Effective Health Care Program

Comparative Effectiveness Review
Number 123

Stroke Prevention in Atrial Fibrillation

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Number 123

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input.

We welcome comments on this systematic review. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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Key Informants

In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informants' input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

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In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

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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 nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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Stroke Prevention in Atrial Fibrillation

Structured Abstract

Objectives. Oral anticoagulation with vitamin K antagonists (VKAs) has long been the gold standard therapy for stroke prevention in nonvalvular atrial fibrillation (AF). Limitations in monitoring and compliance of VKAs have fueled the development of new antithrombotic strategies, devices, and oral anticoagulants, including oral direct thrombin inhibitors and factor Xa inhibitors. This review updates previous reviews, particularly with regard to these newer treatment options and the optimal risk stratification tools for stroke and bleeding prediction.

Data sources. We searched PubMed®, Embase®, and the Cochrane Database of Systematic Reviews for relevant English-language comparative studies published from January 1, 2000, to August 14, 2012.

Review methods. Two investigators screened each abstract and full-text article for inclusion, abstracted data, rated quality and applicability, and graded evidence. When possible, random-effects models were used to compute summary estimates of effects.

Results. Our review included 122 articles (92 unique studies), comprising 37 studies relevant to predicting thromboembolic risk, 17 relevant to predicting bleeding risk, 43 relevant to interventions for preventing thromboembolic events, 13 relevant to anticoagulation strategies in patients undergoing invasive procedures, and no studies relevant to strategies for switching between warfarin and novel oral anticoagulants or to stroke prevention after a hemorrhagic event. Across the Key Questions addressing prediction of stroke and bleeding risk, evidence was limited by variability in reporting and in underlying treatment of AF. Data suggest that the continuous $CHADS_2$ (Congestive heart failure, Hypertension, Age ≥75, Diabetes mellitus, prior Stroke/transient ischemic attack [2 points]) and continuous 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) scores have the greatest discrimination for stroke risk (c-statistic 0.71 [95% confidence interval (CI), 0.66 to 0.75], and c-statistic 0.70 [95% CI 0.66 to 0.75], respectively; low strength of evidence for both scores) and that the HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly [>65 years], Drugs/alcohol concomitantly) score has the greatest discrimination for bleeding risk (moderate strength of evidence).

Evidence evaluating interventions for stroke prevention was limited by the small number of studies for specific comparisons and lack of direct comparisons of novel anticoagulants, although many included studies were good-quality randomized controlled trials involving more than 5,000 patients. We found that a factor IIa inhibitor (dabigatran 150 mg) was superior to warfarin in reducing the incidence of stroke (including hemorrhagic) or systemic embolism (relative risk [RR] 0.66; 95% CI 0.53 to 0.82), with no significant difference in the occurrence of major bleeding (RR 0.93; 95% CI 0.81 to 1.07) (high strength of evidence for both outcomes). The Xa inhibitor rivaroxaban was noninferior to warfarin in preventing stroke or systemic embolism (moderate strength of evidence), with similar rates of major bleeding and death (high strength of evidence). The Xa inhibitor apixaban was superior to warfarin in reducing the incidence of

stroke or systemic embolism (hazard ratio [HR] 0.79; 95% CI 0.66 to 0.95; high strength of evidence); major bleeding (HR 0.69; 95% CI 0.60 to 0.80; high strength of evidence); and all-cause mortality (HR 0.89; 95% CI 0.80 to 0.998; moderate strength of evidence). Apixaban was also superior to aspirin in reducing the incidence of stroke or systemic embolism (HR 0.45; 95% CI 0.32 to 0.62), with similar hemorrhagic events, including major bleeding (HR 1.13; 95% CI 0.74 to 1.75), in patients who are not suitable for oral anticoagulation (high strength of evidence for both outcomes). However, no studies directly compared the new therapies. Evidence for patients undergoing invasive procedures, switching among anticoagulant therapies, and starting or restarting anticoagulant therapy after previous major bleeding events was insufficient.

Conclusions. Overall, we found that $CHADS_2$ and CHA_2DS_2-VASc scores have the best discrimination ability for stroke events in patients with AF among the risk scores we reviewed, whereas HAS-BLED provides the best discrimination of bleeding risk. Imaging tools require further evidence in regard to their appropriate use in clinical decisionmaking. Improved evidence of the use of these scores among patients on therapy is also required. Newer anticoagulants show early promise of reducing stroke and bleeding events when compared with warfarin, and apixaban shows safety and efficacy in patients who are not candidates for warfarin. However, further studies are required for key clinical scenarios involving anticoagulation use and procedures, switching or bridging therapies, and when to start anticoagulation after a hemorrhagic event.

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Executive Summary

Background

Atrial Fibrillation and Stroke

Atrial fibrillation (AF) is a common type of supraventricular tachyarrhythmia. While a supraventricular tachyarrhythmia is a tachycardic rhythm originating above the ventricular tissue, AF is characterized by uncoordinated atrial activation with consequent deterioration of mechanical function.[1] AF is the most common cardiac arrhythmia 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 adult population,[2,3] occurring in about 2.2 million people in the United States. The prevalence increases to about 6 percent in people age 65 or older and to 10 percent in people age 80 or older.[4] The burden of AF in the United States is increasing. It is estimated that by the year 2050 there will be 12.1 million Americans with AF (95% confidence interval [CI] 11.4 to 12.9), representing more than a twofold (240%) 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 threefold increase from 2000.[5]

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 fivefold 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] Furthermore, AF-related strokes are more severe, with patients twice as likely to be bedridden as patients with stroke from other etiologies, and are also more likely to result in death.[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 50–59 years old to 23 percent for those who are 80–89 years old.[10] Prior stroke has been identified by the Stroke Risk in Atrial Fibrillation Working Group as the strongest risk factor, with an average risk of 10 percent per year for stroke in patients with AF.[13] Aggressive primary prevention and intervention once these risk factors are present are essential to optimally manage the increased risk of developing AF and stroke independently or as a result of AF.

Stroke Prevention Strategies in AF

Management of AF involves three distinct areas: rate control, rhythm control, and prevention of thromboembolic events. This comparative effectiveness review (CER) focuses on the last area. Research for CER 119, "Treatment of Atrial Fibrillation," focusing on the treatment of AF through rate or rhythm control, was conducted in parallel with this CER and is available on the Effective Health Care Web site (www.effectivehealthcare.ahrq.hhs.gov/reports/final.cfm).

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.

Risk Stratification

A number of studies have examined the appropriate populations and therapies for stroke prophylaxis in AF. Despite existing risk stratification tools with overlapping characteristics, the major risk factors for ischemic stroke and systemic embolism in patients with nonvalvular AF are congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and prior stroke or transient ischemic attack (TIA). These risk factors are the elements that form the $CHADS_2$ (Congestive heart failure, Hypertension, Age ≥75, Diabetes mellitus, prior Stroke/transient ischemic attack [2 points]) score.[14] This score ranges from 0 to 6, 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 1.9 percent in patients with a $CHADS_2$ score of 0 to 18.2 percent in patients with a $CHADS_2$ score of 6. However, because of the overlap with factors also associated with increased risk of bleeding, the $CHADS_2$ score currently appears to be underused to guide decisions about antithrombotic therapy.

Lip and colleagues built upon the $CHADS_2$ score and other risk stratification schema to develop the 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), which ranges from 0 to 9 and aims to be more sensitive than the $CHADS_2$ score, specifically seeking to identify patients who are at low risk for stroke based on earlier risk scores but for whom antithrombotic therapy may be beneficial—for example, women and younger patients.[15]

Assessing the risk of bleeding in patients with AF 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 with 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 2–3 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 (MI) or ischemic heart disease, anemia, and concomitant use of antiplatelet therapy in anticoagulated patients. The HAS-BLED scale (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly [>65 years], Drugs/alcohol concomitantly) was developed for estimating bleeding risk in patients with chronic AF treated with warfarin. Scores on this scale range from 0 to 9. A score ≥3 indicates a high risk of bleeding with oral anticoagulation and/or aspirin.[16] The HAS-BLED score may aid decisionmaking in clinical practice and is recommended by the current European Society of Cardiology AF guidelines.[17] However, uncertainty remains, both about whether other clinical or imaging tools might improve prediction of stroke or bleeding risk, and about how the available tools can best be disseminated into routine management of AF patients.

The current underutilization of risk assessment tools could be due to a number of reasons, including perceived lack of evidence to support routine use, limited comparative studies on the different tools, difficulty in using the tools at the bedside, clinical inertia, and inadequate provider knowledge and awareness of the existing tools. Independent assessments of the currently available risk assessment tools for thromboembolic events and major bleeding episodes are needed to highlight the relative strengths of the various tools for predicting events. Also, an assessment of how the application of these tools may improve outcomes could help improve their utility in clinical practice. Finally, the use of imaging tools for assessing thromboembolic risk has not been formally reviewed to date. A comparative and thorough assessment of current tools could assist providers in understanding the clinical value of appropriately judging risk and treating accordingly.

Therapeutic Options for Stroke Prevention in AF

VKAs are highly effective for the prevention of stroke in patients with nonvalvular AF. VKAs such as warfarin have been in use for over 50 years. These compounds create an anticoagulant effect by inhibiting the y-carboxylation of vitamin K–dependent factors (II, VII, IX, and X).[18] In a meta-analysis of 29 randomized controlled trials (RCTs) including 28,000 patients with nonvalvular AF, warfarin therapy led to a 64 percent relative risk 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%).[19]

Over the last decades, oral anticoagulation with VKAs has been the gold standard therapy for stroke prevention in nonvalvular AF. Thromboprophylaxis with VKAs for patients with nonvalvular AF at risk for stroke is, however, suboptimal, due primarily to the many limitations and disadvantages in use of VKAs. VKAs have a narrow therapeutic window and require frequent monitoring and lifestyle adjustments, which make their use less than ideal and adherence sometimes problematic.

The narrow therapeutic window for warfarin has clinical implications in the undertreatment and overtreatment of patients, which increase the risk of thromboembolic events and bleeding, respectively. Warfarin-naïve patients experience a threefold increased risk of bleeding in the first 90 days of treatment compared with patients already on warfarin.[20,21] Failure to prescribe warfarin in eligible patients is a pervasive problem, despite the adoption of performance measures and guidelines advocating its use in patients with nonvalvular AF who have moderate to severe risk of stroke.[22,23] One out of three Medicare AF patients eligible for anticoagulation therapy is not prescribed warfarin. In the Get With The Guidelines (GWTG) registry, only 65 percent of eligible patients with heart failure and AF were prescribed warfarin at discharge.[24,25] Unfortunately, use of warfarin in the GWTG quality improvement program did not increase over time, and when warfarin was not prescribed at discharge after a stroke related to AF, initiation in eligible patients was low in the ambulatory setting.

New devices and systemic therapies have been developed for stroke prophylaxis and are in testing or have been approved for use. Mechanical interventions for stroke prophylaxis have emerged and are growing in use. For example, left atrial appendage (LAA) occlusive devices are an alternative treatment strategy used to prevent blood clot formation in patients with AF. For patients with AF who are elderly (at high risk for falls), have a prior bleeding history, are pregnant, and/or are noncompliant (which can be a significant issue for those on warfarin), LAA occlusion may be a better stroke prevention strategy than oral anticoagulation. Therefore, both

anticoagulation and LAA occlusion need to be considered when evaluating stroke prevention strategies for patients with AF.

New anticoagulants are challenging the predominance of VKAs for stroke prophylaxis in AF. Since 2007, three large trials comparing novel anticoagulants with VKAs have been completed, with a combined sample size of ~50,000 subjects:

- RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy), with approximately 18,000 subjects and evaluating the new direct factor IIa (thrombin) inhibitor dabigatran[26]
- 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 new direct factor Xa inhibitor rivaroxaban[27]
- ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation), with approximately 18,000 subjects and evaluating the new direct factor Xa inhibitor apixaban[28]

At the time of release of this report, all three of these agents (dabigatran, rivaroxaban, and apixaban) have been approved by the U.S. Food and Drug Administration (FDA). Additional anticoagulant therapies in the investigational stage (without FDA approval) include edoxaban and idraparinux.

The evolution of newer anticoagulation agents, like those studied in the large trials above, as well as the risks and benefits when compared with LAA occlusion devices and older antiplatelet and anticoagulation strategies, make stroke prevention in AF an area of further clinical uncertainty. Furthermore, these new therapies highlight the need to reconsider their comparative effectiveness and safety when compared with standard antithrombotic and antiplatelet therapies and with each other.

Even with treatment for stroke prophylaxis in patients with nonvalvular AF, numerous unanswered questions persist around managing patients undergoing invasive or surgical procedures. Patients receiving long-term anticoagulation therapy may need to stop this therapy temporarily before undergoing certain procedures in which the risk of bleeding is high. Because VKAs have a long half-life, patients need to stop these medications approximately 5 days before an invasive procedure. However, 5 days without an oral anticoagulant can increase the risk of ischemic events. Thus, one option often used in clinical practice is "bridging," in which a different, parenteral anticoagulant with a shorter half-life (e.g., low–molecular-weight heparin or unfractionated heparin) is given preprocedure and after the oral anticoagulant is stopped. Usually, this parenteral anticoagulant is restarted and maintained after the procedure together with the VKA until the INR is in the 2–3 range. Although bridging is done in clinical practice, there are data demonstrating that bridging is associated with increased risk of bleeding.[29-33] In summary, the real risk-benefit of bridging from VKAs to a parenteral anticoagulant in patients with AF undergoing an invasive procedure is unknown; it is currently under study in a trial sponsored by the National Institutes of Health called BRIDGE (Bridging Anticoagulation in Patients who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure or Surgery).

In addition, there is uncertainty regarding strategies for switching patients from warfarin to the new generation of direct thrombin inhibitors and about considerations when restarting anticoagulation in patients after a hemorrhagic event. For example, in patients with AF

undergoing surgery or percutaneous procedures, the duration of withholding anticoagulant therapy is not well defined. Also, synthesis of the evidence on the safety and timing of restarting patients on VKAs or antithrombin inhibitors after a hemorrhagic stroke remains lacking. These are complex and common scenarios, and a systematic review of the currently available data can provide clinicians with evidence to incorporate into their clinical practice, while at the same time shedding light on areas that require further research.

Scope and Key Questions

This CER was funded by the Agency for Healthcare Research and Quality (AHRQ) and is designed to evaluate the comparative safety and effectiveness of stroke prevention strategies in patients with nonvalvular AF.

