vs. 1.6% per year on apixaban; HR 0.57; 95% CI 0.37 to 0.87; p=.009) for patients with an estimated glomerular filtration rate (eGFR) ≥60 mL/min per $1.73m^2$ (p value for interaction=0.10) in the ITT population. There was no significant difference in major bleeding in stage III CKD patients by treatment (2.2% per year with aspirin vs. 2.5% per year with apixaban; HR 1.20; 95% CI 0.65 to 2.1).

A substudy[8] of the ARISTOTLE trial[9] compared apixaban 5mg twice daily with warfarin (target INR 2·0–3·0) in different levels of GFR. According to baseline Cockcroft–Gault, there were 7,518 patients (42%) with an eGFR >80 mL/min, 7,587 (42%) with an eGFR between 50 and 80 mL/min, and 3,017 (15%) with an eGFR ≤50 mL/min. In the ITT population, rates of cardiovascular events and bleeding were higher at impaired renal function levels (eGFR ≤80 mL/min). Apixaban was more effective than warfarin in preventing stroke or systemic embolism and in reducing mortality irrespective of renal function, with no significant interaction between the treatment effect and the level of renal dysfunction. These results were consistent regardless of methods for GFR estimation, achieving statistical significance on the subgroup ≤50 mL/min by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) (all-cause mortality and stroke/systemic embolism), subgroup Cockcroft–Gault 50-80 mL/min (stroke/systemic embolism), and subgroup cystatin C >80 mL/min (stroke/systemic embolism). Apixaban was

associated with fewer major bleeding events across all ranges of eGFRs. The relative risk reduction in major bleeding was greater in patients with an eGFR ≤50 mL/min using Cockcroft–Gault (HR 0.50; 95% CI 0.38 to 0.66; p value for interaction=0.005) or CKD-EPI equations (HR 0.48; 95% CI 0.37 to 0.64; p value for interaction=0.003]. When cystatin C was used to estimate GFR, apixaban was associated with fewer bleeding events across all ranges of eGFR, but without any significant interaction with the treatment effect on major bleeding (p value for interaction=0.54).

In sensitivity analyses, trial investigators examined whether the reduction in bleeding in patients with impaired renal function was due to the more frequent use of the lower apixaban dose (2.5mg twice daily). In both sensitivity analyses, the interaction between treatment and renal function remained statistically significant for major bleeding.

Another substudy[10] of the ARISTOTLE trial[9] evaluated outcomes related to change in renal function over time in patients treated with 5mg apixaban twice daily compared to warfarin. In patients with worsening renal function over 12 months of followup, apixaban showed numerically lower relative risk of stroke or systemic embolism (HR 0.80; 95% CI 0.51 to 1.24; p=0.86) as well as major bleeding (HR 0.76; 95% CI 0.54 to 1.07; p=0.73) compared to warfarin, although neither reached statistical significance. These results were similar across levels of renal dysfunction, defined as eGFR >80 mL/min, eGFR 50-80 mL/min and eGFR <50 mL/min.

In the ENGAGE AF study,[11] patients randomized to the high dose edoxaban arm received 60mg daily if their CrCl was over 50 ml/min or 30mg daily if their CrCl was between 30mg/min and 50mg/min. In a substudy,[12] no statistically significant interaction was found between treatment (edoxaban vs. warfarin) and CrCl (30-50 ml/min vs. >50 ml/min) on the primary efficacy outcome of stroke or systemic embolic event (p = 0.94 for interaction). In both renal function groups, there was no statistically significant difference between edoxaban and warfarin (HR 0.87; 95% CI 0.65 to 1.18 for CrCl >50ml/min and HR 0.87; 95% CI 0.72 to 1.04 for CrCl 30-50ml/min). There was also no statistically significant interaction between treatment and CrCl on major bleeding (p=0.62 for interaction). In exploratory analyses, there was no statistically significant interaction between CrCl subgroups (30-50 ml/min, >50-95 ml/min, and >95ml/min) and treatment on stroke or systemic embolic event, systemic embolic events, any stroke, ischemic stroke, hemorrhagic stroke, MI, any cause death, cardiovascular death, fatal bleeding, intracranial hemorrhage, or minor bleeding. There was, however, a statistically significant interaction on GI bleeding (p=0.02 for interaction) in which patients with CrCl of >50-95 ml/min had a higher risk with edoxaban vs. warfarin (HR 1.47; 95% CI 1.15 to 1.87) than the other two CrCl subgroups (HR 1.17; 95% CI 0.78 to 1.76 for CrCl 30-50ml/min and HR 0.67; 95% CI 0.40 to 1.10 for CrCl >95ml/min).

A prespecified study of the RE-LY trial[13] investigated the outcomes of the trial in relation to renal function. Glomerular filtration rate was estimated with the Cockcroft-Gault, Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), and Modification of Diet in Renal Disease (MDRD) equations in all randomized patients with available creatinine at baseline (n=17 951), and cystatin C-based glomerular filtration rate was estimated in a subpopulation with measurements available (n=6190). A glomerular filtration rate ≥80, 50 to <80, and <50mL/min was estimated in 32.6%, 47.6%, and 19.8% and in 21.6%, 59.6%, and 18.8% of patients based on Cockcroft-Gault and CKD-EPI, respectively. Rates of stroke or systemic embolism, major bleeding, and all-cause mortality increased as renal function decreased. The rates of stroke or systemic embolism were lower with dabigatran 150mg and similar with 110mg twice daily compared with warfarin, without significant heterogeneity in subgroups defined by renal

function (interaction P>0.1 for all). For the outcome of major bleeding, there were significant interactions between treatment and renal function according to CKD-EPI and MDRD equations, respectively (P<0.05). The relative reduction in major bleeding with either dabigatran dose compared with warfarin was greater in patients with glomerular filtration rate ≥80 mL/min.

In summary, sub-studies of 5 large RCTs evaluated the effects of DOACs compared to either warfarin or aspirin in patients with some degree of renal disease. These studies demonstrated that compared to participants with normal renal function, participants with renal disease had increased risk of ischemic events, bleeding, and all-cause mortality. In all 5 sub-studies, among participants with renal disease, use of the DOACs were consistently similar to or better than warfarin in the prevention of stroke/SE and bleeding events. One sub-study demonstrated that in patients with stage 3 CKD, compared to aspirin, apixaban was associated with lower risk of stroke and no difference in bleeding.

Patients With Paroxysmal Versus Sustained AF

One substudy[14] of the ACTIVE W RCT[15] analyzed the results in patients with paroxysmal AF (n=1,202) as compared with those who had sustained (persistent or permanent) AF (n=5,495). Patients with paroxysmal AF were younger, had a shorter AF history, more hypertension, and less valvular disease, heart failure, and diabetes mellitus than patients with sustained AF. Irrespective of type of AF, the incidence of stroke and non-CNS embolism was lower for patients treated with oral anticoagulation. There were more bleedings of any type in patients receiving clopidogrel plus aspirin, irrespective of the type of AF, but major bleeding events were similar in all groups (paroxysmal vs. sustained, and oral anticoagulants vs. clopidogrel+aspirin).

A secondary analysis[16] of the ARISTOTLE trial[9] evaluated treatment with apixaban 5mg twice daily compared to warfarin in patients with paroxysmal or persistent AF. Overall, patients with paroxysmal atrial fibrillation were less likely to have stroke or systemic embolism (HR 0.65; 95% CI 0.48 to 0.87; p=0.003) and all-cause mortality was also significantly less (HR 0.72; 95% CI 0.61 to 0.85; p=0.0002). There was no significant interaction with regard to stroke or systemic embolism by type of AF and treatment type (HR Paroxysmal 0.72; 95% CI 0.41 to 1.25; HR Persistent 0.80; 95% CI 0.66 to 0.97; p value for interaction 0.71), all-cause mortality (HR Paroxysmal 0.99; 95% CI 0.72 to 1.37; HR Persistent 0.88; 95% CI 0.78 to 0.99; p value for interaction 0.50) and major bleeding (HR Paroxysmal 0.73; 95% CI 0.49 to 1.08; HR Persistent 0.68; 95% CI 0.59 to 0.80; p value for interaction 0.75) in patients treated with apixaban compared with warfarin.

In summary, analysis of two large RCTs evaluated for differences in treatment effects (clopidogrel plus aspirin vs warfarin or apixaban vs warfarin) for stroke prevention/bleeding by type of AF (paroxysmal or persistent). In neither study was there a difference in treatment effect by type of AF.

Patients With Recently Diagnosed AF

One substudy[17] of the ARISTOTLE RCT[9] evaluated patients with AF first diagnosed within 30 days prior to randomization. Regardless of timing of diagnosis, apixaban had similar benefits on prevention of stroke or systemic embolism and major bleeding compared to warfarin (interaction p values 0.94 and 0.78 respectively).

Patients With AF After Stroke

Eight studies explored stroke prevention treatment in patients with AF who had previously suffered a stroke.[18-25]

The Heparin in Acute Embolic Stroke Trial (HAEST)[20] was a multicenter RCT on the effect of LMWH (dalteparin 100 IU/kg subcutaneously twice a day) or aspirin (160mg every day) for the treatment of 449 patients with acute ischemic stroke and AF. The primary aim was to test whether treatment with LMWH, started within 30 hours of stroke onset, is superior to aspirin for the prevention of recurrent stroke during the first 14 days. The frequency of recurrent ischemic stroke during the first 14 days was 19/244 (8·5%) in dalteparin-allocated patients versus 17/225 (7·5%) in aspirin-allocated patients (OR 1·13; 95% CI 0·57 to 2·24). In the ITT analyses, the OR remained unchanged after adjusting for sex in logistic-regression analysis (1·19; 95% CI 0·60 to 2·36). The secondary events during the first 14 days also revealed no benefit of dalteparin compared with aspirin. There were no significant differences in functional outcome or death at 14 days or 3 months.