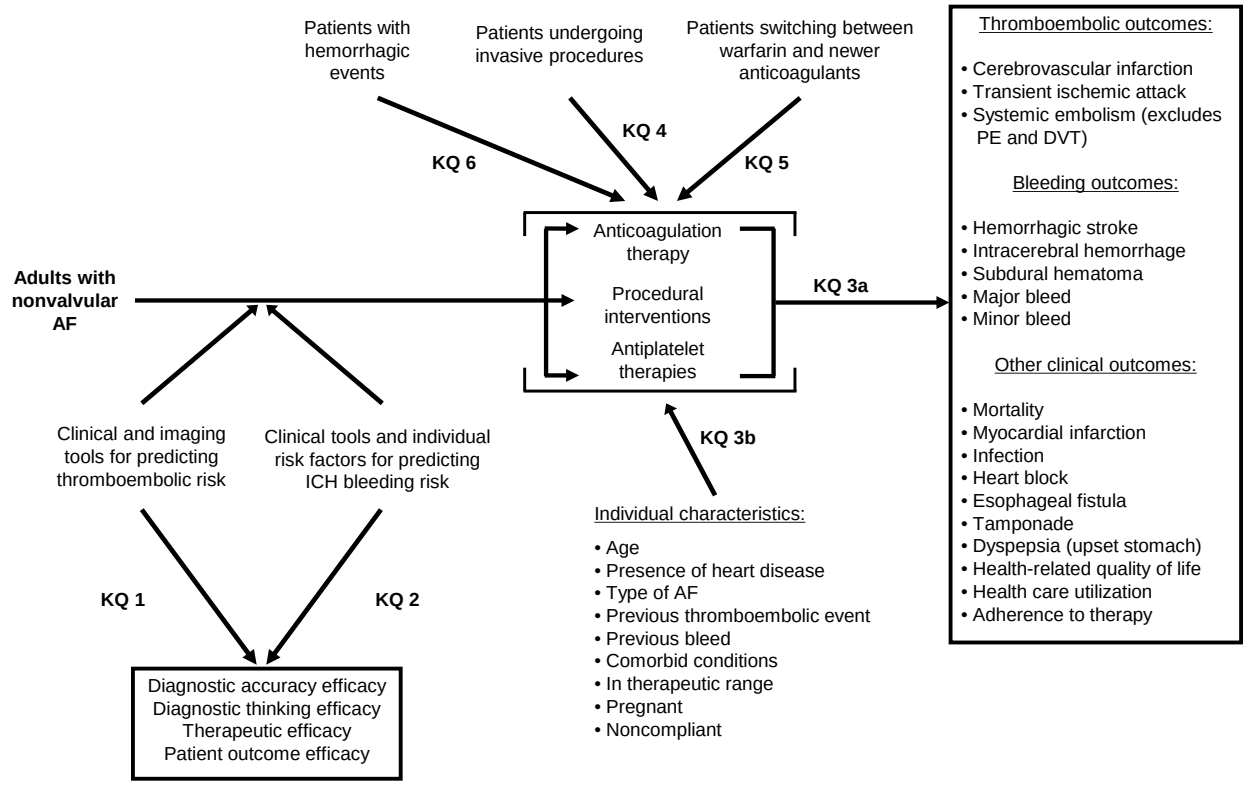
With input from our Key Informants, we constructed Key Questions (KQs) using the general approach of specifying the populations, interventions, comparators, outcomes, timing, and settings of interest (PICOTS). (See the section "Inclusion and Exclusion Criteria" in the Methods chapter of the full report for details.)

The KQs considered in this CER are as follows:

- **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?
- **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?
- **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?
- **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?
- **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?
- **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?

Figure A depicts the KQs within the context of the PICOTS.

Figure A. Analytic framework



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

Methods

The methods for this CER follow those suggested in the AHRQ "Methods Guide for Effectiveness and Comparative Effectiveness Reviews" (Methods Guide)[34] and "Methods Guide for Medical Test Reviews."[35]

Input From Stakeholders

During the topic refinement stage, we solicited input from Key Informants representing medical professional societies/clinicians in the areas of general internal medicine, cardiology, cardiothoracic surgery, neurology, electrophysiology, and primary care; patients; scientific experts; and payers to help define the KQs. The KQs were then posted for public comment for 4 weeks from September 19 to October 17, 2011, and the comments received were considered in the development of the research protocol. We next convened a Technical Expert Panel (TEP) comprising clinical, content, and methodological experts to provide input in defining populations, interventions, comparisons, and outcomes, and in identifying particular studies or databases to search. The Key Informants and members of the TEP were required to disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts. Any potential conflicts of interest were balanced or mitigated. Neither Key Informants nor members of the TEP performed analysis of any kind, nor did any of them contribute to the writing of this report. Members of the TEP were invited to provide feedback on an initial draft of the review protocol, which was then refined based on their input, reviewed by AHRQ, and posted for public access on the AHRQ Effective Health Care Web site.[36]

Literature Search Strategy

To identify relevant published literature, we searched PubMed®, Embase®, and the Cochrane Database of Systematic Reviews (CDSR), limiting the search to studies published from January 1, 2000, to August 14, 2012. We believe that the evidence published from 2000 on represents the current standard of care for patients with AF and relevant comorbidities. Where possible, we used existing validated search filters (such as the Clinical Queries Filters in PubMed). An experienced search librarian guided all searches. We supplemented the electronic searches with a manual search of citations from a set of key primary and systematic review articles.

As a mechanism to ascertain publication bias, we searched ClinicalTrials.gov to identify completed but unpublished studies.

We used several approaches to identify relevant gray literature; these included requests to drug and device manufacturers for scientific information packets and searches of trial registries and conference abstracts for relevant articles from completed studies. Gray literature databases included ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform search portal, and ProQuest COS Conference Papers Index.

Inclusion and Exclusion Criteria

Criteria used to screen articles for inclusion/exclusion at both the title-and-abstract and full-text screening stages are detailed in Table 1 of the full report. For all KQs, the search focused on English-language studies (randomized controlled trials [RCTs] or observational) published since 2000 that were comparative assessments of tools for predicting thromboembolic and bleeding risks, or of stroke prevention therapies for adult patients with nonvalvular AF. The following outcomes were considered: assessment of thromboembolic outcomes (cerebrovascular infarction, TIA, systemic embolism); prevention of bleeding outcomes (hemorrhagic stroke, intracranial hemorrhage [intracerebral hemorrhage, subdural hematoma], major and minor bleed); other clinical outcomes (MI, mortality), as well as diagnostic accuracy and impact on decisionmaking.

Study Selection

Using the prespecified inclusion and exclusion criteria, titles and abstracts were reviewed independently by two investigators 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. Differences were reconciled through review and discussion, or through a third-party arbitrator, if needed. Relevant review articles, meta-analyses, and methods articles were flagged for manual searching of references and cross-referencing against the library of citations identified through electronic database searching. All screening decisions were made and tracked in a Distiller SR database (Evidence Partners Inc., Manotick, Ontario, Canada).

Data Extraction

The research team created data abstraction forms and evidence table templates for each KQ. Based on clinical and methodological expertise, a pair of investigators was assigned to abstract data from each eligible article. Disagreements were resolved by consensus, or by obtaining a third reviewer's opinion if consensus could not be reached.

Quality Assessment of Individual Studies

We evaluated the quality of individual studies using the approach described in the Methods Guide.[34] To assess quality, we used the following strategy: (1) classify the study design, (2) apply predefined criteria for quality and critical appraisal, and (3) arrive at a summary judgment of the study's quality. Criteria of interest for all studies included similarity of groups at baseline, extent to which outcomes were described, blinding of subjects and providers, blinded assessment of the outcome(s), intention-to-treat analysis, differential loss to followup between the compared groups or overall high loss to followup, and conflicts of interest. Criteria specific to RCTs included methods of randomization and allocation concealment. For observational studies, additional elements such as methods for selection of participants, measurement of interventions/exposures, addressing any design-specific issues, and controlling confounding were considered. We used the summary ratings of good, fair, or poor based on the study's adherence to well-accepted standard methodologies and adequate reporting.

For studies of diagnostic tests (KQs 1 and 2), we used the QUality Assessment tool for Diagnostic Accuracy Studies (QUADAS)-2[37] to assess quality. QUADAS-2 describes risk of bias in four key domains: patient selection, index test(s), reference standard, and flow and timing. The questions in each domain are rated in terms of risk of bias and concerns regarding applicability, with associated signaling questions to help with these bias and applicability judgments.

Data Synthesis

We considered meta-analysis for comparisons for which at least three studies reported the same outcome. Feasibility depended on the volume of relevant literature, conceptual homogeneity of the studies (both 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 (KQs 3–6), when appropriate.

When a meta-analysis was appropriate, we used random-effects models to synthesize the available evidence quantitatively using Comprehensive Meta-Analysis software (Version 2; Biostat, Englewood, NJ) and the DerSimonian and Laird method.[38] We tested for 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. When we were able to calculate hazard ratios, we assumed that a hazard ratio 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 for the discrimination abilities of the studied tools. 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 discrimination adequate for genuine clinical utility.[39] 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 discrimination accuracy in the patient dataset 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.

We hypothesized that the methodological quality of individual studies, study type, 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 rated the strength of evidence for each KQ and outcome using the approach described in the Methods Guide.[34,40] We assessed four domains: risk of bias, consistency, directness, and precision. We also assessed publication bias. These 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. 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.[41] We assumed that outcomes based on only one study should not be downgraded for lack of consistency if the study included more than 1,000 patients. Intention-to-treat findings were evaluated when available and form the basis of our strength-of-evidence ratings. When only on-treatment findings were available, our confidence in the stability of our findings was reduced, and therefore the related strength-of-evidence rating was lowered. Finally, when outcomes were assessed by large RCTs and smaller studies, we focused our strength-of-evidence rating on the findings from the large RCTs and then increased or decreased the strength-ofevidence rating depending on whether findings from the smaller studies were consistent or inconsistent with those from the large RCTs.

Applicability

We assessed applicability across our KQs using the method described in the Methods Guide.[34,42] In brief, this method uses the PICOTS format as a way to organize information relevant to applicability. The most important issue with respect to applicability is whether the outcomes are different across studies that recruit different populations (e.g., age groups, exclusions for comorbidities) or use different methods to implement the interventions of interest; that is, important characteristics are those that affect baseline (control-group) rates of events, intervention-group rates of events, or both. We summarized issues of applicability qualitatively.

Results

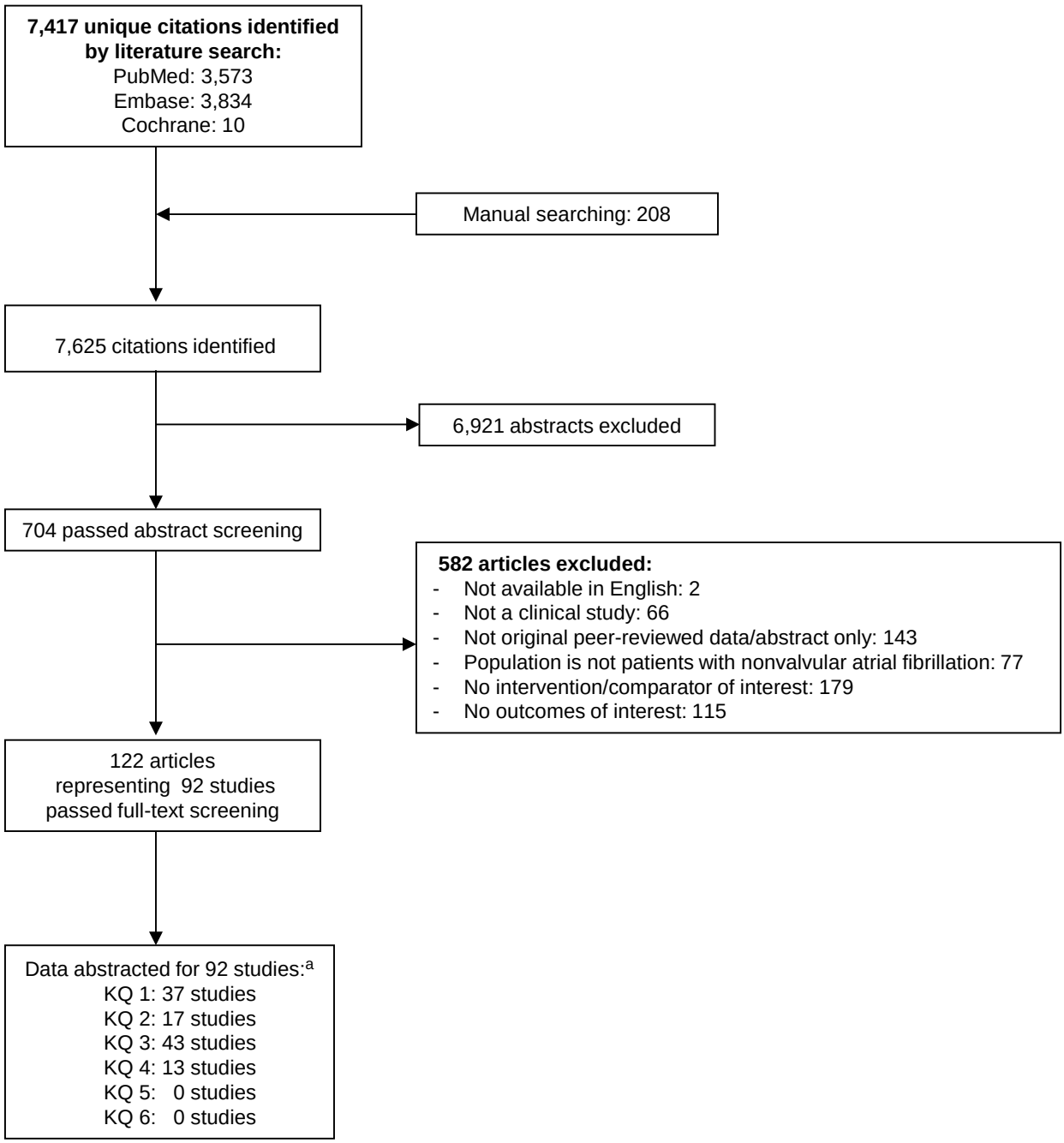
Results of Literature Searches

Figure B depicts the flow of articles through the literature search and screening process. Searches of PubMed®, Embase®, and CDSR yielded 7,417 unique citations. Manual searching of gray literature databases, bibliographies of key articles, and information received through requests for scientific information packets identified 208 additional citations, for a total of 7,625

citations. After applying inclusion/exclusion criteria at the title-and-abstract level, 704 full-text articles were retrieved and screened. Of these, 582 were excluded at the full-text screening stage, leaving 122 articles for data abstraction. These 122 articles described 92 unique studies. The relationship of studies to the review questions is as follows: 37 studies relevant to KQ 1, 17 studies relevant to KQ 2, 43 studies relevant to KQ 3, 13 studies relevant to KQ 4, 0 studies relevant to KQ 5, and 0 studies relevant to KQ 6. (Some studies were relevant to more than one KQ.) Nearly all the studies were conducted in Europe, the United States, or Canada, suggesting that the level of care and comedications overall were roughly similar to those available to the U.S. population.

As described in the Methods chapter in the full report, we searched ClinicalTrials.gov to identify completed but unpublished studies as a mechanism for ascertaining publication bias. We found only 14 potentially relevant trials that had been completed for more than a year and remained unpublished, all of which pertained to KQ 3. However, these 14 unpublished studies provided data on only 8,879 patients, while the 43 published studies included for KQ 3 in this review involved more than 433,500 patients. Therefore we do not believe there is significant publication bias in the evidence base that would impact our overall conclusions for any of the KQs.

Figure B. Literature flow diagram



[a]Some studies were relevant to more than one KQ.
Note: KQ = Key Question.

KQ 1. Predicting Thromboembolic Risk

Key points are as follows:

- Comparison of risk scores between study populations was complicated by multiple factors. 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. No studies performed net reclassification improvement (NRI) in their selected population. As a result, our ability to draw firm conclusions was limited.
- Based on a meta-analysis of eight studies (five good quality, three fair quality; 379,755 patients), there is low strength of evidence that the continuous $CHADS_2$ score provides modest stroke risk discrimination (c-statistic of 0.71; 95% CI 0.66 to 0.75).
- Based on a meta-analysis of five studies (four good quality, one fair quality; 371,911 patients), there is low strength of evidence that the continuous CHA_2DS_2-VASc score provides modest stroke risk discrimination (c-statistic of 0.70; 95% CI 0.66 to 0.75).
- Based on a meta-analysis of five studies (four good quality, one fair quality; 259,253 patients), there is moderate strength of evidence that the categorical Framingham score provides limited stroke risk discrimination (c-statistic of 0.63; 95% CI 0.62 to 0.65).
- Given the imprecision and inconsistency across studies of c-statistics for the categorical $CHADS_2$ and CHA_2DS_2-VASc scores, there is insufficient evidence of their ability to discriminate stroke risk.
- There is insufficient evidence for the relationship between left atrial thrombus on echocardiography and subsequent stroke based on five studies (three good quality, two fair quality; 1,228 patients) that reported discrepant results.
- Of the tools reviewed, the $CHADS_2$ and CHA_2DS_2-VASc continuous risk scores appear to be similar and have the most discrimination of stroke events when compared with the $CHADS_2$ categorical score, the CHA_2DS_2-VASc categorical score, and the Framingham categorical score. This finding was, however, statistically significant only for the comparison with the Framingham categorical score. Other comparisons were not possible given limited data.