A prespecified subgroup analysis[21] of the ROCKET AF study[5] investigated whether the efficacy and safety of rivaroxaban compared with warfarin was consistent among patients with and without previous stroke or TIA. A total of 14,264 patients from 1,178 centers in 45 countries were included. Patients with AF who were at increased risk of stroke ($CHADS_2$ score >2) were randomly assigned (1:1) in a double-blind manner to rivaroxaban 20mg daily or adjusted dose warfarin (to maintain INR 2.0–3.0). Patients and investigators were masked to treatment allocation. The primary outcome was the composite of stroke or non-CNS systemic embolism as a safety outcome. The treatment effects of rivaroxaban and warfarin were compared among patients with and without previous stroke or TIA. The safety analyses were done in the on-treatment population. Efficacy analyses were analyzed by ITT, and 7,468 (52%) patients had a previous stroke (n=4,907) or TIA (n=2,561). The number of events per 100 person-years for the primary outcome in patients treated with rivaroxaban compared with warfarin was consistent among patients with previous stroke or TIA (2.79% rivaroxaban vs. 2.96% warfarin; HR 0.94; 95% CI 0.77 to 1.16) and those without (1.44% vs. 1.88%; HR 0.77; 95% CI 0.58 to 1.01; comparison interaction p=0.23). Similarly, the number of major and non-major clinically relevant bleeding events per 100 person-years in patients treated with rivaroxaban compared with warfarin was consistent among patients with previous stroke or TIA (13.31% rivaroxaban vs. 13.87% warfarin; HR 0.96; 95% CI 0.87 to 1.07) and those without (16.69% vs. 15.19%; HR 1.10; 95% CI 0.99 to 1.21; comparison interaction p=0.08).

One observational study[18] followed a consecutive series of AF patients with first-ever ischemic stroke and evaluated prospectively those with moderate to severe disability (grade 4–5 on the modified Rankin Scale) who were treated during a 5-year followup period with either warfarin or aspirin. Death and recurrent vascular events were documented. Out of a pool of 438 AF patients, 191 were prospectively assessed. During a mean followup of 50.4 months, the cumulative 5-year mortality was 76.7% (95% CI 69.0 to 84.3), and the 5-year recurrence rate was 33.7% (95% CI 23.3 to 44.1). Additionally, two non-cerebral major bleeding events requiring hospital admission and blood transfusion were recorded in the warfarin group. Only one non-cerebral bleeding event was documented in the aspirin group. The annual event rates for all major bleeding complications in aspirin and warfarin groups were 0.7 and 3.3 percent, respectively. Aspirin versus warfarin was an independent predictor of mortality. Prior TIA and aspirin versus warfarin were predictors of vascular recurrence. Anticoagulation was associated with a decreased risk of death (HR 0.44; 95% CI 0.27 to 0.70; p<0.001) and recurrent

thromboembolism (HR 0.36; 95% CI 0.17 to 0.77; p<0.01). The results of this observational study suggest that chronic anticoagulation therapy may be effective in lengthening survival and preventing recurrent thromboembolism in AF patients who have suffered a severely disabling ischemic stroke.

An observational study[19] analyzed recurrent cerebral and non-cerebral ischemic vascular events, major intracerebral and extracerebral bleeding, and vascular death in 401 consecutive patients with ischemic stroke or TIA and AF who were discharged with oral anticoagulation, antiplatelet agents, or heparin only in a clinical routine setting. Patients on oral anticoagulation at time of discharge were significantly younger and had suffered a major stroke less often than patients who received antiplatelet agents or heparin at discharge. One year after discharge, adherence to therapy was higher in patients discharged on oral anticoagulation (72%) than in those on antiplatelet agents (46%; p<0.001). The majority of patients discharged on heparin were subsequently treated with oral anticoagulation. During a median followup of 25 months (IQR, 15–38), 103 (26%) patients experienced a complication: 91 (88%) patients an ischemic complication and 12 (12%) a bleeding complication. The rate of ischemic complications and the overall rate of complications were lowest in patients discharged on oral anticoagulation. Patients on antiplatelet agents at discharge suffered from ischemic complications significantly more often during the followup period than patients on oral anticoagulation or heparin at discharge (30% vs. 16% vs. 23%; p=0.031). Patients on antiplatelet agents suffered their first vascular complication significantly sooner after discharge than patients on oral anticoagulation. Safety outcomes showed that three percent of the patients on antiplatelet agents and four percent of those on oral anticoagulation suffered from major bleeding complications during followup (p=0.028). The rate of intracranial bleeding was higher in patients on oral anticoagulation (3% vs. 1%), but the total numbers were too small to allow a valid statistical comparison. Total mortality was lowest in patients discharged on oral anticoagulation, and vascular mortality also seemed somewhat lower in this group but the difference was not significant.

A predefined analysis[22] was conducted of the outcomes of the RE-LY trial[26] in subgroups of patients with or without previous stroke or transient ischemic attack. The primary efficacy outcome was stroke or systemic embolism, and the primary safety outcome was major hemorrhage. Within the subgroup of patients with previous stroke or TIA, 1,195 patients were from the 110mg dabigatran group, 1,233 from the 150mg dabigatran group, and 1,195 from the warfarin group. Stroke or systemic embolism occurred in 65 patients (2.78% per year) on warfarin compared with 55 (2.32% per year) on 110mg dabigatran (relative risk [RR] 0.84; 95% CI 0.58 to 1.20) and 51 (2.07% per year) on 150mg dabigatran (RR 0.75, 95% CI 0.52 to 1.08). The rate of major bleeding was significantly lower in patients on 110mg dabigatran (RR 0.66; 95% CI 0.48 to 0.90) and similar in those on 150mg dabigatran (RR 1.01; 95% CI 0.77 to 1.34) compared with those on warfarin. The effects of both doses of dabigatran compared with warfarin were not significantly different between patients with previous stroke or TIA and those without for any of the outcomes from RE-LY apart from vascular death (110mg group compared with warfarin group, interaction p=0.038). By these results, the effects of 110mg dabigatran and 150mg dabigatran twice daily in patients with previous stroke or TIA are consistent with those of other patients in RE-LY, for whom, compared with warfarin, 150mg dabigatran reduced stroke or systemic embolism and 110mg dabigatran was noninferior.

A prespecified subgroup analysis[23] of AVERROES[3] included 5,599 patients (mean age 70 years) with AF who were at increased risk of stroke and unsuitable for warfarin therapy. These patients were randomly assigned to receive apixaban 5mg twice daily (n=2,808) or aspirin 81–

324mg per day (n=2,791). The primary efficacy outcome was stroke or systemic embolism in the ITT population; the primary safety outcome was major bleeding. In this subanalysis of patients with previous stroke or TIA, the effects of apixaban in patients with and without previous stroke or TIA were compared. The cumulative HR for stroke or systemic embolism at 1 year was 5.73% (95% CI 4.10 to 8.02) in patients with previous stroke or TIA and 2.36% (1.93 to 2.89) in those without. In patients with previous stroke or TIA treated with apixaban, the rates of stroke or systemic embolism, ischemic stroke, and disabling or fatal stroke were consistently lower than those in patients treated with aspirin. In patients with previous stroke or TIA, 10 events of stroke or systemic embolism occurred in the apixaban group (n=390), cumulative hazard 2.39% per year) compared with 33 in the aspirin group (n=374). This resulted in a cumulative hazard of 2.39 percent in the apixaban group and 9.16 percent per year in the aspirin group (HR 0.29; 95% CI 0.15 to 0.60). In those without previous stroke or TIA, 41 events (n=2,417, 1.68% per year) and 80 events (n=2,415, 3.06% per year) occurred in the apixaban and aspirin groups, respectively (HR 0.51; 95% CI 0.35 to 0.74). Compared with those treated with aspirin, the 1-year risk of stroke or systemic embolism decreased by 73 percent in patients treated with apixaban and with previous stroke or TIA (1-year absolute risk reduction of 6.4%; 95% CI 2.8 to 10.0) and by 45 percent in patients treated with apixaban and without previous stroke or TIA (1-year absolute risk reduction of 1.4%, 95% CI 0.4 to 2.3). The p values for interaction between history of previous stroke or TIA and treatment were not significant, indicating that the results in the subgroups were consistent with the overall result of the study. Major bleeding, the primary safety outcome, was more frequent in patients with history of previous stroke or TIA than in patients without this history (HR 2.88; 95% CI 1.77 to 4.55), but risk of this event did not differ between treatment groups. The effect of apixaban versus aspirin for bleeding complications was consistent in the two subgroups, with nonsignificant interaction p values.

A prespecified subgroup analysis[24] from the ARISTOTLE trial[9] evaluated the efficacy and safety of apixaban compared with warfarin in subgroups of patients with and without previous stroke or TIA. The primary efficacy outcome was stroke or systemic embolism, analyzed by intention to treat. The primary safety outcome was major bleeding in the on-treatment population. Outcomes in patients with and without previous stroke or TIA were compared. Of the trial population, 3,436 (19%) had a previous stroke or TIA. In the subgroup of patients with previous stroke or TIA, the rate of stroke or systemic embolism was 2.46 per 100 patient-years of followup in the apixaban group and 3.24 in the warfarin group (HR 0.76; 95% CI 0.56 to 1.03); in the subgroup of patients without previous stroke or TIA, the rate of stroke or systemic embolism was 1.01 per 100 patient-years of followup with apixaban and 1.23 with warfarin (HR 0.82; 95% CI 0.65 to 1.03). The relative risk reduction of stroke or systemic embolism with apixaban versus warfarin was similar among patients with and those without previous stroke or TIA (p for interaction=0.71). The reduction in rates of cardiovascular death, disabling or fatal stroke, and all-cause mortality with apixaban versus warfarin was similar in patients with and without previous stroke or TIA (p for interaction=0.53, 0.18, and 0.89, respectively). Compared with patients without previous stroke or TIA, patients with previous stroke or TIA were more likely to have major bleeding (HR 1.37; 95% CI 1.17 to 1.62) and intracranial bleeding (2.15, 95% CI 1.57 to 2.96). The relative risk reductions in major bleeding and total bleeding with apixaban versus warfarin were similar in both groups (p for interaction=0.69 and 0·.0, respectively). Intracranial bleeding was reduced in the apixaban groups from 1.49 per 100 patient-years of followup on warfarin to 0.55 per 100 patient-years on apixaban in those with previous stroke or TIA (HR 0.37; 95% CI 0.21 to 0.67) and from 0.65 per 100 patient-years of

followup on warfarin to 0.29 per 100 patient-years on apixaban in those without previous stroke or TIA (0.44, 95% CI 0.30 to 0.66).Based on these results, the effects of apixaban versus warfarin were consistent in patients with AF with and without previous stroke or TIA.