Overall, 37 articles published from 2001 to 2012 investigated our included tools for determining stroke risk in patients with nonvalvular AF and met the other inclusion criteria for KQ 1. These articles explored tools in studies of diverse quality, design, geographical location, and study characteristics. Fourteen included studies were of good quality, 21 of fair quality, and 2 of poor quality. Most studies were conducted in outpatient settings and did not report funding source. The studies were divided between single-center and multicenter design and covered broad geographical locations, with 16 studies conducted in Europe, 8 in the United States, 7 in Asia, and 2 in multiple nations; 1 study did not report geography of enrollment.

The number of patients included in studies ranged from fewer than 100 to 170,291, with overlap in patient populations between some studies; altogether, the included studies analyzed data from almost 500,000 unique patients. The mean age of study participants ranged from 53 to

81 years. None of the studies presented data on ethnicity of subjects. Male sex ranged from 44 percent to 84 percent in the included studies. Study followup duration ranged from 1 to 12 years.

Sixteen studies used prospective cohorts to identify patients, while 19 studies utilized retrospective cohorts, and 2 studies were RCTs.

Many studies examined multiple risk stratification scores concurrently. The tool most commonly examined for risk stratification was the $CHADS_2$ score (27 studies). Ten studies examined the CHA_2DS_2-VASc, and six the Framingham risk tool. Six studies examined the use of transesophageal echocardiography for evaluation of left atrial characteristics and stroke risk, and one study used magnetic resonance imaging to examine this relationship. Finally, four studies described the prediction role of INR values for stroke risk.

Table A summarizes the strength of evidence for the thromboembolic risk discrimination abilities of the included tools. Details about the specific components of these ratings (risk of bias, consistency, directness, and precision) are available in the full report.

Table A. Summary of strength of evidence and c-statistic estimates for KQ 1 (discrimination of thromboembolic risk)

Tool	Number of Studies (Subjects)	Strength of Evidence and Effect Estimate[a]
$CHADS_2$ (categorical)	8 (380,669)	**SOE = Insufficient**
$CHADS_2$ (continuous)	8 (379,755)	**SOE = Low** Modest risk discrimination ability (c-statistic = 0.71; 95% CI 0.66 to 0.75)
CHA_2DS_2-VASc (categorical)	6 (332,009)	**SOE = Insufficient**
CHA_2DS_2-VASc (continuous)	5 (371,911)	**SOE = Low** Modest risk discrimination ability (c-statistic = 0.70; 95% CI 0.66 to 0.75)
Framingham (categorical)	5 (259,253)	**SOE = Moderate** Limited risk discrimination ability (c-statistic = 0.63; 95% CI 0.62 to 0.65)
Framingham (continuous)	4 (262,151)	**SOE = Low** Limited risk discrimination ability (c-statistic ranges between 0.64 and 0.69 across studies)
Imaging	0	**SOE = Insufficient**
INR	0	**SOE = Insufficient**

[a]All SOE ratings of "Insufficient" are shaded.

Note: $CHADS_2$ = 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; SOE = strength of evidence.

KQ 2. Predicting Bleeding Risk

Key points are as follows:

- Comparison of risk scores between study populations was complicated by multiple factors. First, included studies used different approaches to calculating bleeding risk scores of interest due to unavailable data, such as genetic factors in $HEMORR_2HAGES$ (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) 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. Third, although studies consistently reported event rates and c-statistics, measures of calibration, strength of association, and diagnostic accuracy were inconsistently reported.

- Among AF patients on warfarin, nine studies (six good quality, two fair quality, one poor quality; 319,183 patients) compared different risk scores (Bleeding Risk Index [BRI], $HEMORR_2HAGES$, HAS-BLED, and ATRIA [Anticoagulation and Risk Factors in Atrial Fibrillation]) 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. Limited evidence favors HAS-BLED based on two studies demonstrating that it has significantly higher discrimination (by c-statistic) for major bleeding events than other scores among patients on warfarin, but the majority of studies showed no statistically significant differences in discrimination, reducing the strength of evidence. One study showed that HAS-BLED had a significantly higher NRI than ATRIA for patients on warfarin, while another showed that HAS-BLED had a significantly higher NRI than three other scores in a mixed group of patients on and off warfarin (low strength of evidence).
- Among AF patients on warfarin, one study (good quality; 48,599 patients) compared $HEMORR_2HAGES$ and HAS-BLED in predicting intracranial hemorrhage (ICH). This study showed no statistically significant difference in discrimination between the two scores (low strength of evidence).
- Among AF patients on aspirin alone, three studies (two good quality, one fair quality; 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 in discrimination (low strength of evidence).
- Among AF patients not on antithrombotic therapy, six studies (four good quality, two fair quality; 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 in discrimination (low strength of evidence).

Seventeen studies met our inclusion criteria. Athough these studies shared a focus on outpatient settings, they varied in geographical location, study design, quality, and patient characteristics. Five studies analyzed prospective data (including data from RCTs), while 12 analyzed retrospective data (including registries). Eleven studies were conducted primarily in the outpatient setting, three did not report setting, and three were conducted in the inpatient setting. Nearly two-thirds of the studies were multicenter (11/17, 65%); 10 were conducted in Europe, 4 in the United States, and 1 in Asia; 1 study was multinational. Eight studies were of good methodological quality, six were of fair quality, and three were of poor quality.

The number of patients included in studies ranged from fewer than 600 to 170,291, with overlap in patient populations between some studies. Altogether, the included studies analyzed data from approximately 250,000 unique patients. The mean age of study participants ranged from 65 to 80 years. The proportion of male patients ranged from approximately 40 to 60 percent. Study followup duration ranged from 1 to 12 years. Regarding the outcomes assessed, all 17 studies evaluated bleeding risk prediction scores with respect to major bleeding; 2 evaluated bleeding risk prediction scores with respect to ICH as a separate outcome (ICH was also included in definitions of major bleeding); and 1 study reported these outcomes with respect to minor bleeding. Clinical tools of interest included risk scores and INR indexes (INR, time in therapeutic range [TTR], and standard deviation of transformed INR [SDT_{INR}]).

Table B summarizes the strength of evidence for the bleeding risk discrimination abilities of the included tools. This summary table represents only those studies that evaluated the risk discrimination 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 full report.

Table B. Summary of strength of evidence and c-statistic estimates for KQ 2 (discrimination of bleeding risk)

Tool	Number of Studies (Subjects)	Strength of Evidence and Effect Estimate[a]
Summary c-Statistic		
BRI	5 (47,684)	**SOE = Moderate** Limited risk discrimination ability (c-statistic ranging from 0.56 to 0.65)
$HEMORR_2HAGES$	8 (318,246)	**SOE = Moderate** Limited risk discrimination ability (c-statistic ranging from 0.53 to 0.78)
HAS-BLED	8 (313,294)	**SOE = Moderate** Modest risk discrimination ability (c-statistic ranging from 0.58 to 0.80)
ATRIA	4 (15,732)	**SOE = Insufficient**
Comparative Risk Discrimination Abilities		
Major bleeding events among patients with AF on warfarin	9 (319,183)	**SOE = Low** Favors HAS-BLED
Intracranial hemorrhage among patients with AF on warfarin	1 (48,599)	**SOE = Low** No difference
Major bleeding events among patients with AF on aspirin alone	3 (177,538)	**SOE = Low** No difference
Major bleeding events among patients with AF not on antithrombotic therapy	6 (310,607)	**SOE = Low** No difference

[a]All SOE ratings of "Insufficient" are shaded.

Note: 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, Re-bleeding 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

Key points are as follows:

- Based on four retrospective studies (one good quality, two fair quality, and one poor quality) involving 170,642 patients, warfarin reduces the risk of nonfatal and fatal ischemic stroke compared with aspirin (moderate strength of evidence); on the other hand, based on three studies (one good quality, one fair quality, and one poor quality) involving 99,876 patients, warfarin is associated with increased annual rates of severe bleeding complications compared with aspirin (moderate strength of evidence).
- In patients not eligible for warfarin, the combination of aspirin + clopidogrel is more effective than aspirin alone for preventing any stroke. This conclusion is based on one large good-quality trial involving 7,554 patients that showed lower rates of stroke for combination therapy, but the strength of evidence was rated as only moderate because a much smaller study (593 patients) did not find any difference. In the large RCT, the combination of aspirin + clopidogrel was associated with higher rates of major bleeding than aspirin alone (high strength of evidence).

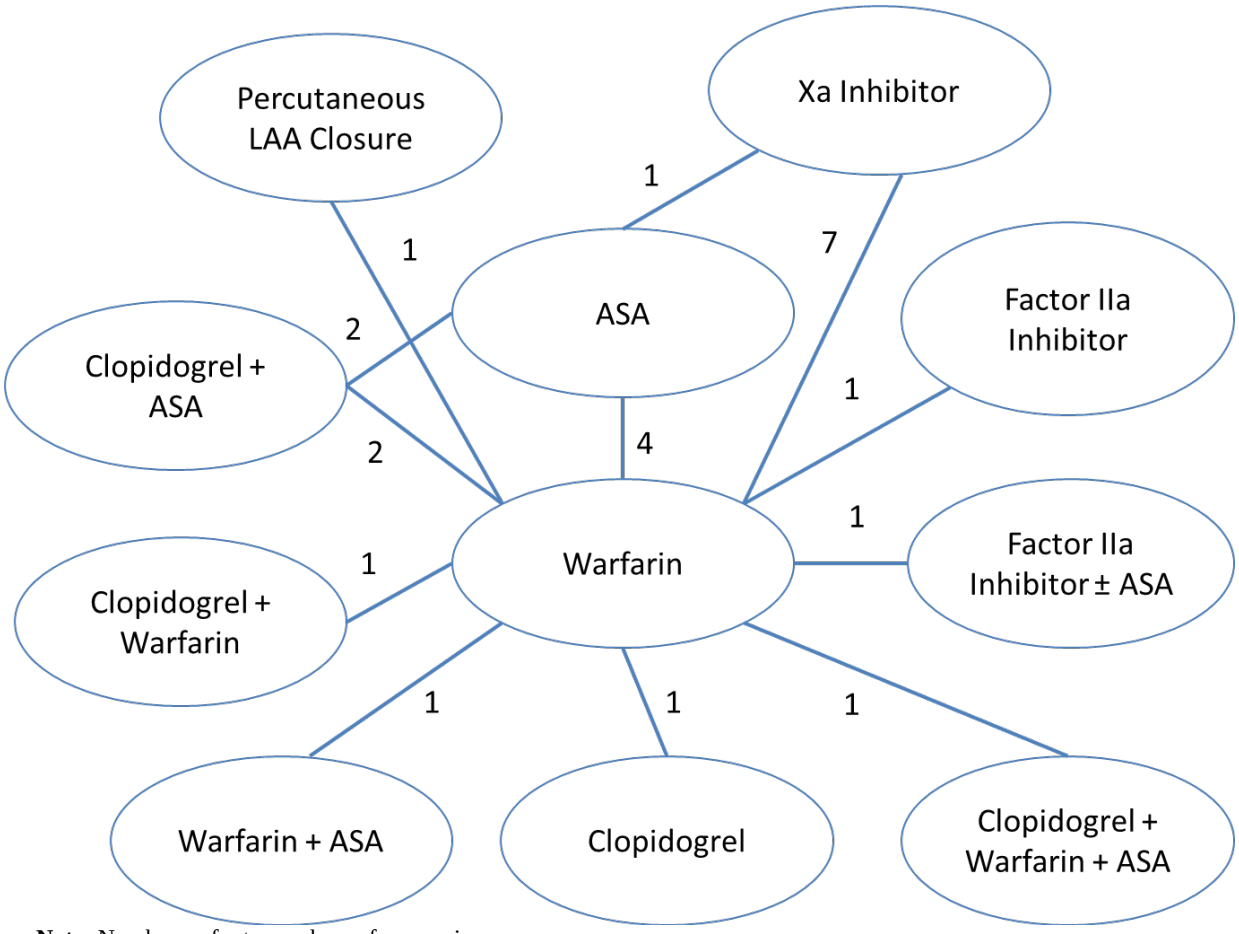
- Based on one large retrospective good-quality study involving 54,636 patients, warfarin reduces the risk of nonfatal and fatal ischemic stroke compared with clopidogrel monotherapy, with no differences in major bleeding (moderate strength of evidence).
- Based on one large good-quality RCT of 6,706 patients, warfarin is superior to aspirin + clopidogrel for the prevention of stroke or systemic embolism and reduction in minor bleeding, although this did not result in a difference in all-cause mortality (high strength of evidence for all three outcomes). There was moderate strength of evidence that warfarin increases hemorrhagic stroke risk and that there is no difference between therapies for MI or death from vascular causes. A retrospective good-quality study of 53,778 patients confirmed the stroke outcome findings.
- Adding clopidogrel to warfarin shows a trend toward a benefit on stroke prevention (low strength of evidence) and is associated with increased risk of nonfatal and fatal bleeding compared with warfarin alone (moderate strength of evidence). These findings are based on one good-quality retrospective study involving 52,349 patients.
- Triple therapy with warfarin + aspirin + clopidogrel substantially increases the risk of nonfatal and fatal bleeding (moderate strength of evidence) and also shows a trend toward increased ischemic stroke (low strength of evidence) compared with warfarin alone. These findings are based on one good-quality retrospective study involving 52,180 patients.
- A factor IIa inhibitor (dabigatran) at a 150 mg dose is superior to warfarin in reducing the incidence of the composite outcome of stroke (including hemorrhagic) or systemic embolism, with no significant difference in the occurrence of major bleeding (high strength of evidence for both outcomes) or all-cause mortality (moderate strength of evidence). However, dabigatran increases MI risk (moderate strength of evidence). These findings are based on one large good-quality RCT involving 12,098 patients from the larger RE-LY trial of 18,113 patients.
- A factor IIa inhibitor (dabigatran) at a 110 mg dose is noninferior to warfarin for the composite outcome of stroke or systemic embolism and is associated with a reduction in major bleeding when compared with warfarin (high strength of evidence for both outcomes), but there is no difference in all-cause mortality (moderate strength of evidence). Dabigatran increases MI risk, although this finding did not reach statistical significance (low strength of evidence). The rates of ICH are significantly lower with both dabigatran doses (150 mg and 110 mg) compared with warfarin (high strength of evidence). These findings are based on one large good-quality RCT involving 12,037 patients from the larger RE-LY trial of 18,113 patients. Of note, the 150 mg dabigatran dose is FDA approved and marketed in the United States; the 110 mg dose is not.
- The Xa inhibitor apixaban is superior to aspirin in reducing the incidence of stroke or systemic embolism, with similar major bleeding risk, in patients who are not suitable for oral anticoagulation (high strength of evidence for both outcomes). These findings are based on one good-quality RCT involving 5,599 patients.
- The Xa inhibitor apixaban is superior in reducing the incidence (separately) of (1) stroke or systemic embolism (high strength of evidence), (2) major bleeding (high strength of evidence), and (3) all-cause mortality (moderate strength of evidence) compared with warfarin. These findings are based on similar findings from one good-quality RCT involving 18,201 patients and one small fair-quality RCT involving 222 Japanese patients.

- The Xa inhibitor rivaroxaban is noninferior to warfarin in preventing stroke or systemic embolism (moderate strength of evidence), with similar rates of major bleeding (moderate strength of evidence) and all-cause mortality (high strength of evidence). These findings are based on one large good-quality RCT involving 14,264 patients and a second good-quality RCT involving 1,280 Japanese patients.
- Percutaneous LAA closure shows trends toward a benefit over warfarin for all strokes and all-cause mortality (low strength of evidence for both outcomes). Although LAA with percutaneous closure results in less frequent major bleeding than warfarin (low strength of evidence), it is also associated with a higher rate of adverse safety events (moderate strength of evidence). These findings are based on one good-quality RCT involving 707 patients. LAA-occluding devices are currently investigational, pending approval by the FDA.
- Based on two substudies of the ROCKET AF and ARISTOTLE trials for rivaroxaban and apixaban, respectively, patients with renal impairment benefited equally for stroke prevention from the new anticoagulant agents compared with warfarin. Results were also similar in a substudy of the AVERROES (Apixaban Versus Acetylsalicylic acid [ASA] to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment) trial comparing apixaban with aspirin, which demonstrated equal benefit in stroke prevention for patients with renal impairment (low strength of evidence).
- Patients with different INR control and with prior stroke seem to benefit equally for stroke prevention from the new anticoagulant agents compared with warfarin or aspirin (low strength of evidence). This finding is based on four studies of patients at centers with different INR control, and seven studies of patients with prior stroke.

Forty-three studies published between 2000 and 2012 were identified. The majority of studies (n=28) were multicenter and included outpatients (n=22). A total of 22 RCTs, 12 retrospective studies, 8 prospective cohorts, and 1 case-control study were included in our analyses. The number of patients included in studies ranged from 30 to 132,372, with a total of 433,502 patients. Nineteen studies were sponsored by industry; 3 were sponsored by government; 3 received funding from nongovernment, nonindustry sources; 5 received funding from multiple sources including government, industry, nongovernment, and nonindustry; and 13 either had no sponsorship or this information was unclear. Twenty-one studies were considered good quality, 15 fair quality, and 7 poor quality.

Figure C represents the treatment comparisons evaluated for this KQ.

Figure C. Overview of treatment comparisons evaluated for KQ 3



Note: Numbers refer to numbers of comparisons.
ASA = aspirin; KQ = Key Question; LAA = left atrial appendage.

As Figure C shows, most comparisons were explored in only a limited number of studies, although many of these were good-quality RCTs involving more than 5,000 patients. The comparisons of Xa inhibitor versus warfarin and aspirin versus warfarin were the only comparisons for which we identified more than two studies. We looked at several subgroups of interest, including patients not eligible for warfarin use, patients with AF, patients with paroxysmal versus sustained AF, patients with AF undergoing cardioversion, patients with AF after stroke, patients with AF and different thromboembolic risks, patients with AF according to INR control, elderly patients with AF, patients with AF undergoing drug-eluting stent implantation, and patients with AF and MI. Patients with renal impairment, with different INR control, and with prior stroke seem to benefit equally from the new anticoagulant agents compared with warfarin (low strength of evidence). Evidence in other patient subgroups was insufficient to support conclusions.

Table C summarizes the strength of evidence for interventions for preventing thromboembolic events. Details about the specific components of these ratings (risk of bias, consistency, directness, and precision) and SOE ratings for additional outcomes (minor bleeding, systemic embolism, and hospitalization) are available in the full report.

Table C. Summary of strength of evidence and effect estimates for KQ 3 (interventions for preventing thromboembolic events)

Outcome	Number of Studies (Subjects)	SOE and Magnitude of Effect[a] (95% CI)
ASA vs. Warfarin		
Ischemic stroke	4 (170,642)	**SOE = Moderate** 4 retrospective studies showing consistent reduction in stroke with warfarin
Bleeding	3 (99,876)	**SOE = Moderate** Warfarin associated with increased rates of bleeding
All-cause mortality	1 (601)	**SOE = Insufficient**
Warfarin + ASA vs. Warfarin Alone		
Ischemic stroke	1 (69,264)	**SOE = Moderate** Increased with warfarin + ASA (HR 1.27; 95% CI 1.14 to 1.40)
Bleeding	1 (69,264)	**SOE = Moderate** Increased with warfarin + ASA (HR 1.83; 95% CI 1.72 to 1.96)
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 = High** Clopidogrel + ASA associated with higher rates (HR 1.57; 95% CI 1.29 to 1.92)
Minor bleeding	1 (7,554)	**SOE = High** Clopidogrel + ASA associated with higher rates (HR 2.42; 95% CI 2.03 to 2.89)
Intracranial bleeding	2 (8,147)	**SOE = Low** Higher rates with clopidogrel + ASA (HR 1.87; 95% CI 1.19 to 2.94)
Extracranial bleeding	2 (8,147)	**SOE = High** Higher rates with clopidogrel + ASA (HR 1.51; 95% CI 1.21 to 1.88)
All-cause mortality	2 (8,147)	**SOE = Moderate** No 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 (8,147)	**SOE = Low** No 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 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 (593)	**SOE = Insufficient**
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)

Table C. Summary of strength of evidence and effect estimates for KQ 3 (interventions for preventing thromboembolic events) (continued)

Outcome	Number of Studies (Subjects)	SOE and Magnitude of Effect[a] (95% C)
Clopidogrel + ASA vs. Warfarin		
Stroke or systemic embolism	2 (60,484)	**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 (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 = High** Increased risk with clopidogrel + ASA (HR 1.23; 95% CI 1.09 to 1.39)
Intracranial bleeding	1 (6,706)	**SOE = Insufficient**
All-cause mortality	1 (6,706)	**SOE = High** No difference (HR 1.01; 95% CI 0.81 to 1.26)
Death from vascular causes	1 (6,706)	**SOE = Moderate** No difference (HR 1.14; 95% CI 0.88 to 1.48)
Myocardial infarction	1 (6,706)	**SOE = Moderate** No difference (myocardial infarction 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		
Stroke or systemic embolism	1 (12,098)	**SOE = High** Dabigatran reduced risk (RR 0.66; 95% CI 0.53 to 0.82)
Ischemic or uncertain stroke	1 (12,098)	**SOE = Moderate** Dabigatran reduced risk (RR 0.76; 95% CI 0.60 to 0.98)
Hemorrhagic stroke	1 (12,098)	**SOE = High** Dabigatran reduced risk (RR 0.26; 95% CI 0.14 to 0.49)
Major bleeding	1 (12,098)	**SOE = High** No difference (RR 0.93; 95% CI 0.81 to 1.07)
Minor bleeding	1 (12,098)	**SOE = Moderate** Dabigatran reduced risk (RR 0.91; 95% CI 0.85 to 0.97)
Intracranial bleeding	1 (12,098)	**SOE = High** Dabigatran reduced risk (RR 0.40; 95% CI 0.27 to 0.60)
All-cause mortality	1 (12,098)	**SOE = Moderate** No difference (RR 0.88; 95% CI 0.77 to 1.00)
Death from vascular causes	1 (12,098)	**SOE = Moderate** Dabigatran reduced risk (RR 0.85; 95% CI 0.72 to 0.99)

Table C. Summary of strength of evidence and effect estimates for KQ 3 (interventions for preventing thromboembolic events) (continued)

Outcome	Number of Studies (Subjects)	SOE and Magnitude of Effect[a] (95% C)
Myocardial infarction	1 (12,098)	**SOE = Moderate** Dabigatran increased risk (RR 1.38; 95% CI 1.00 to 1.91)
Hospitalization	1 (12,098)	**SOE = High** No difference (RR 0.97; 95% CI 0.92 to 1.03)
Adverse events	1 (12,098)	**SOE = Moderate** Dyspepsia more common with dabigatran (11.3% of patients with dabigatran 150 mg vs. 5.8% with warfarin; p <0.001). No differences in liver function or other adverse events between therapies.
Factor IIa Inhibitor (Dabigatran 110 mg) vs. Warfarin		
Stroke or systemic embolism	1 (12,037)	**SOE = High** No difference (RR 0.91; 95% CI 0.74 to 1.11)
Ischemic or uncertain stroke	1 (12,037)	**SOE = Moderate** No difference (RR 1.11; 95% CI 0.89 to 1.40)
Hemorrhagic stroke	1 (12,037)	**SOE = High** Dabigatran reduced risk (RR 0.31; 95% CI 0.17 to 0.56)
Major bleeding	1 (12,037)	**SOE = High** Dabigatran reduced risk (RR 0.80; 95% CI 0.69 to 0.93)
Minor bleeding	1 (12,037)	**SOE = High** Dabigatran reduced risk (RR 0.79; 95% CI 0.74 to 0.84)
Intracranial bleeding	1 (12,037)	**SOE = High** Dabigatran reduced risk (RR 0.31; 95% CI 0.20 to 0.47)
All-cause mortality	1 (12,037)	**SOE = Moderate** No difference (RR 0.91; 95% CI 0.80 to 1.03)
Death from vascular causes	1 (12,037)	**SOE = Moderate** No difference (RR 0.90; 95% CI 0.77 to 1.06)
Myocardial infarction	1 (12,037)	**SOE = Low** Dabigatran increased risk, although the difference did not reach statistical significance (RR 1.35; 95% CI 0.98 to 1.87)
Hospitalization	1 (12,037)	**SOE = High** Dabigatran reduced risk (RR 0.92; 95% CI 0.87 to 0.97)
Adverse events	1 (12,037)	**SOE = Moderate** Dyspepsia more common with dabigatran (11.8% of patients with dabigatran 110 mg vs. 5.8% with warfarin; p <0.001). No differences in liver function or other adverse events between therapies.
Xa Inhibitor (Apixaban) vs. Warfarin		
Stroke or systemic embolism	2 (18,423)	**SOE = High** Apixaban reduced risk (HR 0.79; 95% CI 0.66 to 0.95)
Ischemic stroke	1 (18,201)	**SOE = High** No difference (HR 0.92; 95% CI 0.74 to 1.13)
Hemorrhagic stroke	1 (18,201)	**SOE = High** Apixaban reduced risk (HR 0.51; 95% CI 0.35 to 0.75)
Systemic embolism	2 (18,423)	**SOE = Moderate** No difference (HR 0.87; 95% CI 0.44 to 1.75)
Major bleeding	2 (18,423)	**SOE = High** Apixaban reduced risk (HR 0.69; 95% CI 0.60 to 0.80)
Intracranial bleeding	1 (18,201)	**SOE = High** Apixaban reduced risk (HR 0.42; 95% CI 0.30 to 0.58)
All-cause mortality	2 (18,423)	**SOE = Moderate** Apixaban reduced risk (HR 0.89; 95% CI 0.80 to 0.998)

Table C. Summary of strength of evidence and effect estimates for KQ 3 (interventions for preventing thromboembolic events) (continued)

Outcome	Number of Studies (Subjects)	SOE and Magnitude of Effect[a] (95% C)
Death from cardiovascular causes	1 (18,201)	**SOE = High** No difference (HR 0.89; 95% CI 0.76 to 1.04)
Myocardial infarction	1 (18,201)	**SOE = Moderate** No difference (HR 0.88; 95% CI 0.66 to 1.17)
Adverse events	2 (18,423)	**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	2 (15,544)	**SOE = Moderate** No difference (HR 0.88; 95% CI 0.74 to 1.03)
Ischemic stroke	1 (14,264)	**SOE = Moderate** No difference in on-treatment analyses (HR 0.94; 95% CI 0.75 to 1.17)
Hemorrhagic stroke	2 (15,544)	**SOE = Low** In on-treatment analyses, 1 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 (14,264)	**SOE = Moderate** Rivaroxaban reduced risk in on-treatment analyses (HR 0.23; 95% CI 0.09 to 0.61)
Major bleeding	2 (15,544)	**SOE = Moderate** No difference in 2 studies in on-treatment analyses (HR 1.04 [95% CI 0.90 to 1.20] in one study; HR 0.85 [95% CI 0.50 to 1.43] in other study)
Intracranial bleeding	2 (15,544)	**SOE = Moderate** Rivaroxaban reduced risk in on-treatment analyses (HR 0.67; 95% CI 0.47 to 0.93)
All-cause mortality	1 (14,264)	**SOE = High** No difference (HR 0.92; 95% CI 0.82 to 1.03)
Death from cardiovascular causes	1 (14,264)	**SOE = Moderate** No difference in on-treatment analyses (HR 0.89; 95% CI 0.73 to 1.10)
Myocardial infarction	1 (14,264)	**SOE = Moderate** No difference in on-treatment analyses (HR 0.81; 95% CI 0.63 to 1.06)
Xa Inhibitor (Apixaban) vs. ASA		
Stroke or systemic embolism	1 (5,599)	**SOE = High** Apixaban reduced risk (HR 0.45; 95% CI 0.32 to 0.62)
Ischemic stroke	1 (5,599)	**SOE = High** Apixaban reduced risk (HR 0.37; 95% CI 0.25 to 0.55)
Hemorrhagic stroke	1 (5,599)	**SOE = Moderate** Trend toward a reduction in risk with apixaban (HR 0.67; 95% CI 0.24 to 1.88)
Major bleeding	1 (5,599)	**SOE = High** No difference (HR 1.13; 95% CI 0.74 to 1.75)
Minor bleeding	1 (5,599)	**SOE = Moderate** Apixaban increased risk (HR 1.20; 95% CI 1.00 to 1.53)
Intracranial bleeding	1 (5,599)	**SOE = Low** Trend toward a reduction in risk with apixaban (HR 0.85; 95% CI 0.38 to 1.90)
All-cause mortality	1 (5,599)	**SOE = Low** Trend toward a reduction in risk with apixaban (HR 0.79; 95% CI 0.62 to 1.02)
Death from vascular causes	1 (5,599)	**SOE = Moderate** No difference (HR 0.87; 95% CI 0.66 to 1.17)

Table C. Summary of strength of evidence and effect estimates for KQ 3 (interventions for preventing thromboembolic events) (continued)

Outcome	Number of Studies (Subjects)	SOE and Magnitude of Effect[a] (95% C)
Myocardial infarction	1 (5,599)	**SOE = Moderate** No difference (HR 0.86; 95% CI 0.50 to 1.48)
Hospitalization	1 (5,599)	**SOE = High** Apixaban reduced risk (HR 0.79; 95% CI 0.69 to 0.91)
Adverse events	1 (5,599)	**SOE = Moderate** No differences in liver function or other adverse events between therapies
Percutaneous LAA Closure vs. Warfarin		
Ischemic stroke	1 (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 difference between therapies
All strokes	1 (707)	**SOE = Low** Trend toward a benefit of LAA (RR 0.71; 95% CI 0.35 to 1.64)
Major bleeding	1 (707)	**SOE = Low** Less frequent with LAA (3.5% vs. 4.1%)
All-cause mortality	1 (707)	**SOE = Low** Trend toward a benefit of LAA (RR 0.62; 95% CI 0.34 to 1.24)
Adverse events	1 (707)	**SOE = Moderate** Higher rate with LAA (RR 1.69; 95% CI 1.01 to 3.19)

[a]All SOE ratings of "Insufficient" are shaded.
Note: ASA = aspirin; CI = confidence interval; HR = hazard ratio; KQ = Key Question; LAA = left atrial appendage; RCT = randomized controlled trial; RR = relative risk; SOE = strength of evidence.

KQ 4. Anticoagulation Strategies for Patients Undergoing Invasive Procedures

Key points are as follows:

- The included studies of oral anticoagulation after percutaneous coronary intervention (PCI) with stenting (three good-quality retrospective studies; 689 patients) were relatively small and reached different conclusions regarding the effectiveness of triple therapy (warfarin + aspirin + clopidogrel) compared with other combinations of therapies for both bleeding and ischemic outcomes (insufficient strength of evidence for all outcomes assessed).
- Studies of bridging therapies (seven retrospective studies; two good quality, four fair quality, one poor quality; 2,797 patients) were hampered by the variety of procedures (radiofrequency ablation [RFA], other surgeries) and strategies assessed, and provided inconclusive findings (insufficient strength of evidence for all outcomes assessed).
- Two studies investigating the safety of dabigatran versus warfarin in the periprocedural period (RFA) reported higher bleeding rates among patients using dabigatran, while the single study comparing dabigatran with warfarin in patients undergoing PCI found no differences in bleeding or ischemic complications (three studies; two good quality, one poor quality; 5,037 patients; insufficient strength of evidence).