In a substudy of the ENGAGE AF study[25], in which with prior ischemic stroke or TIA were compared with patients without prior ischemic stroke or TIA, no statistically significant interaction was found between prior stroke/TIA and treatment (high dose edoxaban vs. warfarin) for stroke or systemic embolic event, any stroke, hemorrhagic stroke, ischemic stroke, any cause death, or cardiovascular death.

Studies were inconsistent in terms of the interventions evaluated and their findings. Three studies compared anticoagulation to aspirin therapy. [18,20,23]. Anticoagulation with either apixaban or warfarin was superior to aspirin therapy in preventing recurrent thromboembolism.[18,23] Four studies compared direct oral anticoagulants to warfarin therapy. [21,22,24,25] These studies demonstrated that there was no difference in risk of stroke or systemic embolism when comparing direct oral anticoagulants (edoxaban, rivaroxaban, apixaban, dabigatran 110mg BID) to warfarin therapy. The only exception was the dabigatran 150mg BID dose showed reduced risk of stroke or systemic embolism compared to warfarin therapy.

Patients With AF and Different Thromboembolic Risks

Six studies explored the comparative safety and effectiveness of stroke prevention therapy in patients with different thromboembolic risks.[15,27-31]

An observational study[27] sought to determine the efficacy and safety of warfarin and aspirin in patients with nonvalvular AF, with separate analyses according to predicted thromboembolic and bleeding risk. Nationwide registries allowed the identification of all patients discharged with nonvalvular AF in Denmark (n=132,372). For every patient, the risk of stroke and bleeding was calculated by $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED. In different groups according to thromboembolic risks, warfarin consistently lowered the risk of thromboembolism compared with aspirin; the combination of warfarin+aspirin did not yield any additional benefit. In patients at high thromboembolic risk, HRs (95% CIs) for thromboembolism were (adjusted for all baseline characteristics): CHA_2DS_2-VASc ≥2: HR 1.81 (1.73 to1.90), 1.14 (1.06 to 1.23) for aspirin and warfarin+aspirin, respectively, compared with warfarin; $CHADS_2$ ≥2: HR 1.73 (1.64 to 1.83), 1.05 (0.96 to 1.15), for aspirin and warfarin+aspirin, respectively, compared with warfarin. The risk of bleeding was increased with warfarin, aspirin, and warfarin+aspirin compared with no treatment; the HRs were 1.0 (warfarin; reference), 0.93 (aspirin; 0.89–0.97), 1.64 (warfarin+aspirin; 1.55–1.74), and 0.84 (no treatment; 0.81–0.88), respectively. This large cohort study corroborates the effectiveness of warfarin and no effect of aspirin treatment on the risk of stroke/thromboembolism. Also, the risk of bleeding was increased with both warfarin and aspirin treatment, but the net clinical benefit was clearly positive, in favor of warfarin in patients with increased risk of stroke/thromboembolism.

A prospective cohort study[28] analyzed the effectiveness and safety of oral anticoagulants in 796 outpatients with nonvalvular AF in daily clinical practice, according to embolic risk evaluated by means of $CHADS_2$ score. Oral anticoagulation was prescribed to 564 (71%) patients. After 2.4 ± 1.9 years of followup, the embolic event (TIA, ischemic stroke, peripheral embolism) rates (per 100 patient-years) for each stratum of the $CHADS_2$ score for patients with/without oral anticoagulants were: 1/4.1; p=0.23 ($CHADS_2$=0); 0.6/7.1; p=0.0018 ($CHADS_2$=1); 0.5/5.1; p=0.0014 ($CHADS_2$=2); 2.4/12.5; p=0.0017 ($CHADS_2$=3) and 2.9/20; p=0.013 ($CHADS_2$≥4). The severe bleeding rates for the same $CHADS_2$ score strata were 3/0.8,

0.8/0.7, 1.3/0.7, 0.4/0, and 2.9/5 in patients with/without oral anticoagulants (nonsignificant.). This study demonstrated that oral anticoagulants appeared safe and effective in patients with $CHADS_2 \geq 1$.

In ACTIVE W,[15] oral anticoagulation was more efficacious than combined clopidogrel plus aspirin in preventing vascular events in patients with AF. A subanalysis of ACTIVE W[32] evaluated the findings according to risk stratification using the $CHADS_2$ score. Treatment-specific rates of stroke and major bleeding were calculated for patients with a $CHADS_2=1$ and compared with those with a $CHADS_2 >1$. The ACTIVE W primary outcome (stroke, noncentral nervous system systemic embolism, all-cause mortality, and MI) occurred more frequently in patients on clopidogrel+aspirin, both with $CHADS_2=1$ (3.28% per year versus 1.92% per year, RR=1.72; p=0.01) and with $CHADS_2 >1$ (7.14% per year versus 5.18% per year, RR 1.40; p=0.0035). $CHADS_2$ status did not significantly affect the relative benefit of oral anticoagulants for this outcome (P for interaction=0.41). Observed stroke rates for those with a $CHADS_2=1$ were 1.25 percent per year on clopidogrel+aspirin and 0.43 percent per year on oral anticoagulants (RR 2.96; 95% CI 1.26 to 6.98; p=0.01). Among patients with a $CHADS_2>1$, the stroke rates were 3.15 percent per year on clopidogrel+aspirin and 2.01 percent per year on oral anticoagulants (RR 1.58; 95% CI 1.11 to 2.24; p=0.01; p for interaction between stroke risk category and efficacy of oral anticoagulants=0.19). The risk of major bleeding during oral anticoagulants was significantly lower among patients with $CHADS_2=1$ (1.36% per year) compared with $CHADS_2>1$ (2.75% per year) (RR 0.49; 95% CI 0.30 to 0.79; p=0.003). For patients with $CHADS_2=1$, the rate of major bleeding was 2.09 percent per year on clopidogrel+aspirin, which was higher than the rate of 1.36 percent per year on oral anticoagulants (RR 1.55; 95% CI 0.91 to 2.64; p=0.11). For patients with $CHADS_2>1$, major bleeding occurred at a rate of 2.63 percent per year on clopidogrel+aspirin and 2.75 percent per year on oral anticoagulants (RR 0.97; 95% CI 0.69 to 1.35; p=0.84). The relative risk of major bleeding with clopidogrel+aspirin, compared with oral anticoagulants was not significantly different between patients with high and low $CHADS_2$ scores (p for interaction=0.15); however, the absolute risk of major bleeding on oral anticoagulants was significantly lower among patients with $CHADS_2=1$ compared with $CHADS_2>1$ (RR=0.49; 95% CI 0.30 to 0.79; p=0.0003). Based on these results, patients with a $CHADS_2=1$ had a low risk of stroke, yet still derived a modest (<1% per year) but statistically significant absolute reduction in stroke with oral anticoagulants compared with clopidogrel+aspirin and had low rates of major hemorrhage on oral anticoagulants.

A subgroup analysis[29] of the RE-LY trial[26] evaluated the prognostic importance of $CHADS_2$ risk score in patients with AF receiving oral anticoagulants, including warfarin and the direct thrombin inhibitor dabigatran. Of the18,112 patients, the distribution of $CHADS_2$ scores were as follows: 0–1, 5,775 patients; 2, 6,455 patients; and 3–6, 5,882 patients. Annual rates of the primary outcome of stroke or systemic embolism among all participants were 0.93, 1.22, and 2.24 percent in patients with a $CHADS_2$ score of 0–1, 2, and 3–6 respectively. Annual rates of other outcomes among all participants with $CHADS_2$ scores of 0–1, 2, and 3–6, respectively, were 2.26, 3.11, and 4.42 percent (major bleeding); 0.31, 0.40, and 0.61 percent (intracranial bleeding); and 1.35, 2.39, and 3.68 percent (vascular mortality) (p <0.001 for all comparisons). Rates of stroke or systemic embolism, major and intracranial bleeding, and vascular and total mortality each increased in the warfarin and dabigatran groups with increasing $CHADS_2$ score. The reduction in stroke or systemic embolism with dabigatran 150mg twice daily versus warfarin was consistent across the $CHADS_2$ risk groups. Across $CHADS_2$ risk groups, the rates of stroke

or systemic embolism were similar with dabigatran 110mg twice daily and warfarin. The rates of intracranial bleeding with dabigatran 150mg or 110mg twice daily were lower than those with warfarin; there was no significant heterogeneity in subgroups defined by $CHADS_2$ scores.

A fair-quality observational study[30] that included 8,962 patients with AF and a CHA_2DS_2-VASc score=0 showed that among untreated patients, the rates of stroke/thromboembolism, major bleeding, and mortality were 0.64 percent, 1.12 percent, and 1.08 percent per year, respectively. Use of oral anticoagulation and/or antiplatelet therapy was not associated with a reduction in stroke/thromboembolism (RR 0.99; 95% CI 0.25 to 3.99; p=0.99) and was not associated with a different prognosis in terms of bleeding events, improved survival, or a composite outcome of stroke/thromboembolism, bleeding, and death (RR 0.80; 95% CI 0.40 to1.61; p=0.53).

Finally, a secondary analysis[31] of the ARISTOTLE trial[9] compared apixaban 5mg twice daily versus warfarin (target INR 2·0–3·0) in patients with different levels of risk of stroke and of bleeding in AF, according to patients' $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores. Irrespective of $CHADS_2$ score, patients assigned to apixaban had significantly lower rates of stroke or systemic embolism, mortality, International Society on Thrombosis and Haemostasis (ISTH) major bleeding, intracranial bleeding, and any bleeding than did those assigned warfarin, with no evidence of statistical heterogeneity. The benefits of apixaban compared with warfarin for all outcomes (including events during treatment only) across CHA_2DS_2-VAScccategories were similar to those seen across $CHADS_2$ score categories. No difference was recorded for MI. Irrespective of HAS-BLED score, patients assigned to apixaban had lower rates of stroke or systemic embolism, mortality, ISTH major bleeding, Thrombolysis in Myocardial Infarction (TIMI) major or minor bleeding, Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) severe or moderate bleeding, and any bleeding, including events during treatment only, than did those assigned to warfarin. The reduction in intracranial bleeding with apixaban compared with warfarin was greater in patients with a HAS-BLED score of 3 or higher (HR 0·22; 95% CI 0·10 to 0·48) than was the reduction seen in those with a HAS-BLED score of 0–1 (HR 0·66; 95% CI 0·39 to 1·12), but not significantly so (p value for interaction=0·0604). Finally, regardless of $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED score, patients who received apixaban had fewer events than did patients who received warfarin, with lower rates of the composite of stroke, systemic embolism, ISTH major bleeding, and all-cause mortality.

The studies were inconsistent in terms of the comparisons evaluated and the findings. Two studies showed a decrease in risk of thromboembolism when comparing warfarin therapy to aspirin and clopidogrel regardless of calculated risk. [15,27]. When comparing direct oral anticoagulants (apixaban or dabigatran) to warfarin therapy, a decrease in risk of thromboembolism was seen with direct oral anticoagulant agents. [30,31] Lastly, one study looking at only patients with CHA_2DS_2-VASc score=0 showed no different in risk of thromboembolism between those using oral anticoagulation and/or antiplatelet therapy.[30]

Patients With AF According to INR Control

Four studies evaluated treatment safety and effectiveness according to center-based INR control.[33-36] In the first study,[33] incident ischemic strokes were evaluated in a cohort of 13,559 patients with nonvalvular AF. Of 596 ischemic strokes, 32 percent occurred during warfarin therapy, 27 percent during aspirin therapy, and 42 percent during neither type of therapy. Among patients who were taking warfarin, an INR of <2.0 at admission, as compared with an INR of ≥2.0, independently increased the odds of a severe stroke in a proportional odds logistic-

regression model (OR 1.9; 95% CI 1.1 to 3.4) across three severity categories of stroke and the risk of death within 30 days (HR 3.4; 95% CI 1.1 to 10.1). The proportion of patients who had a severe or fatal stroke did not differ significantly between those with an admission INR of 1.5–1.9 and those with an INR of <1.5. After adjustment for potential confounders in the proportional odds model, the medication group remained an independent risk factor for the severity of stroke when patients who had an INR ≥2.0 were compared with those who had an INR of <2.0 or those who were taking neither aspirin nor warfarin. An INR of 1.5–1.9 at admission was associated with a mortality rate similar to that for an INR of <1.5 (18% and 15%, respectively). The 30-day mortality rate among patients who were taking aspirin at the time of the stroke was similar to that among patients who were taking warfarin and who had an INR <2.0. The rate of ischemic stroke was highest at INR values <2.0, especially values <1.5. By contrast, there was no marked absolute increase in the rate of intracranial hemorrhage at INR values <4.0. Based on these results, anticoagulation that results in an INR ≥2.0 in patients with nonvalvular AF reduces the frequency of ischemic stroke, its severity, and the risk of death from stroke.

A second observational study included an analysis of warfarin subgroups according to INR control compared with no therapy.[34] Ischemic stroke rate relative risk (RR) was 0.93 (95% CI 0.71 to1.22) in patients below therapeutic range (INR<2), 0.69 (0.57 to0.83) in the group within therapeutic range (INR 2–3), 0.82 (0.57 to 1.20) in patients above therapeutic range (INR >3), and 0.62 (0.56 to 0.69) in the group with unknown therapeutic range. Intracranial hemorrhage RR was 1.16 (95% CI 0.62 to 2.16) in patients below therapeutic range (INR <2), 1.13 (0.74 to 1.72) in the group within therapeutic range (INR 2–3), 3.26 (1.67 to 6.38) in patients above therapeutic range (INR >3), and 1.29 (0.98 to 1.69) in the group of unknown therapeutic range.

A post-hoc analysis[35] of the ARISTOTLE trial[9] evaluated apixaban 5mg twice daily compared to warfarin treatment with differing times in therapeutic range. Overall, apixaban significantly reduced the rate of stroke or systemic embolism compared to warfarin (HR 0.79; 95% CI 0.66–0.95). The treatment benefit of apixaban was similar across the lowest and highest quartiles of individual time in therapeutic range (iTTR) without interaction between quality of INR control and frequency of events (iTTR 24.3-60.5 HR 0.70; 95% CI 0.52 to 0.94; iTTR 71.2-83.2 HR 0.87; 95% CI 0.57 to 1.33; p value for interaction 0.060). There were also similar treatment effects with regards to all cause death in the lowest (HR 0.87; 95% CI 0.71 to 1.06) and highest quartiles of iTTR (HR 0.89; 95% CI 0.67 to 1.16; p value for interaction 0.67). Additionally, the same benefit of apixaban with regards to bleeding outcomes was observed across the lowest and highest quartiles of iTTR.

A substudy[36] of the ROCKET AF trial[5] examined rivaroxaban once daily versus warfarin treatment with differing times in therapeutic range. For all patients randomized to warfarin, the mean time in therapeutic range (TTR) was 55%. Patients treated with rivaroxaban were compared to those treated with warfarin, across four quartiles of TTR: Q1=0 to 50.6%; Q2=50.7 to 58.5%; Q3=58.6 to 65.7%; Q4=65.7 to 100%. There was no significant difference in the primary outcomes of stroke or systemic embolism in patients treated with rivaroxaban across center TTR (cTTR) for warfarin (HR Q1 0.70; 95% CI 0.47 to 1.04; HR Q2 0.90; 95% CI 0.64 to 1.26; HR Q3 0.88; 95% CI 0.62 to 1.25; HR Q4 0.73; 95% CI 0.50 to 1.06; p value for interaction 0.71). However, patients treated with rivaroxaban did have lower risk of major or NMCR bleeding compared to patients in the lowest quartile of warfarin cTTR with a significant interaction between treatment and time in therapeutic range (Q1 HR 0.80; 95% CI 0.66 to 0.98;

Q2 HR 0.96; 95% CI 0.81 to 1.14; Q3 HR 1.03; 95% CI 0.87 to 1.22; Q4 HR 1.25; 95% CI 1.10 to 1.41; p value for interaction 0.001).

The first two studies from this group suggest that compared to aspirin or no therapy, an INR ≥ 2 lowers the risk of ischemic stroke. However, INR values above the therapeutic range may lead to higher rates of hemorrhagic stroke. The second two studies compared treatment with warfarin to a factor Xa inhibitor and showed that there was no difference in the treatment effect of rivaroxaban and apixaban across the ranges of INR values examined with regards to stroke or systemic embolism outcomes. There is mixed data regarding the interaction between INR control and treatment with regards to bleeding outcomes.

Elderly Patients With AF

Fourteen studies specifically explored the safety and effectiveness of stroke prevention therapies in the elderly.[37-50] A single-center, retrospective, observational study[37] included data from patients aged ≥65 years with chronic nonvalvular AF treated at an urban academic geriatrics practice over a 1-year period. Eligible patients were receiving noninvasive management of AF with warfarin or aspirin. A total of 112 patients (mean age, 82 years) were identified; 106 were included in this analysis (80 women, 26 men). Warfarin was prescribed in 85 percent (90 patients); aspirin in 15 percent (16). The distributions of both the $CHADS_2$ and Outpatient Bleeding Risk Index scores were not significantly different between the warfarin and aspirin groups. The proportions of patients treated with warfarin were not significantly different between the groups with a high risk for hemorrhage and the groups at lower risk. At 12 months in the 90 patients initially treated with warfarin, the rate of stroke was 2 percent (2 patients); major hemorrhage, 6 percent (5); and death, 20 percent (18). The number of patients who received aspirin was too small to provide sufficient power to detect significant treatment differences.

A prospective clinical study[38] of four clinical services of geriatric medicine included 209 inpatients, (mean age 84.7±7 years; women 60.8%) with chronic AF. The patients were distributed into two groups (anticoagulant or aspirin) according to medical decision. The evolution of the patients was recorded after 3 months. One hundred and two patients (48.8%) received anticoagulant and 107 patients received aspirin. Patients in the aspirin group were significantly older (86.5±6.5 vs. 82.9±7.1 years), had more frequent social isolation, had higher systolic blood pressure, and had more important subjective bleeding risk and risk of falls. After 3 months, the two groups did not significantly differ for death, bleeding, or ischemic events.

A prospective RCT[39] included 973 patients aged 75 years or over (mean age 81·5 years, SD 4·2) with AF from primary care who were randomly assigned to warfarin (target INR 2–3) or aspirin (75mg per day). The primary outcome was fatal or disabling stroke (ischemic or hemorrhagic), intracranial hemorrhage, or clinically significant arterial embolism. Analysis was by intention to treat. There were 24 primary events (21 strokes, 2 other intracranial hemorrhages, and 1 systemic embolus) in people assigned to warfarin, and 48 primary events (44 strokes, 1 other intracranial hemorrhage, and 3 systemic emboli) in people assigned to aspirin in the ITT population (yearly risk 1.8% vs. 3.8%, relative risk 0.48; 95% CI 0.28 to 0.80; p=0·003). Yearly risk of extracranial hemorrhage was 1.4 percent (warfarin) versus 1.6 percent (aspirin) (relative risk 0.87, 95% CI 0.43 to 1.73).

An RCT[40] of primary thromboprophylaxis for AF included patients aged >80 and <90 randomized to receive dose-adjusted warfarin (INR 2.0–3.0) or aspirin 300mg. The primary outcome measure was a comparative frequency of combined outcomes comprising death,

thromboembolism, serious bleeding, and withdrawal from the study. Seventy-five patients (aspirin 39; warfarin 36) were entered (mean age 83.9, 47% male). Patients on aspirin had significantly more adverse events (13/39; 33%) than patients on warfarin (2/36; 6%; p=0.002). Ten of 13 aspirin adverse events were caused by side effects and serious bleeding; there were three deaths (two aspirin, one warfarin).

Another RCT[41] recruited patients over 75 years of age without previous stroke or systemic embolism. Patients were randomized into three groups, (A) aspirin 100mg/day, (B) fixed-dose warfarin 1mg/day; and (C) adjusted-dose warfarin with a target range of INR between 1.6 and 2.5. The study was discontinued 6 months after the enrollment of the first patient for safety reasons. Over a mean followup period of 3.7 months, two patients from group B (n=14) developed a dangerous prolongation of the INR (7.0 and 4.2), which led to the discontinuation of fixed-dose warfarin. Another patient from the same group experienced a major bleeding event 1 month after enrollment in the study (INR 5.5). The percentage of INR measurements within the target range was significantly lower in group B (48.7%) than in group C (83.7%) (p<0.001).