A total of 13 studies were included in our analysis, of which 7 were prospective cohort studies and 5 were retrospective cohort studies. These studies assessed anticoagulation during or after ablation procedures, other operative procedures, or PCI. Studies were conducted in the

United States, South America, Asia, and Europe between 1999 and 2011. Seven of the studies were considered good quality, four fair quality, and two poor quality. The funding source was reported by only five studies: two government funded, two sponsored by industry, and one receiving funding from both government and industry.

The mean age of subjects ranged from 55 to 78.6 years. A total of 8,523 subjects were enrolled. Three studies evaluated oral anticoagulation after PCI with stenting, seven evaluated bridging therapies, and three evaluated dabigatran in the periprocedural setting.

Table D summarizes the strength of evidence for anticoagulation therapies for patients undergoing invasive procedures. Details about the specific components of these ratings (risk of bias, consistency, directness, and precision) are available in the full report.

Table D. Summary of strength of evidence for KQ 4 (anticoagulation therapies for patients undergoing invasive procedures)

Outcome	Number of Studies (Subjects)	Strength of Evidence[a]
OAC After PCI With Stenting		
Major bleeding	3 (689)	**SOE = Insufficient**
Mortality	2 (585)	**SOE = Insufficient**
Myocardial infarction	2 (585)	**SOE = Insufficient**
Bridging Therapies		
Major and minor bleeding	6 (2,167)	**SOE = Insufficient**
Mortality	5 (1,932)	**SOE = Insufficient**
Other thomboembolic outcomes	5 (1,932)	**SOE = Insufficient**
Use of Dabigatran in Periprocedural Setting		
Major and minor bleeding	3 (5,037)	**SOE = Insufficient**

[a]All SOE ratings were "Insufficient" and are shaded.

Note: KQ = Key Question; OAC = oral anticoagulation; PCI = percutaneous coronary intervention; SOE = strength of evidence.

KQ 5. Strategies for Switching Between Warfarin and Novel Oral Anticoagulants

There is currently no safety or effectiveness evidence to answer this question based on the absence of any peer-reviewed published studies in this area (insufficient strength of evidence for all outcomes of interest).

KQ 6. Stroke Prevention After a Hemorrhagic Event

There is currently no safety or effectiveness evidence to answer this question based on the absence of any peer-reviewed published studies in this area (insufficient strength of evidence for all outcomes of interest).

Discussion

Key Findings

In this CER, we reviewed 92 unique studies represented by 122 publications and involving over 1,164,900 patients that evaluated stroke and bleeding prediction tools and stroke prevention strategies in patients with nonvalvular AF. The current evidence base was greatest for the comparative safety and effectiveness of stroke prevention therapies and tools for predicting

thromboembolic and bleeding risk. The evidence was very limited or nonexistent regarding AF patients undergoing invasive procedures, patients switching among anticoagulant therapies, and starting or restarting anticoagulant therapy in patients with previous major bleeding events.

As the current review underscores, further efforts are needed to refine risk prediction tools, since existing tools provide at best moderate guidance for predicting stroke risk. Also, with newer antiplatelet agents on the market for AF patients, understanding how these risk tools perform for estimating bleeding risk will be of increasing importance. Additionally, more prescriptive guidelines on how to use risk scores and apply necessary therapies, and how to balance stroke and bleeding risks, possibly in the form of physician decision support tools, will be important for clinical decisionmaking.

At the time the current U.S. guidelines for management of AF were developed (2006,[1] with a focused update in 2011[43]), the primary focus was on risk stratification and treatment with antiplatelets (generally aspirin) or VKAs (generally warfarin). Since that time, newer anticoagulants have entered the marketplace.

Trials of dabigatran, rivaroxaban, and apixaban have demonstrated favorable efficacy and safety results compared with warfarin, but conclusions about the comparative efficacy and safety of the newer oral anticoagulants cannot be drawn because these medications have not been directly compared with one another, and indirect (cross-trial) comparisons may not be reliable. In addition, the trials of these newer agents used different dosing strategies, were performed in different health systems, used varying event definitions, and recruited populations at varying risk for stroke and bleeding. The newer oral anticoagulants do, however, have different attributes and important advantages over warfarin. After many years without options, they offer new alternatives for the treatment of patients with nonvalvular AF who are at risk for stroke. Specifically, our review adds the following to what is already known within the field of stroke prevention for patients with AF:

- New oral anticoagulants preserve the benefits of warfarin for stroke prevention, and two of them (apixaban and higher dose dabigatran) have been demonstrated in large RCTs to be more effective than warfarin.
- In addition to these stroke prevention benefits, the new oral anticoagulants appear to be safer than warfarin in that:
    - All of them caused less intracranial bleeding than warfarin.
    - Two of them (apixaban and lower dose dabigatran) caused less major bleeding, including gastrointestinal bleeding, than warfarin.
- For patients not suitable for oral anticoagulation, apixaban was more effective than aspirin in stroke prevention. In addition, apixaban was better tolerated than and as safe as aspirin.
- All the new oral anticoagulants tested in a blinded fashion were better tolerated than warfarin, and rates of study drug discontinuation were lower with the new agents than with warfarin.
- Apixaban reduced all-cause mortality in patients with AF. Dabigatran and rivaroxaban appear to have similar all-cause mortality as warfarin.

Despite all the potential advantages of the new drugs demonstrated in the clinical trials when compared with warfarin, the new drugs still do not have a well-validated and -studied immediate antidote. Similarly, although there are data showing that fresh frozen plasma or vitamin K can help in normalizing INRs for warfarin-treated patients, there are not good data on actually

stopping or reversing bleeding events for them. 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 novel drugs 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. This half-life is similar to the time needed to reverse INR (not bleeding) of patients on warfarin with vitamin K. The shorter half-life of these novel agents may, however, be a disadvantage in poorly compliant patients, emphasizing the need for additional evidence outside of RCTs and within actual clinical practice.

Finally, gaps have been identified in the current evidence for increasingly common clinical scenarios for patients on therapies for stroke prevention. Evidence is needed on the best strategies for patients undergoing invasive procedures, patients switching among anticoagulant therapies, and starting or restarting anticoagulant therapy in patients with previous major bleeding events.

Applicability

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 (9% of studies overall, representing 3%, 0%, 16%, and 0% of KQ 1, KQ 2, KQ 3, and KQ 4 studies, respectively); concerns about large differences between demographics of study populations and community patients in terms of age, renal function, and comorbidities (4% of studies overall, representing 5%, 0%, 5%, and 0% of KQ 1, KQ 2, KQ 3, and KQ 4 studies, respectively); and concerns about use of older versions of an intervention no longer in common use (3% of studies overall, representing 5%, 6%, 2%, and 0% of KQ 1, KQ 2, KQ 3, and KQ 4 studies, respectively).

Research Gaps

In our analyses, we identified research gaps for all the KQs examined, as described below.

KQs 1 and 2: Predicting Thromboembolic and Bleeding Risk

While there are several scores available in clinical practice to predict stroke and bleeding in patients with AF, the major limitation of these scores is the overlap of clinical factors that go into both types of scores. We therefore think that the evidence gaps for these two questions are best addressed together.

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. Another challenge is that both stroke events and bleeding events are on a spectrum of severity. 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 SDT_{INR} and TTR are needed to establish which variable has better predictive accuracy for major bleeding.

Another issue of note was not addressed in this review: in an era of personalized medicine, it may be important to have the "omics" profile (genomics, proteomics, metabolomics) incorporated into the risk scores, which could help to more accurately stratify AF patients according to their thromboembolic and bleeding risks.

Additionally, even assuming that an optimal risk prediction score can be identified, further work is needed to clarify how scores should be used prospectively in clinical practice.

Finally, for future studies of available tools, reporting the raw data rather than c-statistics would allow more informative assessment of the predictive model performance. If we had had such raw data, we could have considered the NRI or integrated discrimination index, which summarize the incremental benefit of a score when added to a model with other covariates.

Therefore, the four specific evidence gaps identified from KQ 1 and KQ 2 are as follows:

- In patients with nonvalvular AF, what are the comparative diagnostic accuracy and impact on clinical decisionmaking of *clinical tools* with modest or better predictive value for predicting the overall clinical risk of patients, combining both their risk of stroke and their risk of bleeding?
- In patients with nonvalvular AF, what are the comparative diagnostic accuracy and impact on clinical decisionmaking of *imaging tools* with modest or better predictive value for predicting the overall clinical risk of patients, combining both their risk of stroke and their risk of bleeding?
- What are the benefits, harms, and costs of incorporating genomics, proteomics, and metabolomics into risk scores for the prediction of thromboembolic and/or bleeding risk?
- What is the most effective way to prospectively use thromboembolic and/or bleeding risk scores with evidence of modest or better predictive value in clinical practice? Specifically, how can we increase dissemination of point-of-care tools to improve risk assessment and treatment choices for clinicians?

KQ 3: Interventions for Preventing Thromboembolic Events

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. Given the risks associated with AF, the growing number of patients with AF, and the costs and risks associated with stroke prevention for AF, a better understanding of the comparative safety and effectiveness of newer anticoagulant therapies is of paramount importance. There is also a need for future studies in special populations and clinical scenarios. In addition, 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 should be avoided. Patients with AF usually have comorbidities that require the use of antithrombotic agents other than those used to treat AF. Many antithrombotic agents are available at different doses for different clinical indications. Thus, there is a need for studies assessing the safety and effectiveness of different combinations of antithrombotics at different doses, as well as their duration. For example, nothing is known about the use of triple therapy in patients with coronary artery disease/acute coronary syndrome and AF in the new era with new antiplatelet agents (prasugrel and ticagrelor) and new anticoagulant agents (dabigatran, rivaroxaban, apixaban).

There are also many novel invasive treatments for AF. Studies are needed to determine if and how anticoagulation strategies should be modified for patients receiving these procedures. For example, studies are needed to determine the comparative effectiveness and safety of new oral anticoagulants and percutaneous LAA closure for stroke prevention in nonvalvular AF patients. Studies are needed to determine if and when it is safe to discontinue all oral anticoagulants after successful AF ablation. Studies also are needed to determine the thromboembolic and bleeding risk associated with the procedures themselves over the long term.
Therefore, we have identified the following specific evidence gaps related to KQ 3:

- What are the comparative safety and effectiveness of specific anticoagulation therapies, antiplatelet therapies, and procedural interventions for preventing thromboembolic events?
    - For the above evidence gap, we suggest focusing specifically on the comparative effectiveness of factor IIa inhibitors, Xa inhibitors, and other novel anticoagulants and procedural interventions.
    - Safety issues include reversal of anticoagulant effects for severe bleeding events and monitoring of therapeutic status.
- What are the comparative safety and effectiveness of specific anticoagulation therapies, antiplatelet therapies, and procedural interventions for preventing thromboembolic events specific to patients who have recently undergone rate or rhythm control procedures for treating their AF?For this evidence gap, we suggest focusing on methods of determining the comparative effectiveness and safety of available stroke prevention therapies, and strategies for determining longer term therapy given successful AF treatment.
- What are the comparative safety and effectiveness of specific anticoagulation therapies, antiplatelet therapies, and procedural interventions for preventing thromboembolic events specific to special subpopulations—patients with advanced renal failure or on dialysis, elderly patients, and others? For this evidence gap, we suggest focusing specifically on the comparative effectiveness of factor IIa inhibitors, Xa inhibitors, and other novel anticoagulants and procedural interventions

KQ 4: Anticoagulation Strategies in Patients Undergoing Invasive Procedures

Our review identified limited studies assessing the optimal strategy for anticoagulation either peri-RFA or in the setting of other operative procedures. In addition, the few studies available suggest that ischemic event rates are likely to be extremely low; thus, trials powered adequately to assess the impact of different strategies, especially on ischemic events, would have to be large. Given the number of these procedures performed per year, as well as the apparent uncertainty about optimal treatment of the patients undergoing such procedures, RCTs to answer these questions are sorely needed. Trials should be done with traditional anticoagulants as well as the newer antiplatelet and antithrombotic agents. Given the number of treatment strategies available, initial research might be focused on comparing continued anticoagulant therapy versus bridging therapies versus interruption of therapy (i.e., stopping anticoagulant therapy before the procedure). Given the current insufficient evidence pertinent to this KQ, we think that the original KQ represents the remaining evidence gap and need for future research. Perhaps an additional evidence gap, given the need for a large sample size in an RCT addressing this question, would be explore whether study designs other than RCTs would possibly help decrease the evidence gap in this area.

KQs 5 and 6: Switching Between Warfarin and Novel Oral Anticoagulants and Stroke Prevention After a Hemorrhagic Event

We found no peer-reviewed published studies for either of these KQs, and so these are both clearly remaining evidence gaps, needing future evidence generation before evidence synthesis is possible.

Due to the increasing popularity of the new Xa agents, RCTs are needed to establish evidence to guide providers in managing patients with AF who are currently on warfarin and being switched to the newer Xa agents. Trials should seek to provide directions for managing patients who may be at different risk levels (as defined by $CHADS_{2,}$ CHA_2DS_2-VASc, or Framingham risk scores), including type of AF, sex, age, and other coexisting risk factors. Additionally, evidence needs to be published in peer-reviewed journals on how to manage patients being switched off the newer Xa agents and onto warfarin.

Similarly, trials are needed to determine the comparative safety and effectiveness of available strategies for resuming anticoagulation therapy following a hemorrhagic event. These trials should be evaluated in patients based on type of hemorrhagic event, as well as based on traits that may affect risk of bleeding, such as age, comorbidities, and other medical therapies.

Conclusions

Overall, we found that $CHADS_2$ and CHA_2DS_2-VASc scores have the best prediction for stroke events in patients with AF among the risk scores we reviewed, whereas HAS-BLED provides the best prediction for bleeding risk. Imaging tools require further evidence in regard to their appropriate use in clinical decisionmaking. Improved evidence of the use of these scores among patients on therapy is also required. Newer anticoagulants show early promise of reducing stroke and bleeding events when compared with warfarin, and apixaban shows safety and efficacy in patients who are not candidates for warfarin. However, further studies are required for key clinical scenarios involving anticoagulation use and procedures, switching or bridging therapies, and when to start anticoagulation after a hemorrhagic event.

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Abbreviations

AF	atrial fibrillation
AHRQ	Agency for Healthcare Research and Quality
ARISTOTLE	Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation
ATRIA	Anticoagulation and Risk Factors in Atrial Fibrillation
AVERROES	Apixaban Versus Acetylsalicylic acid (ASA) to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment
BRI	Bleeding Risk Index
BRIDGE	Bridging Anticoagulation in Patients who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure or Surgery
CDSR	Cochrane Database of Systematic Reviews
CER	Comparative Effectiveness Review
$CHADS_2$	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
ESC	European Society of Cardiology
FDA	U.S. Food and Drug Administration
GWTG	Get With The Guidelines
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, Re-bleeding risk (2 points), Hypertension (uncontrolled), Anemia, Genetic factors, Excessive fall risk, Stroke
HR	hazard ratio
ICH	intracranial hemorrhage
INR	international normalized ratio
KQ	Key Question
LAA	left atrial appendage
MI	myocardial infarction
NIH	National Institutes of Health
NRI	net reclassification improvement
PCI	percutaneous coronary intervention
PICOTS	populations, interventions, comparators, outcomes, timing, and settings of interest
QUADAS-2	QUality Assessment tool for Diagnostic Accuracy Studies-2
RCT	randomized controlled trial

RE-LY	Randomized Evaluation of Long-Term Anticoagulation Therapy
RFA	radiofrequency ablation
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
SDT_{INR}	standard deviation of transformed international normalized ratio
TEP	Technical Expert Panel
TIA	transient ischemic attack
TTR	time in therapeutic range
VKA	vitamin K antagonist

Introduction

Background

Atrial Fibrillation and Stroke

Atrial fibrillation (AF) is a common type of supraventricular tachyarrhythmia. While a supraventricular tachyarrhythmia is any tachycardic rhythm originating above the ventricular tissue, AF is characterized by uncoordinated atrial activation with consequent deterioration of mechanical function.[1] AF is the most common cardiac arrhythmia 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 adult population,[2,3] occurring in about 2.2 million people in the United States. The prevalence increases to about 6 percent in people age 65 or older and to 10 percent in people age 80 or older.[4] The burden of AF in the United States is increasing. It is estimated that by the year 2050 there will be an estimated 12.1 million Americans with AF (95% confidence interval [CI] 11.4 to 12.9), representing more than a two-fold (240%) 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 3-fold increase from 2000.[5]

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] Furthermore, AF-related strokes are more severe, with patients twice as likely to be bedridden as patients with stroke from other etiologies, and are also more likely to result in death.[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 50–59 years old to 23 percent for those who are 80–89 years old.[10] Congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and prior stroke or transient ischemic attack (TIA) are considered independent risk factors for stroke as well as risk factors for AF. These risk factors are the elements that form the classic $CHADS_2$ risk score for stroke prevention (Congestive heart failure, Hypertension, Age ≥75, Diabetes mellitus, prior Stroke/transient ischemic attack [2 points]).[13,14] This score ranges from 0–6, 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 1.9 percent in patients with a $CHADS_2$ score of 0, to 18.2 percent in patients with a $CHADS_2$ score of 6. Aggressive primary prevention and intervention once these risk factors are present are essential to optimally manage the increased risk of developing AF and stroke independently or as a result of AF.