A prospective observational study[42] included 207 older people (>75 years) with AF and first ever ischemic stroke. During the followup period (mean 88.4 months, range 3–120), the study population was under either oral anticoagulants (n=72) or aspirin (n=135). The cumulative 10-year mortality and recurrence rates were 92.5 percent (95% CI 85.7 to 99.3) and 66.1 percent (95% CI 43.1 to 89.1), respectively. Increasing age, functional dependency at hospital discharge, and antiplatelet versus anticoagulation therapy were independent determinants of mortality. Antiplatelet versus anticoagulation therapy was the sole determinant of vascular recurrence. Anticoagulation was associated with decreased risk of death (HR 0.47; 95% CI 0.31 to 0.72; p=0.001)) and recurrent thromboembolism (HR 0.31; 95% CI 0.16 to 0.62; p=0.002). These results suggest that the benefits of anticoagulation for secondary stroke prevention in AF patients extend to elderly.

A retrospective cohort analysis[43] evaluated persons discharged on warfarin after an AF admission using data from Medicare's National Stroke Project. It examined antiplatelet therapy among warfarin users and the impact on major bleeding rates. Prediction of concurrent antiplatelet use and hospitalization with a major acute bleed within 90 days after discharge from the index AF admission was assessed. A total of 10,093 warfarin patients met inclusion criteria with a mean age of 77 years; 19.4 percent received antiplatelet therapy. Antiplatelet use was less common among women, older persons, and persons with cancer, terminal diagnoses, dementia, and bleeding history. Persons with coronary disease were more likely to receive an antiplatelet agent. Antiplatelets increased major bleeding rates from 1.3 percent to 1.9 percent (P=0.052). In the multivariate analysis, factors associated with bleeding events included age (OR, 1.03; 95% CI 1.002 to 1.05), anemia (OR, 2.52; 95% CI 1.64 to 3.88), a history of bleeding (OR, 2.40; 95% CI 1.71 to 3.38), and concurrent antiplatelet therapy (OR, 1.53; 95% CI 1.05 to 2.22).

A substudy[44] of the BAFTA trial[39] evaluated 665 patients aged 75 or over with AF based in the community who were randomized within the BAFTA trial and were not taking warfarin throughout or for part of the study period. A total of 54 (8%) patients had an ischemic stroke, four (0.6%) had a systemic embolism, and 13 (2%) had a TIA. Based on this single trial population, current risk stratification schemes in older people with AF have only limited ability to predict the risk of stroke.

Another study[45] examined the effectiveness of oral anticoagulation on risk of stroke of any nature (fatal and nonfatal ischemic and/or hemorrhagic stroke) in patients with nonvalvular AF or flutter living in the County of North Jutland, Denmark. This study used the Hospital

Discharge Registry covering the county (490,000 inhabitants) from 1991 to 1998 to identify 2,699 men and 2,425 women with AF or flutter, aged 60–89 years. The risk of stroke associated with use of oral anticoagulation compared with no use was estimated, after adjustment for age, diabetes and underlying cardiovascular diseases. A total of 838 of 2,699 men (31%) and 552 of 2,425 women (23%) with AF had one or more recorded prescriptions of oral anticoagulation. The incidence rates of stroke were 31 per 1000 person-years of followup in men, and 30 per 1000 person-years of followup in women. The adjusted relative risks of stroke during anticoagulation were 0.6 (95% CI 0.4 to 1.0) in men, and 1.0 (95% CI 0.7 to 1.6) in women compared with nonuse periods. The adjusted relative risks of stroke associated with use of oral anticoagulation compared with no use varied by age in men, but not in women. In men aged 60–74 years the adjusted relative risk associated with use of oral anticoagulation compared with no use was 0.5 (95% CI 0.3 to 0.9), and in men aged 75–89 years the adjusted relative risk of stroke associated with oral anticoagulation compared with no use was 0.9 (95% CI 0.4 to 1.8). The adjusted relative risk of stroke increased with age. In men and women, the risk of stroke amongst patients aged 80–89 years was increased by a factor of 2.0 and 2.9 relative to the stroke risk amongst patients aged 60–69 years.

The RE-LY trial[26] randomized 18,113 patients to receive dabigatran 110 or 150mg twice a day or warfarin dose adjusted to an INR of 2.0–3.0 for a median followup of 2.0 years. A substudy of this trial[46] assessed the impact of age on the findings and found that there was a significant treatment-by-age interaction, such that dabigatran 110mg twice a day compared with warfarin was associated with a lower risk of major bleeding in patients aged <75 years (1.89% vs. 3.04%; p<0.001) and a similar risk in those aged ≥75 years (4.43% vs. 4.37%; p=0.89; p for interaction <0.001), whereas dabigatran 150mg twice a day compared with warfarin was associated with a lower risk of major bleeding in those aged <75 years (2.12% vs. 3.04%; p<0.001) and a trend toward higher risk of major bleeding in those aged ≥75 years (5.10% vs. 4.37%; p=0.07; p for interaction <0.001). The interaction with age was evident for extracranial bleeding, but not for intracranial bleeding, with the risk of the latter being consistently reduced with dabigatran compared with warfarin irrespective of age. Based on these results, patients with AF at risk for stroke, both doses of dabigatran compared with warfarin have lower risks of both intracranial and extracranial bleeding in patients aged <75 years. In those aged ≥75 years, intracranial bleeding risk is lower but extracranial bleeding risk is similar or higher with both doses of dabigatran compared with warfarin.

A subgroup analysis of the RE-LY trial[51], attempted to estimate effects of dabigatran, compared with warfarin, on stroke, bleeding and mortality in patients with AF in the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) trial according to age and analyzed treatment effects using age as a continuous variable and using age categories. The results showed that the benefits of dabigatran versus warfarin regarding stroke (HR range 0.63 (95% CI 0.46 to 0.86) to 0.70 (0.31 to 1.57) for dabigatran 150 mg twice daily), HR range 0.52 (0.21 to 1.29) to 1.08 (0.73 to 1.60) for dabigatran 110 mg twice daily) and intracranial bleeding were maintained across all age groups (interaction p values all not significant). There was a highly significant interaction (p value interaction <0.001) between age and treatment for extracranial major bleeding, with lower rates with both doses of dabigatran compared with warfarin in younger patients (HR 0.78 (0.62 to 0.97) for 150 mg twice daily, HR 0.72 (0.57 to 0.90) for 110 mg twice daily) but similar (HR 1.50 (1.03 to 2.18) for 110 mg twice daily) or higher rates (HR 1.68 (1.18 to 2.41) for 150 mg twice daily) in older patients (≥80 years).

A subgroup analysis of the AVERROES trial looked at the Efficacy and safety of apixaban compared with aspirin in the elderly. compared with aspirin, apixaban was more efficacious for preventing strokes and systemic embolism in patients ≥85 years (absolute rate [AR] 1% per year on apixaban versus 7.5% per year on aspirin; hazard ratio [HR] 0.14, 95% confidence interval [CI] 0.02-0.48) compared with younger patients (AR 1.7% per year on apixaban versus 3.4% per year on aspirin; HR 0.50, 95% CI 0.35-0.69) (P-value for interaction = 0.05). Major hemorrhage was higher in patients ≥85 years compared with younger patients but similar with apixaban versus aspirin in both young and older individuals (4.9% per year versus 1.0% per year on aspirin and 4.7% per year versus 1.2% per year on apixaban) with no significant treatment-by-age interaction (P-value = 0.65).

Two substudies[48,49] of the ARISTOTLE RCT[9] examined the treatment effects of apixaban 5mg twice daily versus warfarin in elderly patients. In the study by Halvorsen, older patients were at higher overall risk for all cardiovascular events. Risk for events increased in a step-wise manner with age (age <65 vs. age 65-74 vs. age ≥ 75) for stroke or systemic embolism (adj HR age 65-74 1.47; 95% CI 1.11 to 1.94; Adj HR age ≥ 75 1.62; 95% CI 1.18 to 2.22; adjusted p=0.10), all-cause mortality (adj HR age 65-74 1.01; CI 0.84 to 1.21; adj HR age ≥ 75 1.53; 95% CI 1.26 to 1.85; adjusted p<0.0001) and major bleeding (adj HR age 65-74 1.52; 95% CI 1.20 to 1.92; adj HR age ≥75 2.18; 95% CI 1.69 to 2.81; adjusted p<0.0001). Across older age groups, patients treated with apixaban had lower rates of stroke or systemic embolism (HR age 65-74 0.72; 95% CI 0.54 to 0.96; HR age ≥ 75 0.71; 95% CI 0.53 to 0.95; interaction with continuous age p=0.11). Similarly, apixaban reduced the risk of major bleeding compared to treatment with warfarin, across older age groups (HR age 65-74 0.71; 95% CI 0.56 to 0.89; HR age ≥75 0.64; 95% CI 0.52 to 0.79; interaction with continuous age p=0.63). There was no significant difference between treatment groups in stroke or systemic embolism or major bleed in patients <65. Further analysis of patients ≥ 75 years old showed a trend toward increasing benefit of apixaban compared to warfarin therapy with regards to bleeding in patients as renal function worsened (HR eGFR >80 0.60; 95% CI 0.28 to 1.32; HR eGFR >50-80 0.79; 95% CI 0.37 to 1.06; HR eGFR >30-50 0.53; 95% CI 0.37 to 0.76; HR eGFR ≤ 30 0.35; 95% CI 0.14 to 0.86; interaction p value 0.16).

The study by Alexander evaluated patients with one criteria for dose reduction (at least two were required to reduce dose to 2.5mg twice daily): 80 years or older, weight ≤ 60 kg and creatinine level of at least 1.5mg/dL. Among patients with weight ≤ 60 kg, those receiving apixaban had a statistically significant decreased risk of major bleeding event (HR 0.6; 95% CI 0.4 to 0.9). Patients 80 years or older and those with creatinine level of at least 1.5mg/dL, were numerically less likely to have a major bleeding event with apixaban, although this did not reach statistical significance (HR 0.7; 95% CI 0.5-1.1 and HR 0.7; 95% CI 0.5 to 1.2 respectively).

A retrospective study of 233 patients aged 80 years or older with AF evaluated the efficacy and safety of oral anticoagulation therapy with low (2.0) versus standard (2.5) INR targets. Hemorrhages and thromboses occurred only in the group with standard INR.[47].