Stroke Prevention Strategies in AF

Management of AF involves three distinct areas: rate control, rhythm control, and prevention of thromboembolic events. This Comparative Effectiveness Review (CER) focuses on the last

area. CER 119, focusing on the treatment of AF through rate or rhythm control, was conducted in parallel with this CER and is available on the Effective Health Care Web site (www.effectivehealthcare.ahrq.hhs.gov/reports/final.cfm).

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.

Risk Stratification

Stroke prevention in AF is complex. 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 below, 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.

A number of studies have examined the appropriate populations and therapies for stroke prevention in AF. Despite existing risk stratification tools with overlapping characteristics, the major risk factors for ischemic stroke and systemic embolism in patients with nonvalvular AF are congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and prior stroke or TIA. As stated previously, these risk factors are the elements that form the $CHADS_2$ score, one of the most widely studies and applied clinical risk scores from stroke in AF.[13] However, because of the overlap with factors also associated with increased risk of bleeding, the $CHADS_2$ score currently appears to be underused to guide decisions about antithrombotic therapy.

Lip and colleagues built upon the $CHADS_2$ score and other risk stratification schema to develop the 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), which ranges from 0–9 and aims to be more sensitive than the $CHADS_2$ score, specifically seeking to identify patients at low risk for stroke based on earlier risk scores but for whom antithrombotic therapy may be beneficial, for example, women and younger patients.[15] Additionally, the Framingham risk score for predicting future cardiovascular events has been also used to predict stroke in AF. Other scores have been examined, as well as other clinical risk factors but these have not been shown to provide incremental improvement or better discrimination of risk than the $CHADS_2$, CHA_2DS_2-VASc, and Framingham scores.

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 with 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 INR (international normalized ratio) value, which provides the result of the actual prothrombin time over a normalized value. It has been demonstrated that an INR value of 2–3 provides the best trade-off 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 scale (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly [> 65 years], Drugs/alcohol concomitantly) 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 on this scale range from 0–9. A score ≥3 indicates a high risk of bleeding with oral anticoagulation and/or aspirin.[16] The HAS-BLED score may aid decisionmaking in clinical practice and is recommended by the current European Society of Cardiology (ESC) AF guidelines.[17] However, uncertainty remains, both about whether other clinical or imaging tools might improve prediction of stroke or bleeding risk, and about how the available tools can best be disseminated into routine management of AF patients.

The current underutilization of risk assessment tools could be due to a number of reasons, including perceived lack of evidence to support routine use, limited comparative studies on the different tools, difficulty in using the tools at the bedside, clinical inertia, and inadequate provider knowledge and awareness of the existing tools. Independent assessments of the currently available risk assessment tools for thromboembolic events and major bleeding episodes are needed to highlight the relative strengths of the various tools for predicting events. A comparative and thorough assessment of current tools could assist providers in understanding the clinical value of appropriately judging risk and treating accordingly. Also, an assessment of how application of these tools may improve outcomes could help improve their utility in clinical practice.

Finally, the use of imaging tools for assessing thromboembolic risk has not been formally reviewed to date. Understanding the role and accuracy of these tools with a comparative assessment would provide clinicians with improved decisionmaking in the use of these technologies in patients with AF and the outcomes associated with specific imaging results.

Therapeutic Options for Stroke Prevention in AF

Vitamin K antagonists (VKAs) are highly effective for the prevention of stroke in patients with nonvalvular AF. VKAs such as warfarin have been in use for over 50 years. These compounds create an anticoagulant effect by inhibiting the y-carboxylation of vitamin K-dependent factors (II, VII, IX, and X).[18] 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%).[19] Aspirin has commonly been recognized as an alternative strategy for prevention of stroke, despite limited evidence, for those intolerant of warfarin or at high-risk for bleeding on warfarin, such as the elderly. The best estimate of stroke reduction by antiplatelet drugs is

reported to be approximately 20 percent. No major benefit of adding clopidogrel to aspirin in patients with nonvalvular AF has been found.[20]

Over the last decades, oral anticoagulation with VKAs has been the gold standard therapy for stroke prevention in nonvalvular AF. Thromboprophylaxis with VKAs for patients with nonvalvular AF at risk for stroke is, however, suboptimal, due primarily to the many limitations and disadvantages in use of VKAs. VKAs have a narrow therapeutic window and require frequent monitoring and lifestyle adjustments, which make their use less than ideal and adherence sometimes problematic.

The narrow therapeutic window for warfarin has clinical implications in the undertreatment and overtreatment of patients, which increase the risk of thromboembolic events and bleeding, respectively. Warfarin-naïve patients experience a three-fold increased risk of bleeding in the first 90 days of treatment compared with patients already on warfarin.[21,22] This increased risk of bleeding in warfarin-naïve patients also contributes to the underuse of warfarin in the elderly population with AF. Failure to prescribe warfarin in eligible patients is a pervasive problem, despite the adoption of performance measures and guidelines advocating its use in patients with nonvalvular AF who have moderate to severe risk of stroke.[23,24] One out of three Medicare AF patients eligible for anticoagulation therapy is not prescribed warfarin. In the Get With The Guidelines (GWTG) registry, only 65 percent of eligible patients with heart failure and AF were prescribed warfarin at discharge.[25,26] Unfortunately, use of warfarin in the GWTG quality improvement program did not increase over time, and when warfarin was not prescribed at discharge after a stroke related to AF, initiation in eligible patients was low in the ambulatory setting. Thus, a large number of patients with AF who might benefit from warfarin are either not being offered treatment, are refusing to take it, or are stopping it.

New devices and systemic therapies have been developed for stroke prophylaxis and are in testing or have been approved for use. Mechanical interventions for stroke prophylaxis have emerged and are growing in use. For example, left atrial appendage (LAA) occlusive devices are an alternative treatment strategy used to prevent blood clot formation in patients with AF. These devices currently remain investigational pending approval by the FDA. For patients with AF who are elderly (at high risk for falls), have a prior bleeding history, are pregnant, and/or are noncompliant (which can be a significant issue for those on warfarin), LAA occlusion may be a better stroke prevention strategy than oral anticoagulation. Therefore, both anticoagulation and LAA occlusion need to be considered when evaluating stroke prevention strategies for patients with AF.

New anticoagulants are challenging the predominance of VKAs for stroke prophylaxis in AF. Since 2007, three large trials comparing novel anticoagulants with VKAs have been completed, with a combined sample size of ~50,000 subjects:

- RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy), with approximately 18,000 subjects and evaluating the new direct Factor IIa (thrombin) inhibitor dabigatran[27]
- 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 new direct factor Xa inhibitor rivaroxaban[28]
- ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation), with approximately 18,000 subjects and evaluating the new direct factor Xa inhibitor apixaban[29]

At the time of release of this report, all three of these agents (dabigatran, rivaroxaban, and apixaban) have been approved by the FDA. Additional anticoagulant therapies in the investigational stage (without FDA approval) include edoxaban and idraparinux.

The evolution of newer anticoagulation agents, like those studied in the large trials above, as well as the risks and benefits when compared with LAA occlusion devices and older antiplatelet and anticoagulation strategies, make stroke prevention in AF an area of further clinical uncertainty that supports both the importance and appropriateness of further evidence development and a new systematic review of existing evidence. Furthermore, these new therapies highlight the need to reconsider their comparative effectiveness and safety when compared with standard antithrombotic and antiplatelet therapies and with each other. Even though the ESC 2012 guidelines for AF recommend that the critical assessment necessary in the new era of newer oral anticoagulation is the identification of 'truly low risk', e.g. those who do not need oral anticoagulation, from those who have at least 1 or more risk factors for stroke and should be recommended oral anticoagulation, appropriate and accurate risk assessment is required as these new anticoagulants are still not without bleeding risk.

Even with treatment for stroke prophylaxis in patients with nonvalvular AF, numerous unanswered questions persist around managing patients undergoing invasive or surgical procedures. Patients receiving long-term anticoagulation therapy may need to stop this therapy temporarily before undergoing certain procedures where the risk of bleeding is high. Because VKAs have a long half-life, patients need to stop these medications approximately 5 days before an invasive procedure. However, 5 days without an oral anticoagulant can increase the risk of ischemic events. Thus, one option often used in clinical practice is a "bridging" therapy, in which a different, parenteral anticoagulant with a shorter half-life (e.g., low-molecular-weight heparin or unfractionated heparin) is given preprocedure and after the oral anticoagulant is stopped. Usually, this parenteral anticoagulant is restarted and maintained after the procedure, together with the VKA, until the INR is in the 2–3 range. Although bridging is done in clinical practice, there are data demonstrating that it is associated with increased risk of bleeding.[30-34] In summary, the real risk-benefit of bridging from VKAs to a parenteral anticoagulant in patients with AF undergoing an invasive procedure is unknown, and is currently under study in an National Institutes of Health (NIH) sponsored trial called BRIDGE (Bridging Anticoagulation in Patients who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure or Surgery).

In addition, there is uncertainty regarding strategies for switching patients from warfarin to the new generation of direct thrombin inhibitors and considerations when restarting anticoagulation in patients after a hemorrhagic event. For example, in patients with AF undergoing surgery or percutaneous procedures, the duration of withholding anticoagulant therapy is not well defined. Also, synthesis of the evidence on the safety and timing of restarting patients on VKAs or antithrombin inhibitors after a hemorrhagic stroke remains lacking. These are complex and common scenarios, and a systematic review of the currently available data can provide clinicians with evidence to incorporate into their clinical practice, while at the same time shedding light on areas that require further research.

Scope and Key Questions

Scope of the Review

This CER was funded by the Agency for Healthcare Research and Quality (AHRQ) and is designed to evaluate the comparative safety and effectiveness of stroke prevention strategies in patients with nonvalvular AF. Further details are provided under "Key Questions" and "Analytic Framework," below, and in the section on "Inclusion and Exclusion Criteria" in the Methods chapter. To increase applicability to the U.S. setting, we restrict our review to interventions available in the United States. For each Key Question (KQ), we further consider whether the comparative safety and effectiveness of the interventions evaluated differs 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.

Over the last decades, oral anticoagulation with VKAs has been the gold standard therapy for stroke prevention in nonvalvular AF. Limitations with monitoring and compliance of VKAs have fueled the development of new antithrombotic strategies, devices, and oral anticoagulants, including oral direct thrombin inhibitors and oral factor Xa inhibitors. After 60 years with essentially one class of drug for stroke prevention in nonvalvular AF, today there are several agents that are available to treat these AF populations of varying $CHADS_2$ risk. So, there is a real challenge in how to select the treatment option most suitable for a given patient, as well as how to best utilize the available risk stratification tools to assist physicians in making important decisions. In the light of this new clinical scenario around patients with AF, comparative safety and effectiveness analyses of these novel agents and new strategies for patients with AF are needed. Existing systematic reviews of the evidence either do not include the most recent clinical evidence, or have not yet been performed exploring a broader spectrum of important clinical and policy questions of interest. Thus, a review of the available data will not only address these uncertainties, but it will define gaps in knowledge and identify important future research needs.

By summarizing data that support improved stroke prevention strategies in patients with AF, we hope to enhance patient-centered outcomes and reduce health care utilization and costs. Thus, our findings will have direct implications for improved patient care and for the allocation of Medicare and other health care resources. This project will benefit patients, providers, payers, and policymakers. Patients will benefit from more robust data on the comparative safety and effectiveness of different stroke prevention strategies for AF. Providers will benefit by gaining a better understanding of which patients benefit the most from available strategies. Policymakers will be able to design and implement programs to make better use of scarce health care resources while improving the health status of adult patients with AF.

Key Questions

With input from our Key Informants, we constructed KQs 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).

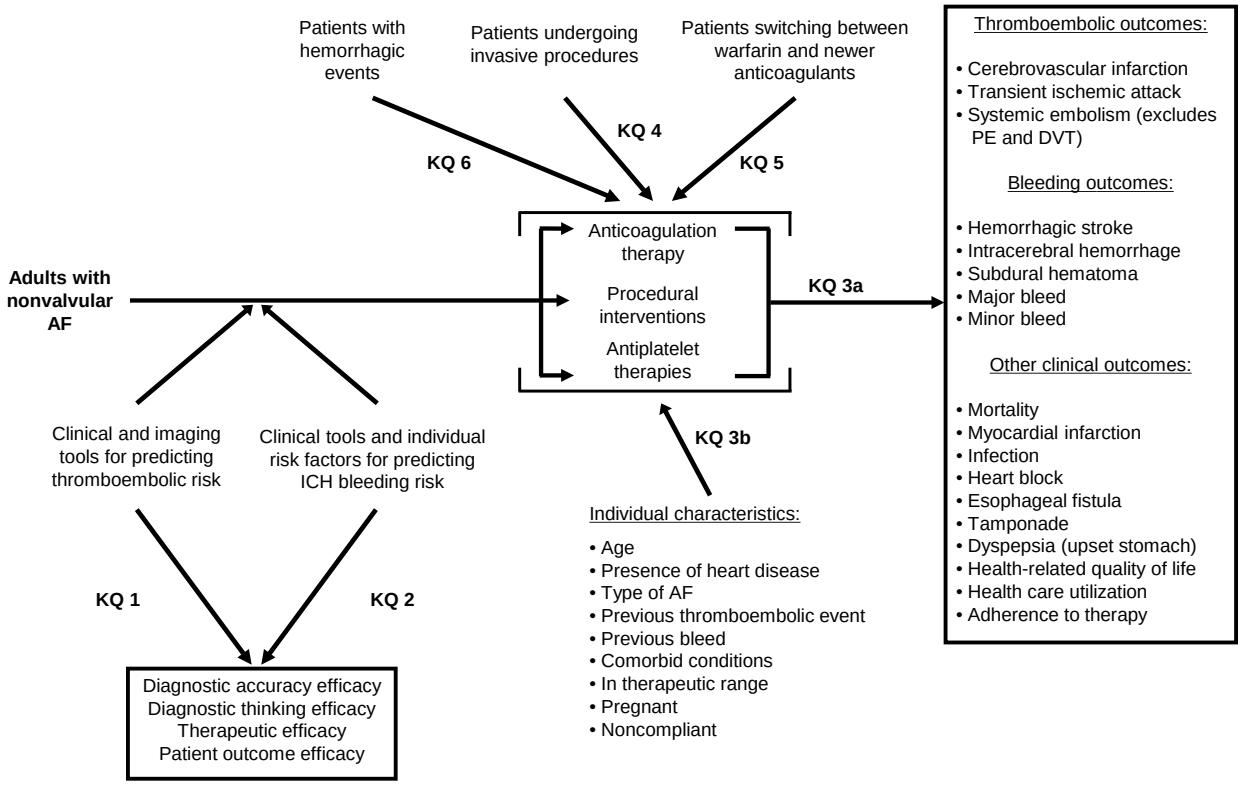
The KQs considered in this CER are:

- **KQ 1:** In patients with nonvalvular atrial fibrillation, what are the comparative diagnostic accuracy and impact on clinical decisionmaking (diagnostic thinking, therapeutic, and patient outcome efficacy) of available clinical and imaging tools 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, 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?
- **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?
- **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?
- **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?

Analytic Framework

Figure 1 depicts the analytic framework for this project.

Figure 1. Analytic framework



Abbreviations: AF=atrial fibrillation; DVT=deep vein thrombosis; ICH=intracranial hemorrhage; KQ=Key Question; 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); 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); strategies for patients who are undergoing invasive procedures (KQ 4); strategies for patients who switch between warfarin and direct thrombin inhibitors (KQ 5); and strategies for patients with hemorrhagic events (KQ 6). The 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).

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)[35] and "Methods Guide for Medical Test Reviews" (hereafter referred to as the Medical Test Guide).[36] The main sections in this chapter reflect the elements of the protocol established for the CER; certain methods map to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.[37]

Topic Refinement and Review Protocol

During the topic refinement stage, we solicited input from Key Informants representing medical professional societies/clinicians in the areas of general internal medicine, cardiology, cardiothoracic surgery, neurology, electrophysiology, and primary care; patients, scientific experts; and payers, to help define the Key Questions (KQs). The KQs were then posted for public comment for 4 weeks from September 19 to October 17, 2011, and the comments received were considered in the development of the research protocol. We next convened a Technical Expert Panel (TEP) comprising clinical, content, and methodological experts to provide input to the draft protocol in defining populations, interventions, comparisons, and outcomes, and in identifying particular studies or databases to search. The final review protocol was posted for public access on the AHRQ Effective Health Care Web site.[38] Before involvement in the CER process, the Key Informants and members of the TEP were required to disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts. Any potential conflicts of interest were balanced or mitigated. Key Informants and members of the TEP did not perform analysis of any kind, and did not contribute to the writing of this report.

Literature Search Strategy

Search Strategy

To identify relevant published literature, we searched PubMed®, Embase®, and the Cochrane Database of Systematic Reviews (CDSR), limiting the search to studies published from January 1, 2000, to August 14, 2012. We applied a date limitation of 2000 forward because we believe that the evidence published from 2000 on represents the current standard of care for patients with AF and relevant comorbidities. We acknowledge that this criterion eliminates several valuable older studies published prior to 2000 that offer data comparing warfarin and aspirin, and thus provide additional context for these older studies in an introductory section of KQ 3. Where possible in our search strategies, we used existing validated search filters (such as the Clinical Queries Filters in PubMed). An experienced search librarian guided all searches. Exact search strings are included in Appendix A. We supplemented the electronic searches with a manual search of citations from a set of key primary and systematic review articles.[19,33,39-94] We also considered studies identified through suggestions from external peer and public reviewers. Final updating of all database searches was performed during the review period. All citations were imported into an electronic database (EndNote® X4; Thomson Reuters, Philadelphia, PA).

We used several approaches to identify relevant gray literature; these included requests to drug and device manufacturers for scientific information packets and searches of trial registries and conference abstracts for relevant articles from completed studies. Gray literature databases searched included ClinicalTrials.gov (final search date August 22, 2012); the World Health Organization International Clinical Trials Registry Platform search portal (final search date August 17, 2012); and ProQuest COS Conference Papers Index (final search date August 14, 2012). Search terms used for these sources are provided in Appendix A.

Inclusion and Exclusion Criteria

The PICOTS (Populations, Interventions, Comparators, Outcomes, Timings, and Settings of interest) criteria used to screen articles for inclusion/exclusion at both the title-and-abstract and full-text screening stages are detailed in Table 1.

Table 1. Inclusion and exclusion criteria

PICOTS Element	Inclusion Criteria	Exclusion Criteria
Populations	• Humans • Adults (age ≥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) o Permanent AF (an ongoing, long-term episode) o Patients with AF who experience acute coronary syndrome • Subgroups of potential interest include: o Patients who have comorbid conditions such as, dementia, or renal or hepatic failure o Patients with multiple coexisting conditions (e.g., combinations of hypertension, diabetes, congestive heart failure, coronary artery disease, and high cholesterol) o Patients with prior stroke (by type of event) o Patients with prior bleed (by type of bleed) o Patients in the therapeutic range (versus those not in range) o Type of AF (paroxysmal, persistent, and permanent) o Patients stratified by age o Pregnant patients o Patients stratified by race/ethnicity o Patients who are noncompliant with treatment.	• 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

Table 1. Inclusion and exclusion criteria, (continued)

PICOTS Element	Inclusion Criteria	Exclusion Criteria
Interventions	• Clinical and imaging tools for assessment/evaluation of thromboembolic risk: o Clinical: ▪ $CHADS_2$ score ▪ CHA_2DS_2-VASc score ▪ Framingham risk score o Imaging: ▪ Transthoracic echo (TTE) ▪ Transesophageal echo (TEE) ▪ CT scans ▪ Cardiac MRIs • Clinical tools and individual risk factors for assessment/evaluation of intracranial hemorrhage bleeding risk: o Patient age o Prior stroke o Type of AF (paroxysmal, persistent, permanent) o International normalized ratio (INR) o Dementia/cognitive impairment o Falls risk o HAS-BLED score o CHADS2 score o CHA_2S_2-VASc score o Framingham risk score o $HEMORR_2HAGES$ score o ATRIA score o Bleeding Risk Index (BRI) • Anticoagulation therapy (all oral anticoagulants): o Warfarin (Coumadin®) o Vitamin K antagonists (VKAs) o Dabigatran (Pradaxa®) o Rivaroxaban (Xarelto®) o Apixaban (Eliquis®) o Edoxaban (DU-176b) • Procedural interventions: o Surgical procedures (surgical resection/removal of left atrial appendage [LAA]) o Minimally invasive procedures (Atriclip device) o Transcatheter procedures (WATCHMAN device, AMPLATZER cardiac plug, PLAATO device) • Antiplatelet therapy: o Clopidogrel (Plavix®) o Aspirin (ASA) o ASA + dipyridamole (Aggrenox®) o Dipyridamole (Persantine®) o Combinations of antiplatelets • Anticoagulation bridging therapies: o FDA-approved low molecular weight heparins (e.g., bemiparin, certoparin, dalteparin,	None

Table 1. Inclusion and exclusion criteria, (continued)

PICOTS Element	Inclusion Criteria	Exclusion Criteria
	enoxaparin, nadroparin, parnaparin, reviparin, tinzaparin) o IV heparin o Dabigatran (off-label usage)	
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 • KQ 4: Other anticoagulation therapies • KQ 5: Other anticoagulation bridging strategies • KQ 6: Other strategies for resuming anticoagulation therapy following a hemorrhagic event	For KQs 3 and 4, studies that did not include an active comparator
Outcomes	Study assesses a patient-centered outcome of interest: • Assessment of thromboembolic outcomes: o Cerebrovascular infarction o Transient ischemic attack (TIA) o Systemic embolism (note: excludes pulmonary embolism and deep vein thrombosis) • Prevention of bleeding outcomes: o Hemorrhagic stroke o Intracranial hemorrhage (intracerebral hemorrhage, subdural hematoma) o Major bleed (stratified by type and location) o Minor bleed (stratified by type and location) • Occurrence of other clinical outcomes: o Mortality o Myocardial infarction o Infection o Heart block o Esophageal fistula o Tamponade o Dyspepsia (upset stomach) o Health-related quality of life and functional capacity o Health services utilization (hospital admissions, office visits, prescription drug use) o Long-term adherence to therapy • Assessment of clinical and imaging tool efficacy for predicting thromboembolic risk and bleeding events: o Diagnostic accuracy efficacy o Diagnostic thinking efficacy o Therapeutic efficacy o Patient outcome efficacy	Study does not include any outcomes of interest
Timing	• Timing of followup not limited	None
Settings	• Inpatient and outpatient	None

Table 1. Inclusion and exclusion criteria, (continued)

PICOTS Element	Inclusion Criteria	Exclusion Criteria
Study design	• Original data • All sample sizes • RCTs, prospective and retrospective observational studies, or registries	• Not a clinical study (e.g., editorial, nonsystematic review, letter to the editor, case series)
Publications	• English-language publications only • Relevant systematic reviews, meta-analyses, or methods articles (used for background only)[a] • Published on or after January 1, 2000	• Non-English-language publications [b]

[a]Systematic reviews and meta-analyses were excluded from direct abstraction; those representing key sources were hand-searched as potential sources of additional citations to consider in the review. Articles providing methods information only (i.e., not reporting data) were not considered among the formal set of included articles, but were used to supplement the abstractions of the studies they referenced.

[b]Given the high volume of literature available in English-language publications (including the majority of known important studies), and concerns about the applicability of non-English publication studies to settings in the United States, non-English articles were excluded.

Abbreviations: AF=atrial fibrillation; ASA=aspirin; ATRIA=Anticoagulation and Risk Factors in Atrial Fibrillation; BRI=Bleeding Risk Index; $CHADS_2$=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; CT=computed tomography; FDA=U.S. Food and Drug Administration; 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, Re-bleeding risk (2 points), Hypertension (uncontrolled), Anemia, Genetic factors, Excessive fall risk, Stroke; INR=international normalized ratio; IV=intravenous; KQ=Key Question; LAA=left atrial appendage; MRI=magnetic resonance imaging; PICOTS=Populations, Interventions, Comparators, Outcomes, Timings, and Settings of interest; RCTs=randomized controlled trials; TIA=transient ischemic attack; TEE=transesophageal echocardiography; TTE=transthoracic echocardiography; VKAs=vitamin K antagonists

Study Selection

Using the prespecified inclusion and exclusion criteria described in Table 1, 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 if needed.

Relevant systematic review articles, meta-analyses, and methods articles were flagged for manual searching of references and cross-referencing against the library of citations identified through electronic database searching.

For citations retrieved by searching the gray literature, the above-described procedures were modified such that a single screener initially reviewed all search results; final eligibility of citations for data abstraction was determined by duplicate screening review. All screening decisions were made and tracked in a Distiller SR database (Evidence Partners Inc, Manotick, ON, Canada).

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. To aid in both reproducibility and standardization of data collection, researchers received data abstraction instructions directly on each form created specifically for this project within the DistillerSR database.

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 the treatment (e.g., pharmacotherapy dosing, methods of procedural therapies), patient characteristics (e.g., etiology of AF, history of prior bleed or stroke), and study design (e.g., randomized controlled trial [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. Data necessary for assessing quality and applicability, as described in the Methods Guide,[35] 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.

Quality (Risk of Bias) Assessment of Individual Studies

We evaluated the quality of individual studies using the approach described in the Methods Guide.[35] To assess quality, we used the following strategy: (1) classify the study design, (2) apply predefined criteria for quality and critical appraisal, and (3) arrive at a summary judgment of the study's quality. We applied criteria for each study type derived from core elements described in the Methods Guide. Criteria of interest for all studies included similarity of groups at baseline, extent to which outcomes were described, blinding of subjects and providers, blinded assessment of the outcome(s), intention-to-treat analysis, differential loss to followup between the compared groups or overall high loss to followup, and conflicts of interest. Criteria specific to RCTs included methods of randomization and allocation concealment. For observational studies, additional elements such as methods for selection of participants, measurement of interventions/exposures, addressing any design-specific issues, and controlling confounding were considered. To indicate the summary judgment of the quality of individual studies, we used the summary ratings of good, fair, or poor based on the classification scheme presented in Table 2.

Table 2. Definitions of overall quality ratings

Quality Rating	Description
Good	A study with the least bias; results are considered valid. A good study has a clear description of the population, setting, interventions, and comparison groups; uses a valid approach to allocate patients to alternative treatments; has a low dropout rate; and uses appropriate means to prevent bias, measure outcomes, and analyze and report results.
Fair	A study that is susceptible to some bias but probably not enough to invalidate the results. The study may be missing information, making it difficult to assess limitations and potential problems. As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses. The results of some fair-quality studies are possibly valid, while others are probably valid.
Poor	A study with significant bias that may invalidate the results. These studies have serious errors in design, analysis, or reporting; have large amounts of missing information; or have discrepancies in reporting. The results of a poor-quality study are at least as likely to reflect flaws in the study design as to indicate true differences between the compared interventions.

For studies of diagnostic tests (KQs 1 and 2), we used the QUality Assessment tool for Diagnostic Accuracy Studies (QUADAS)-2[95] to assess quality. QUADAS-2 describes risk of bias in four key domains: patient selection, index test(s), reference standard, and flow and timing. The questions in each domain are rated in terms of risk of bias and concerns regarding applicability, with associated signaling questions to help with these bias and applicability judgments.

Studies of different designs were graded within the context of their respective designs. Thus, RCTs were graded as good, fair, or poor, and observational studies were separately graded as good, fair, or poor.

Data Synthesis

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 1–2) and drug class or procedure (KQs 3–6), when appropriate.

When at least three comparable studies reported the same outcome, we used the random-effects model analysis option in Comprehensive Meta-Analysis software (Version 2.2057; Biostat, Englewood, NJ) and the DerSimonian and Laird method.[96] to synthesize the available evidence quantitatively. 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. 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 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 discrimination adequate for genuine clinical utility.[97] 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 discrimination 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.

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 rated the strength of evidence for each KQ and outcome using the approach described in the Methods Guide.[35,98] and Medical Test Guide.[36] We assessed four domains: risk of bias, consistency, directness, and precision (Table 3).

Table 3. Strength of evidence—required domains

Domain	Rating	How Assessed
Risk of bias	Low Medium High	Assessed primarily through study design (RCT versus observational study) and aggregate study quality
Consistency	Consistent Inconsistent Unknown/not applicable	Assessed primarily through whether included studies appear to have the same direction of effect or the same magnitude of effect
Directness	Direct Indirect	Assessed by whether the evidence links interventions directly to health outcomes of specific importance for the review, and for comparative effectiveness studies, whether the comparisons have been done in head-to-head studies
Precision	Precise Imprecise	Based primarily on the size of the confidence intervals of effect estimates and highlighting the degree of certainty surrounding an effect estimate with respect to a given outcome, based on the sufficiency of sample size and number of events

Abbreviation: RCT=randomized controlled trial

We also assessed publication bias. These 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. 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.[99] 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 findings were evaluated when available and form the basis of our strength of evidence ratings. When only on-treatment findings were available, our confidence in the stability of our findings was reduced, and therefore the related strength-of-evidence rating was lowered. Finally, when outcomes were assessed by large RCTs and smaller studies, we focused our strength of evidence rating on the findings from the large RCTs and then increased or decreased the strength of evidence rating depending on whether findings from the smaller studies were consistent or inconsistent with those from the large RCTs.

This four-level rating scale consists of the following definitions:

- **High—**High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
- **Moderate—**Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
- **Low—**Low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.
- **Insufficient—**Evidence either is unavailable or does not permit estimation of an effect.

Applicability

We assessed applicability across the KQs using the method described in the Methods Guide.[35,100] 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

The peer review process is our principal external quality-monitoring device. Nominations for peer reviewers were solicited from several sources, including the TEP and interested Federal agencies. Experts in general cardiology, heart failure, electrophysiology, neurology, internal medicine, stroke prophylaxis, pharmacological treatments for AF, geriatrics, primary care, health services research, epidemiology, and biostatistics, along with individuals representing stakeholder and user communities, were invited to provide external peer review of the draft report. AHRQ, an associate editor, and members of the TEP also provided comments. In addition, the draft report was posted on the AHRQ Web site for public comment for 4 weeks, from August 31 to September 28, 2012. We have addressed all reviewer comments, revising the text as appropriate, and have documented our responses in a disposition of comments report that will be made available 3 months after the Agency posts the final report on the AHRQ Web site.

A list of peer reviewers who submitted comments on the draft report is provided in the front matter of this document.