Finally, a substudy[50] of the ROCKET AF[5] RCT evaluated once daily rivaroxaban versus warfarin in elderly patients with AF. Outcomes in patients <75 were compared with those in patients ≥75. Patients 75 or older had lower BMI (27.3 vs. 29.0; p<0.0001), had higher mean $CHADS_2$ score (3.69 vs. 3.30; p<0.0001) and lower rates of congestive heart failure (58.6% vs. 65.5%; p<0.0001) and diabetes (33.8% vs. 45.1%; p<0.0001). Compared to patients treated with warfarin, those randomized to treatment with rivaroxaban had similar rates of stroke/systemic embolism (HR Age ≥75 0.80; 95% CI 0.63 to 1.02; HR Age<75 0.95; 95% CI 0.76 to 1.19; p

value for interaction 0.31) and major bleeding (HR Age ≥75 1.11; 95% CI 0.92 to 1.34; HR Age<75 0.96; CI 0.78 to 1.19; p value for interaction 0.34), regardless of age. The only significant observed difference between treatment groups was in risk of hemorrhagic stroke for patients <75 years old (HR 0.47; 95% CI 0.25 to 0.88).

Fourteen studies including observational, small RCTs, and sub-studies of large RCTs compared the effect of different strategies to prevent stroke and bleeding in elderly participants with AF. Of 7 studies comparing the effects of warfarin vs aspirin in older adults, compared to aspirin, warfarin was generally found to be associated with lower risk of stroke/SE/bleeding for both primary and secondary prevention. In studies comparing the effects of DOACs vs warfarin, the DOACs were generally found to be associated with similar or decreased risk of stroke/SE/bleeding compared with warfarin among older adults.

Patients With AF and Myocardial Infarction

One substudy of the RE-LY trial[26] evaluated the use of therapies for stroke prevention in AF patients with MI.[52] In this analysis, the relative effects of dabigatran versus warfarin on myocardial ischemic events were consistent in patients with or without a baseline history of MI or coronary artery disease. Patients with a baseline history of coronary artery disease (CAD) or previous MI are at risk for recurrent ischemic events. There were 1,886 (31%) CAD/MI patients in the dabigatran 110mg group, 1,915 (31%) in the dabigatran 150mg group, and 1,849 (31%) in the warfarin group. The relative effects of dabigatran compared with warfarin were highly consistent between patients with prior CAD/MI compared with those without (all probability values for interaction were nonsignificant).

Elderly Patients With AF and Myocardial Infarction

One observational study[53] evaluated the effects of a combination of antithrombotics in 7,619 NSTEMI patients aged ≥65 years with AF. Relative to aspirin alone, antithrombotics were associated with increased bleeding risk (adj HR 1.22; 95% CI 1.03 to 1.46 for aspirin+clopidogrel vs. aspirin alone; adj HR 1.46; 95% CI 1.21 to 1.80 for warfarin+aspirin vs. aspirin alone). Patients treated with triple therapy of aspirin+clopidogrel+warfarin had the greatest bleeding risk (HR 1.65; 95% CI 1.30 to2.10). The rates of major cardiac outcomes (death, readmission for MI, or stroke) were similar between groups, although relative to aspirin alone, there was a trend toward lower risk for the warfarin+aspirin group (HR 0.88; 95% CI 0.78 to 1.00).

Patients With AF and Carotid Artery Disease

A single secondary analysis [54] of the ROCKET AF trial [5] evaluated outcomes in patients with AF and carotid artery disease, treated with either warfarin or rivaroxaban. After adjustment, there was no significant difference in rates of stroke or systemic embolism in patients with carotid artery disease compared to those without. Similarly, there was no significant difference in the primary safety endpoint of major/NMCR bleeding between the patients with or without carotid artery disease. Compared to those without carotid artery disease, patients with carotid artery disease had similar prevention of stroke and systemic embolism with apixaban versus warfarin (interaction p value 0.96). Similarly, there was no significant interaction between treatment and presence of carotid artery disease with major or NMCR bleeding (interaction p

value 0.62). This single study suggests no difference in the treatment effects of rivaroxaban and warfarin in patients with carotid artery disease.

Patients With AF and Peripheral Arterial Disease

One secondary analysis[55] of the ARISTOTLE trial[9] evaluated outcomes in patients with AF and peripheral arterial disease (PAD), treated with apixaban versus warfarin. Compared to those without PAD, patients with PAD had similar prevention of stroke and systemic embolism with apixaban versus warfarin (PAD HR 0.63; 95% CI 0.32 to 1.25; No PAD HR 0.80; 95% CI 0.66 to 0.96; interaction p value for PAD versus no PAD 0.52). There was similarly no significant interaction between presence of PAD and treatment group on major bleeding (interaction p value 0.58). While data is only available from one study, this suggests that patients with PAD had similar benefit from treatment with apixaban as compared to those without.

Patients With AF and Underlying Anemia

One analysis[56] of the ARISTOTLE RCT[9] examined patients with anemia treated with apixaban versus warfarin. There was no difference in the benefits of reduced stroke or systemic embolization events (Anemia HR 0.56; 95% CI 0.34 to 0.95; No Anemia HR 0.84; 95% CI 0.68 to 1.01; interaction p value for anemia versus no anemia 0.17) with apixaban in patients with anemia. The incidence of new anemia during treatment was lower in patients with apixaban (HR 0.91; 95% CI 0.84 to 0.98; p=0.037) and there was no significant interaction between underlying anemia and treatment group on any of the bleeding outcomes. This single analysis suggests that the same benefits of apixaban, including decreased risk of stroke or systemic embolism, extend to patients with underlying anemia without differential change in bleeding risk.

Patients With AF and History of Bleeding

A secondary analysis[57] of the ARISTOTLE RCT[9] evaluated clinical outcomes in patients with history of bleeding treated with 5mg twice daily of apixaban versus warfarin. Patients treated with apixaban had consistently lower rates of bleeding overall and this extended to patients with prior history of bleeding. The only p value for interaction that was significant for apixaban versus warfarin was for major or clinically relevant non-major bleeding (History of bleeding HR 0.82; 95% CI 0.66-1.00; No History of Bleeding HR 0.64; 95% CI 0.57 to 0.72; p value for interaction 0.046). While only informed by one study, this suggests that the lower rates of bleeding observed with treatment with apixaban compared to warfarin are generally similar for patients with a history of bleeding. This benefit may not include lower rates of major or clinically relevant non-major bleeding; further data is necessary to clarify this borderline result.

Patients With AF and Chronic Obstructive Pulmonary Disease

Another analysis[58] of the ARISTOTLE trial[9] evaluated the treatment effects of apixaban versus warfarin in patients with chronic obstructive pulmonary disease (COPD). Overall, all-cause mortality was higher in patients with a diagnosis of COPD (adj HR 1.60; 95% CI 1.36 to 1.88; $p<0.001$) while there was no significant difference in major bleeding. There was no significant difference in the effect of apixaban on all-cause mortality (COPD HR 0.80, 95% CI 0.62 to 1.04; No COPD HR 0.92; 95% CI 0.82 to 1.04; p value for interaction 0.35), stroke or

systemic embolism (COPD HR 0.92; 95% CI 0.52 to 1.63; No COPD HR 0.78; 95% CI 0.65 to 0.95; p value for interaction 0.62), or major bleeding (COPD HR 0.83; 95% CI 0.57 to 1.02; No COPD HR 0.67; 95% CI 0.60 to 0.75; p value for interaction 0.42) in patients with and without COPD. This single analysis from the ARISTOTLE trial gives data to suggest that there is no treatment difference in the benefits observed with apixaban in patients with or without COPD.

Patients With AF by Sex

One secondary analysis[59] of the ARISTOTLE trial[9] evaluated the treatment of men versus women with apixaban 5mg twice daily or warfarin. After adjustment, there was no difference between women and men with regard to stroke or systemic embolism (Adj HR 0.91; 95% CI 0.74 to 1.12; p=0.38) but women had significantly less all-cause mortality and cardiovascular death (adjusted HR 0.63; 95% CI 0.55 to 0.73; p<0.001). When evaluated by treatment, there was no significant interaction with sex (women HR 0.73; 95% CI 0.54 to 0.97; men HR 0.84; 95% CI 0.66 to 1.05; p value for interaction 0.45), and major bleeding (women HR 0.56; 95% CI 0.44 to 0.72; men HR 0.88; 95% CI 0.64 to 0.90; p value for interaction 0.06).

In a secondary analysis of the AVERROES study[60] the effect of treatment with aspirin compared with apixaban on ischemic stroke and major bleeding was assessed in women compared with men. Female patients with atrial fibrillation are at increased stroke risk compared with male patients, and the underlying reasons for higher risk are uncertain. Women compared with men tended to be older (aspirin, 71.8 versus 68.8 years; apixaban, 71.4 versus 68.6 years), with a higher proportion of those aged ≥75 years. Also, women had less peripheral artery disease (aspirin, 2.4% versus 3.7%; apixaban, 1.4% versus 3.0%), more heart failure, and higher mean CHADS2 (congestive heart failure, hypertension, age of 75 years or older, diabetes [1 point each], stroke or transient ischemic attack [2 points]) scores (aspirin, 2.2 versus 2.0; apixaban, 2.1 versus 2.0). Women compared with men had higher ischemic stroke rates (aspirin, 3.99% versus 2.28%; apixaban, 1.55% versus 0.82%) but similar bleeding rates (aspirin, 1.29% versus 1.22%; apixaban, 1.15% versus 1.36%). The relative effect of apixaban compared with aspirin was similar in men and women for both ischemic stroke (women, 1.55 % versus 3.99%; hazard ratio, 0.39; 95% confidence interval, 0.23-0.64; men, 0.82 % versus 2.28%; hazard ratio, 0.36; 95% confidence interval, 0.19-0.63; p value for interaction 0.84) and major bleeding (women, 1.15 % versus 1.29%; hazard ratio, 1.15; 95% confidence interval, 0.59-2.23; men, 1.36% versus 1.22%; hazard ratio, 1.13; 95% confidence interval, 0.64-2.02; p value for interaction 0.97).

In only two studies assessing potentially differences in treatment effect by sex both included apixaban but the comparators were different – one was warfarin and one was aspirin. No interaction between sex and treatment was found for major bleeding (for either comparator, warfarin or aspirin) or for ischemic stroke (as compared to aspirin).

Patients With AF and Diabetes

A substudy[61] of the ARISTOTLE RCT[9], analyzed the treatment effect of apixaban 5mg twice daily versus warfarin in patients with and without diabetes. Overall, patients with diabetes were younger, had higher weights, were more likely to have hypertension and prior stroke or systemic embolism, and had higher CHA_2DS_2-VASc Scores. Compared with warfarin, patients with diabetes and who received apixaban were numerically less likely to have stroke or systemic embolism (HR 0.75; 95% CI 0.53 to 1.05) or death from any cause (HR 0.89; 95% CI 0.66 to 1.20). There were no significant interactions related to diabetes for the efficacy endpoints. All-cause bleeding was significantly lower in patients with diabetes who received apixaban (HR

0.73; 95% CI 0.66 to 0.81). While ISTH major bleeding was not significantly lower in patients with diabetes who were treated with apixaban, it was significantly lower in those without diabetes (diabetes HR 0.96; 95% CI 0.74 to 1.25; no diabetes HR 0.60; 95% CI 0.51 to 0.52; p value for interaction 0.0034). This interaction remained after adjustment.

A substudy[62] of the ROCKET AF Trial[5] evaluated treatment effect of rivaroxaban daily versus warfarin in patients with and without diabetes. Overall, 5,695 (39.9%) of patients enrolled in the ROCKET AF trial had diabetes. Patients with diabetes had higher rates of vascular death (3.24 vs. 2.63; p=0.0001) and myocardial infarction (1.35 vs. 0.75; p<0.0001). There was not significant interaction between treatment and diabetes status for the outcomes of stroke/SE (HR diabetes 0.82; 95% CI 0.63 to 1.08; HR no diabetes 0.92; 95% CI 0.75 to 1.13; p value for interaction 0.53) and major/NMCR bleeding (HR diabetes 0.98; 95% CI 0.88 to 1.10; HR no diabetes 1.09; 95% CI 0.99 to 1.20; p value for interaction 0.17). However, in a composite endpoint of stroke/systemic embolism/vascular death/MI, patients with diabetes who were treated with rivaroxaban had slightly lower risk (HR diabetes 0.84; 95% CI 0.72 to 0.99; HR no diabetes 1.01; 95% CI 0.88 to 1.17; p value for interaction 0.097), although the interaction was not significant.

In a supplemental analysis of RE-LY trial.[63] Of 18,113 patients in RE-LY, 4221 patients (23.3%) had DM. Patients with DM were younger (70.9 vs. 71.7 years), more likely to have hypertension (86.6% vs. 76.5%), coronary artery disease (37.4% vs. 24.9%) and peripheral vascular disease (5.6% vs. 3.2%); (all p < 0.01). Time in therapeutic range for warfarin-treated patients was 65% for diabetic versus 68% for non-diabetic patients (p < 0.001). Regardless of assigned treatment, stroke or systemic embolism was more common among patients with DM (1.9% per year vs. 1.3% per year; p<0.001). DM was also associated with an increased risk of death (5.1% per year vs. 3.5% per year; p<0.001) and major bleeding (4.2% per year vs. 3.0% per year; p<0.001). The absolute reduction in stroke or systemic embolism with dabigatran compared to warfarin was greater among patients with DM than those without DM (dabigatran 110mg: 0.59% per year vs. 0.05% per year; dabigatran 150mg: 0.89% per year vs. 0.51% per year). There was however, no statistically significant interaction between treatment (dabigatran 110mg or dabigatran 150 mg vs. warfarin) and diabetes for stroke or systemic embolism, ischemic stroke, hemorrhagic stroke, death, major bleeding, or intracranial bleeding.

The results from three studies assessing the potential impact of diabetes on treatment effect were inconsistent; no impact on treatment effect was seen between dabigatran and warfarin on any of the included efficacy or safety outcomes; a statistically significant interaction between treatment (apixaban vs warfarin) was found only for major bleeding (diabetics did not have the same statistically significant reduction in major bleeding as non-diabetics); and a statistically significant interaction between treatment (rivaroxaban vs warfarin) was found only for a composite endpoint of stroke/systemic embolism/vascular death/MI (diabetics had a statistically significant reduction that was not seen in non-diabetics).

Patients With AF and Aspirin Treatment

A secondary analysis[64] of the ARISTOTLE trial,[9], evaluated the use of apixaban 5mg twice daily compared to warfarin in patients with concomitant aspirin therapy. Overall, patients treated with aspirin were more likely to be male, have a history of MI, PCI, CABG or PAD and to have diabetes or hypertension. After adjustment for baseline confounders and variables associated with aspirin use, patients treated with aspirin had higher rates of thromboembolic events (stroke or systemic embolism, ischemic stroke, myocardial infarction) and higher rates of bleeding.

Apixaban treatment led to similar reductions in stroke or systemic embolism (Aspirin HR 0.58; 95% CI 0.39 to 0.85; No Aspirin HR 0.84; 95% CI 0.66 to 1.07; p value for interaction 0.10) and consistent reductions in major bleeding (aspirin HR 0.77; 95% CI 0.60 to 0.99; no aspirin HR 0.65; 95% CI 0.55 to 0.78; p value for interaction 0.29) in patients treated with and without aspirin.

One study[65] also evaluated the use of aspirin by treatment group in the ROCKET-AF trial.[5] Overall, 5,205 (46.5%) of patients had chronic aspirin use at baseline. Patients on aspirin were younger (median age 72 versus 73 years old) and had slightly higher $CHADS_2$ scores (mean 3.5 versus 3.4). Among all patients, those with baseline aspirin use had higher risk of all-cause death (HR 1.27; 95% CI 1.13 to 1.42; p<0.0001) and vascular death (HR 1.29; 95% CI 1.11 to 1.49; p=0.0006) as well as major or NMCR bleeding (HR 1.32; 95% CI 1.21 to 1.43; p<0.0001) or major bleeding (HR 1.46, 95% CI 1.25 to 1.71; p<0.0001). There was no significant interaction between treatment and use of aspirin versus none on any of the efficacy or safety outcomes (stroke/SE, stroke/SE/vascular death, all-cause death, vascular death, stroke, SE, MI, major/NMCR bleeding, major bleeding, ICH, fatal major bleeding, hemorrhagic stroke).

In an ENGAGE AF substudy,[66] patients who received a single antiplatelet drug during the study at the discretion of their physician were compared to those who did not receive a single antiplatelet drug during the study. A total of 4,912 patients received a single antiplatelet drug during the study of which 92.5% were aspirin. In the high dose edoxaban vs. warfarin comparisons, there were no statistically significant interactions between treatment and use of single antiplatelet drug vs. none on stroke or systemic embolic events, ischemic stroke, hemorrhagic stroke, MI, cardiovascular death, major bleeding, intracranial bleeding, or any bleeding. Similar results were seen for the low dose edoxaban vs. warfarin comparisons and for the large subset of aspirin only users.

From a total of three studies, no impact on treatment effect between apixaban, rivaroxaban, low dose edoxaban or high dose edoxaban vs warfarin was seen in patients with concomitant aspirin administration.

Patients With AF and Hypertension

One secondary analysis[67] of the ROCKET AF[5] RCT evaluated outcomes based on screening systolic blood pressure and hypertension. At baseline, 12,902 patients had a history of controlled or uncontrolled hypertension (HTN). Compared to patients without hypertension, those with hypertension had a trend toward higher risk for stroke or systemic embolism (HTN HR 1.22; 95% CI 0.89 to 1.66; uncontrolled HTN HR 1.42; 95% CI 1.03 to 1.95; p value 0.06). There was no significant interaction between treatment and HTN status (no HTN versus controlled hypertension versus uncontrolled hypertension) on all ischemic/thrombotic or bleeding outcomes. While there is only data from one study available, this suggests that there is no difference in the observed treatment effects of rivaroxaban and warfarin among patients with varying degrees of HTN.

Patients With AF and Heart Failure

In an ENGAGE AF substudy,[68] the 8145 patients in the ENGAGE AF study in either the warfarin or high dose edoxaban treatment groups who had heart failure (6344 with NYHA I-11 and 1801 with NYHA III-IV) were compared to the 5926 who did not have heart failure. There was no statistically significant interaction between heart failure groups (no heart failure, NYHA I-II, and NYHA III-IV) and treatment for stroke or systemic embolic events, ischemic stroke,

hemorrhagic stroke, any cause death, cardiovascular death, cardiovascular hospitalization, major bleeding, intracranial hemorrhage, or GI bleeding.

A secondary analysis[69] of the ROCKET AF RCT[5] evaluated treatment with rivaroxaban once daily versus warfarin in patients with heart failure. Overall, 9033 (63.7%) of patients in the ROCKET AF trial had heart failure diagnosis (clinical HF or EF <40%) at the time of randomization. Patients with heart failure were significantly more likely to have stroke/systemic embolism/vascular death (HR 1.28; 95% CI 1.11 to 1.47; p=0.0006) as well as all-cause death (HR 1.34; 95% CI 1.37 to 1.98; p<0.0001) and vascular death (HR 1.65; 95% CI 1.37 to 1.98; p<0.0001). There was no significant interaction with regards to heart failure status for efficacy or safety outcome between treatment groups. However, patients with heart failure who were treated with rivaroxaban were significantly less likely to experience hemorrhagic stroke (HR 0.38; 95% CI 0.19 to 0.76).

Data from these two studies give similar findings and suggest that patients had similar ischemic and bleeding outcomes based on the treatment received regardless of heart failure status.

Patients With AF and Left Ventricular Hypertrophy

In a post-hoc analysis of the Randomized Evaluation of Long-term anticoagulation therapY (RE-LY) Study[70] the hypothesis that left ventricular hypertrophy (LVH) interferes with the antithrombotic effects of dabigatran and warfarin in patients with atrial fibrillation (AF) was tested. LVH was defined by electrocardiography (ECG) and included patients with AF on the ECG tracing at entry. LVH was present in 2353 (22.7%) out of 10 372 patients. In patients without LVH, the rates of primary outcome (composite of stroke and systemic embolism) were 1.59% per year with warfarin, 1.60% with dabigatran 110 mg (HR vs. warfarin 1.01, 95% confidence interval (CI) 0.75-1.36) and 1.08% with dabigatran 150 mg (HR vs. warfarin 0.68, 95% CI 0.49-0.95). In patients with LVH, the rates of primary outcome were 3.21% per year with warfarin, 1.69% with dabigatran 110 mg (HR vs. warfarin 0.52, 95% CI 0.32-0.84) and 1.55% with 150 mg (HR vs. warfarin 0.48, 95% CI 0.29-0.78). The interaction between LVH status and dabigatran 110 mg vs. warfarin was significant for the primary outcome (P = 0.021) and stroke (P = 0.016), but not for major bleeding (p=0.235). However, there was no statistically significant interaction between LVH status and dabigatran 150 mg vs. warfarin for the primary outcome (p=0.244), any stroke (P=0.147) or major bleeding (p=0.888).

In this single study, the treatment effect (reduced risk of stroke or systemic embolism, reduced risk of any stroke and no difference in major bleeding) between the FDA approved 150 mg dose of dabigatran and warfarin was not statistically significantly impacted by LVH.

Patients With AF and History of Falls

A single substudy [71] of the ARISTOTLE trial [9] evaluated the comparison of treatment with apixaban versus warfarin in patients with a history of falling. Overall, patients with a history of falling had similar risk of stroke or systemic embolism (adj HR 1.12; 95% CI 0.72 to 1.72; p=0.618) after adjustment compared to those without a history of falls. However, there was an increase in the risk of major or NMCR bleeding (adj HR 1.27; 95% CI 1.03 to 1.58; p=0.028), any bleeding (adj HR 1.19; 95% CI 1.05 to 1.34; p=0.005) and intracranial bleeding (HR 1.96; 95% CI 1.06 to 3.61; p=0.032) in patients with prior history of falling. When outcomes were evaluated based on treatment group, no significant interaction was found between a history of falls and treatment with apixaban versus warfarin for any of the ischemic or bleeding endpoints.

This single study suggests that while patients with a history of falls have increased risk of bleeding overall, there was no significant difference in outcomes based on treatment with apixaban compared to warfarin.

Patients With AF and a History of Cancer

One substudy [72] of the ARISTOTLE trial [9] examined the treatment of patients with atrial fibrillation and a history of cancer with apixaban compared to warfarin. Overall, three was no difference in the rates of stroke or systemic embolism in patients with a history of cancer compared to those without (HR 0.93; 95% CI 0.63 to 1.37; p=0.710). After adjustment, there was no relationship between cancer history and risk of major or NMCR bleeding (HR 1.25; 95% CI 1.04 to 1.151; p=0.0181). Similarly, evaluation of outcomes based on treatment group showed no significant interaction between a history of cancer and treatment with apixaban or warfarin on either ischemic of bleeding endpoints. There was a trend toward a significant interaction between cancer status and treatment effect only for death from any cause, although this did not reach statistical significance. This single study suggests that there is no difference in the treatment effect observed with apixaban in patients with a history of cancer compared to those without.

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Appendix H. PCORI Methodology Standards Checklist

PCORI Methodology Standards Checklist: SER Update					
Contract No.	**290-2015-00004-I**				
Task Order No.	**9**				
EPC	**Duke University**				
Project Title	**Stroke Prevention in Patients With Atrial Fibrillation: A Systematic Review Update**				
Standard Category	**Abbrev.**	**Standard**	**Is this standard applicable to this SER update?**	**List sections and pages of the SER report where you address this standard**	**If applicable, describe how and why the SER update deviated from this standard?**
Cross-Cutting Standards					
Standards for Formulating Research Questions	RQ-1	Identify Gaps in Evidence	Yes	ES6, 5, 198	
	RQ-2	Develop a Formal Study Protocol	Yes	9	
	RQ-3	Identify Specific Populations and Health Decision(s) Affected by the Research	Yes	11, 116, 161-181	

PCORI Methodology Standards Checklist: SER Update					
	RQ-4	Identify and Assess Participant Subgroups	Yes	161-181	
	RQ-5	Select Appropriate Interventions and Comparators	Yes	11-12	
	RQ-6	Measure Outcomes that People Representing the Population of Interest Notice and Care About	Yes	13	
Standards Associated with Patient-Centeredness	PC-1	Engage people representing the population of interest and other relevant stakeholders in ways that are appropriate and necessary in a given research context.	Yes	5-6, 9, 20	
	PC-2	Identify, Select, Recruit, and Retain Study Participants Representative of the Spectrum of the Population of Interest and Ensure that Data Are Collected Thoroughly and Systematically from All Study Participants	N/A		
	PC-3	Use Patient-Reported Outcomes When Patients or People at Risk of a Condition Are the Best Source of Information	N/A		

PCORI Methodology Standards Checklist: SER Update					
	PC-4	Support dissemination and implementation of study results	N/A		
Standards for Data Integrity and Rigorous Analyses	IR-1	Assess Data Source Adequacy	Yes	9-19	
	IR-2	Describe Data Linkage Plans, if Applicable	N/A		
	IR-3	A priori, Specify Plans for Data Analysis that Correspond to Major Aims	Yes	17-18	
	IR-4	Document Validated Scales and Tests	Yes	16-17	
	IR-5	Use Sensitivity Analyses to Determine the Impact of Key Assumptions	Yes	Forest Plots	
	IR-6	Provide Sufficient Information in Reports to Allow for Assessments of the Study's Internal and External Validity	Yes	9-20, Appendixes	
Standards for Preventing and	MD-1	Describe in Protocol Methods to Prevent and Monitor Missing Data	N/A		

PCORI Methodology Standards Checklist: SER Update					
Handling Missing Data	MD-2	Describe Statistical Methods to Handle Missing Data in Protocol	N/A		
	MD-3	Use Validated Methods to Deal with Missing Data that Properly Account for Statistical Uncertainty Due to Missingness	N/A		
	MD-4	Record and Report All Reasons for Dropout and Missing Data, and Account for All Patients in Reports	N/A		
	MD-5	Examine Sensitivity of Inferences to Missing Data Methods and Assumptions, and Incorporate into Interpretation	N/A		
Standards for Heterogeneity of Treatment Effect (HTE)	HT-1	State the Goals of HTE Analyses	N/A		
	HT-2	For all HTE Analyses, Pre-specify the analysis plan; for Hypothesis driven HTE Analyses, Pre-specify Hypotheses and supporting evidence base	N/A		

PCORI Methodology Standards Checklist: SER Update					
	HT-3	All HTE claims must be based on appropriate statistical contrasts among groups being compared, such as interaction tests or estimates of differences in treatment effect	N/A		
	HT-4	For Any HTE Analysis, Report All Pre-specified Analyses and, at Minimum, the Number of Post-hoc Analyses, Including all Subgroups and Outcomes Analyzed	N/A		
Standards for Specific Study Designs and Methods					
Standards for Data Registries	DR-1	Requirements for the Design and Features of Registries	N/A		
	DR-2	Standards for Selection and Use of Registries	N/A		
	DR-3	Robust Analysis of Confounding Factors	N/A		
Standards for Data Networks as Research-	DN-1	Requirements for the Design and Features of Data Networks	N/A		

PCORI Methodology Standards Checklist: SER Update					
Facilitating Structures	DN-2	Standards for Selection and Use of Data Networks	N/A		
Causal Inference Standards	CI-1	Define Analysis Population Using Covariate Histories	N/A		
	CI-2	Describe Population that Gave Rise to the Effect Estimate(s)	N/A		
	CI-3	Precisely Define the Timing of the Outcome Assessment Relative to the Initiation and Duration of Exposure	N/A		
	CI-4	Measure Confounders before Start of Exposure. Report data on confounders with study results	N/A		
	CI-5	Report the assumptions underlying the construction of Propensity Scores and the comparability of the resulting groups in terms of the balance of covariates and overlap	N/A		

PCORI Methodology Standards Checklist: SER Update					
	CI-6	Assess the Validity of the Instrumental Variable (i.e. how the assumption are met) and report the balance of covariates in the groups created by the IV for all IV analyses	N/A		
Standards for Adaptive and Bayesian Trial Designs	AT-1	Specify Planned Adaptations and Primary Analysis	N/A		
	AT-2	Evaluate Statistical Properties of Adaptive Design	N/A		
	AT-3	Specify Structure and Analysis Plan for Bayesian Adaptive Randomized Clinical Trial Designs	N/A		
	AT-4	Ensure Clinical Trial Infrastructure Is Adequate to Support Planned Adaptation(s)	N/A		
	AT-5	Use the CONSORT statement, with Modifications, to Report Adaptive Randomized Clinical Trials	N/A		
Standards for Studies of Diagnostic Tests	DT-1	Specify Clinical Context and Key Elements of Diagnostic Test Study Design	N/A		

PCORI Methodology Standards Checklist: SER Update					
	DT-2	Study Design Should be Informed by Investigations of the Clinical Context of Testing	N/A		
	DT-3	Assess the Effect of Factors Known to Affect Diagnostic Performance and Outcomes	N/A		
	DT-4	Structured Reporting of Diagnostic Comparative Effectiveness Study Results	N/A		
	DT-5	Focus studies of diagnostic tests on patient centered outcomes, using rigorous study designs with preference for randomized controlled trials	N/A		
Standards for Systematic Reviews	SR-1	Adopt the Institute of Medicine (IOM) standards for systematic reviews of comparative effectiveness research, with some qualifications.	Yes	9-20	

Appendix I. Expert Guidance and Review

Expert Guidance and Review

Stakeholders, including Key Informants and Technical Experts, participated in two virtual workshops by PCORI in December 2016 and January 2017 to help formulate the research protocol. Details on the virtual workshop, including a list of participants, can be found at https://www.pcori.org/events/2016/updating-systematic-reviews-pcori-virtual-multi-stakeholder-workshop-treatment-atrial (December 2016) and https://www.pcori.org/events/2017/updating-systematic-reviews-pcori-virtual-multi-stakeholder-workshop-newer-oral (January 2017).

Key Informants in the workshop included end users of research, such as patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Technical Experts in the workshop included multidisciplinary groups of clinical, content, and methodological experts who provided input in defining populations, interventions, comparisons, and outcomes and identified particular studies or databases to search. They were selected to provide broad expertise and perspectives specific to the topic under development.

During the virtual workshop, stakeholders reviewed scoping for the updated review, prioritized key questions, and discussed where the evidence base has accumulated since the prior review and emerging issues in preventing strokes in patients with atrial fibrillation. This review's protocol was developed based upon findings from the workshop.

Key Informants and Technical Experts do not do analysis of any kind nor do they contribute to the writing of the report. They have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanisms.

Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report does not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential non-financial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential non-financial conflicts of interest identified.

The list of Peer Reviewers follows:

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