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 six 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.

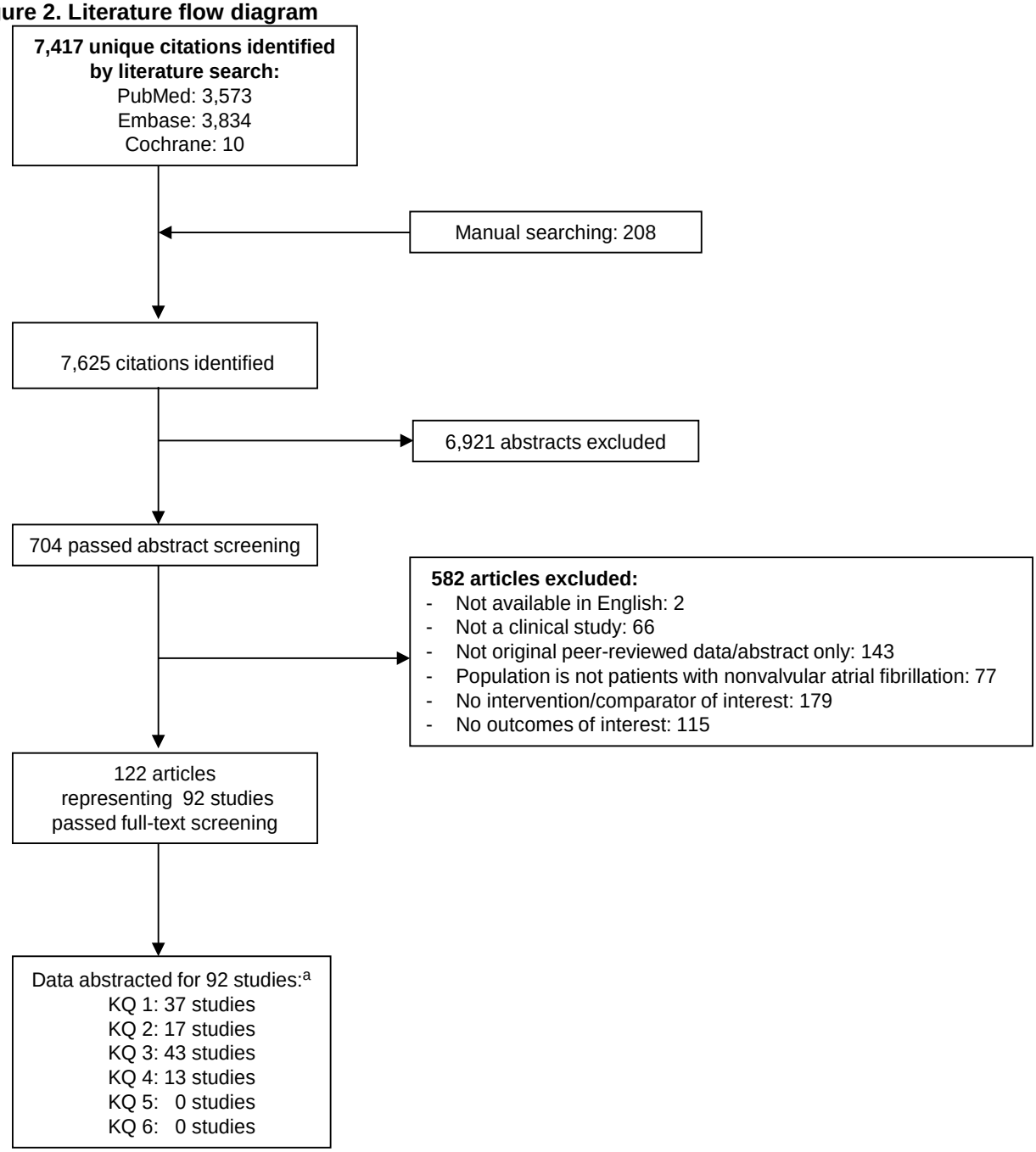
A list of abbreviations and acronyms used in this chapter is provided at the end of the report.

Results of Literature Searches

Figure 2 depicts the flow of articles through the literature search and screening process. Searches of PubMed®, Embase®, and CDSR yielded 7,417 unique citations. Manual searching of gray literature databases, bibliographies of key articles, and information received through requests for scientific information packets identified 208 additional citations, for a total of 7,625 citations. After applying inclusion/exclusion criteria at the title-and-abstract level, 704 full-text articles were retrieved and screened. Of these, 582 were excluded at the full-text screening stage, leaving 122 articles for data abstraction. These 122 articles described 92 unique studies. The relationship of studies to the review questions is as follows: 37 studies relevant to KQ 1, 17 studies relevant to KQ 2, 43 studies relevant to KQ 3, 13 studies relevant to KQ 4, 0 studies relevant to KQ 5, and 0 studies relevant to KQ 6 (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 92 included studies.

Figure 2. Literature flow diagram



[a]Some studies were relevant to more than one KQ.
Abbreviation: KQ=Key Question

Description of Included Studies

Overall, we included 92 studies represented by 122 publications: 37 studies were relevant to KQ 1, 17 studies to KQ 2, 43 studies to KQ 3, 13 studies to KQ 4, 0 studies to KQ 5, and 0 studies to KQ 6. Studies were conducted wholly or partly in continental Europe (49%), the United States or Canada (33%), Asia (22%), the UK (13%), South or Central America (5%), Australia or New Zealand (5%), Africa (3%), and unspecified or other locations (4%). 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. Our search yielded 186 trial records. A single reviewer identified 59 of these records as potentially relevant to this review. Of those 59 records, 32 had expected completion dates of 1 year or more prior to our search. From that group of 32 trials, we identified publications for 18. The remaining 14 trial records for which we did not identify publications were all considered potentially relevant to KQ 3. However these 14 unpublished studies provided data on only 8,879 patients, while the 43 published studies included for KQ 3 in this review involved more than 433,500 patients. Therefore we do not believe 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 for predicting thromboembolic risk?

Key Points

- Comparison of risk scores between study populations was complicated by multiple factors. 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. No studies performed net reclassification improvement (NRI) in their selected population. As a result, our ability to draw firm conclusions was limited.
- Based on a meta-analysis of 8 studies (5 good quality, 3 fair quality; 379,755 patients), there is low strength of evidence that the continuous $CHADS_2$ score provides modest stroke risk discrimination (c-statistic of 0.71; 95% CI 0.66 to 0.75).
- Based on a meta-analysis of 5 studies (4 good quality, 1 fair quality; 371,911 patients), there is low strength of evidence that the continuous CHA_2DS_2-VASc score provides modest stroke risk discrimination (c-statistic of 0.70; 95% CI 0.66 to 0.75).
- Based on a meta-analysis of 5 studies (4 good quality, 1 fair quality; 259,253 patients), there is moderate strength of evidence that the categorical Framingham score provides limited stroke risk discrimination (c-statistic of 0.63; 95% CI 0.62 to 0.65).

- Given the imprecision and inconsistency across studies of c-statistics for the categorical $CHADS_2$ and CHA_2DS_2-VASc scores, there is insufficient evidence of their ability to discriminate stroke risk.
- There is insufficient evidence for the relationship between LA thrombus on echocardiography and subsequent stroke based on 5 studies (3 good quality, 2 fair quality; 1,228 patients) that reported discrepant results.
- Of the tools reviewed, the $CHADS_2$ and CHA_2DS_2-VASc continuous risk scores appear to be similar and have the most discrimination of stroke events when compared with the $CHADS_2$ categorical score, the CHA_2DS_2-VASc categorical score, and the Framingham categorical score. This finding was, however, statistically significant only for the comparison with the Framingham categorical score. Other comparisons were not possible given limited data.

Description of Included Studies

An expert panel recently recommended that for all patients with AF, stroke risk should be assessed using an established risk scoring tool.[101] Per the expert panel, if a patient's stroke risk is high enough to require anticoagulation, providers should use a bleeding risk scoring tool to estimate the net clinical benefit of anticoagulation: "For the majority of patients, the net benefit of stroke prophylaxis supersedes the 'net harm' of serious bleeding events, even among older patients."[101] Therefore, assessment of stroke and bleeding risk is not an opportunity to look for reasons not to anticoagulate, but rather an opportunity to assure that all patients with sufficient stroke risk are treated appropriately while addressing correctable risk factors for bleeding. 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, 37 studies described in 38 publications from 2001 to 2012 investigated our included tools for determining stroke risk in patients with nonvalvular AF and met the other inclusion criteria for KQ 1 (Appendix Table F-1).[13,15,27,102-136] Two articles reporting analyses based on the ATRIA study cohort[118,121] are counted here as one study grouping due to overlapping patient populations; they address different research questions and are represented in separate rows of Appendix Table F-2 and in separate sections under "Detailed Synthesis," below. The included articles explored tools in studies of diverse quality, design, geographical location, and study characteristics. Fourteen included studies were of good quality,[13,15,27,104,106,109,117-122,124,129,130] 21 of fair quality,[103,105,107,108,110-116,123,126-128,131-136] and 2 of poor quality.[102,125] Five studies enrolled patients from an inpatient setting;[102,115,117,133,136] the majority (23) were from outpatient settings,[13,15,27,104-107,109,110,113,116,118-129,131] and 3 studies enrolled patients from both types of settings.[108,114,130] In 6 studies, the location of enrollment was not reported.[103,111,112,132,134,135] The studies covered broad geographical locations with 16 studies conducted in Europe,[102-104,109,110,114,120,125,126,128-130,132,134-136] 8 in the United States,[13,107,108,111,112,118,121-123] 3 in the UK,[105,115,116] 7 in Asia,[106,113,117,124,127,131,133] and 2 in multiple nations;[15,27] 1 study did not report geography of enrollment.[119] Fourteen studies were conducted at multiple sites,[13,15,27,102,103,116,118-121,126,129,130,132,136] and 18 studies were conducted at a single center.[106-115,117,123,124,127,128,131,133,135] In 5 studies, this information was unclear or not reported.[104,105,122,125,134] Four studies were supported solely by industry.[27,115,116,119] Two studies received solely government support,[13,135] and in one study funding was partially composed of government support.[117] Seven studies received funding from multiple sources including government, industry, nongovernment and

nonindustry.[15,118,121,122,128,130,131,133] Three studies had no funding support,[103,104,132] while in 17 studies funding was unclear or not reported.[102,105-107,109,111,113,114,120,123-127,129,134,136]

Studies examined patients enrolled or with encounters between the years of 1948[122] and 2008.[108] The number of patients included in studies ranged from fewer than 100[124] to 170,291[130] with overlap in patient populations between some studies; altogether, the included studies analyzed data from almost 500,000 unique patients. The mean age of study participants ranged from 53–81 years. None of the studies presented data on ethnicity of subjects. Study gender distributions ranged from 44 percent male[128] to 84 percent male[123] in the included studies. Study followup duration ranged from 1–12 years. Sixteen studies provided specific information on event definition [15,27,103,107,109,111,114,118-122,128,131,134,135] and of these, 4 described a clinical adjudication process to validate these events,[27,118,119,121,122] while the other studies either relied on billing or other administrative data source or did not report how events were classified.

Sixteen studies used prospective cohorts to identify patients,[103,106,107,109-111,113,114,120,122-124,128,130,133,135] while 19 studies utilized retrospective cohorts,[13,15,102,104,105,108,112,115-118,121,125-127,129,131,132,134,136] and 2 studies were RCTs.[27,119] Two studies were derivation studies for risk scores for $CHADS_2$ and CHA_2DS_2-VASc, respectively,[13,15] the remaining studies were validation studies (excluding the imaging studies that have minimal overlap in criteria examined).

Many studies examined multiple risk stratification scores concurrently. The tool most commonly examined for risk stratification was the $CHADS_2$ score (27 studies[13,15,27,102-107,109,110,112-116,118,119,126-132,135]) Ten studies examined CHA_2DS_2-VASc;[15,102,104,105,109,119,129,130,135] the Framingham risk score was evaluated in six studies.[15,105,118,119,122,130] Six studies examined the use of echocardiography for evaluation of left atrial characteristics and stroke risk,[111,117,120,123,124,133] and one study used magnetic resonance imaging (MRI) to examine this relationship.[108] Finally, four studies described the predictive role of INR values for stroke risk.[118,120,128,131]

Detailed Synthesis

$CHADS_2$ Risk Tool

Twenty-seven 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; Table 4).[13,15,27,102-107,109,110,112-116,118,119,126-132,135,136] Twenty-three of the studies included patients on oral anticoagulant therapy.[27,102,103,105-107,109,110,112-116,118,119,126-128,131,132,134-136] One study examined $CHADS_2$ risk and stroke outcomes among patients undergoing coronary revascularization with PCI[126] one study in patients after surgical Maze procedure,[107] one in elderly patients (mean age 74 years),[109] two in Japanese patients,[113,127] and one in Mediterranean patients.[128]

The use of $CHADS_2$ to predict stroke risk varied among the studies. Four studies reported $CHADS_2$ score and stroke outcomes by individual $CHADS_2$ score.[13,104,106,116] Nine 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).[15,27,103,105,109,114,118,119,131] Three studies examined the revised $CHADS_2$ score classification as continuous variables,[102,109,130] and five studies did not report results by categorical or continuous $CHADS_2$ score.[107,115,118,132,135] The remaining studies used varying categorical classifications.

Table 4. Thromboembolic events by $CHADS_2$ score and concomitant stroke prevention therapy (antiplatelet and/or anticoagulant) use

Study	No. of Patients	Results (Thromboembolic Event Rates)	Followup Period	Risk of Bias
Patients <u>on</u> therapy				
Naganuma, 2012[131]	845	$CHADS_2$=0: 0.9 $CHADS_2$=1: 2.5* $CHADS_2$=2: 2.9* $CHADS_2$ ≥3: 4.8* *Per patient-year	Median 27 months	Low
Olesen, 2012[132]	87,202	<u>1-year</u> $CHADS_2$=0: 1.59* <u>12-year</u> $CHADS_2$=0: 1.28* *Per 100 patient-years	Maximum 12 years	Low
Olesen, 2012[129]	47,576	$CHADS_2$=0: 1.59*, 1.28** $CHADS_2$=1: 4.92*, 3.61** *Per 100 patient-years, 1 year followup **Per 100 patient-years, 12 years followup	12 years	Low
Potpara, 2012[135]	345	$CHADS_2$=0: 1.8%* *Per 100 patient-years	Mean 12.1 years; 4,166.5 patient-years	Unclear
Poli, 2011[103]	3,302	$CHADS_2$=0–1: 0.1* $CHADS_2$=1–2: 0.7* $CHADS_2$=3–6: 1.2* *Per 100 patient-years	10,019 patient-years, median (IQR)=2.3 (0.8-4.4)	Low
Poli, 2011[109]	662	<u>Classic:</u> $CHADS_2$=0: 0% $CHADS_2$=1–2: 3.9% $CHADS_2$=3–6: 6.2% <u>Revised:</u> $CHADS_2$=0: 0% $CHADS_2$=1: 4.4% $CHADS_2$=2–6: 5.2%	Mean 3.6 years	Low

Table 4. Thromboembolic events by $CHADS_2$ score and concomitant stroke prevention therapy (antiplatelet and/or anticoagulant) use (continued)

Study	No. of Patients	Results (Thromboembolic Event Rates)	Followup Period	Risk of Bias
Patients <u>on</u> therapy				
Ruiz-Nodar, 2011[126]	604	$CHADS_2$ ≤1: 5.4% $CHADS_2$ >1: 4.8%	Mean 642.2 days	Low
Van Staa, 2011[105]	79,844	$CHADS_2$=Low: 1.0* $CHADS_2$=Moderate: 3.7* $CHADS_2$=High: 8.3* *number of cases per 100 patient-years	Mean 4 years	High
Ad, 2010[107]	385	Of the patients that experienced stroke/TIA, the median CHADS2 score was 0.5	Mean 32.77 months	Low
Komatsu, 2010[127]	344	$CHADS_2$=0: 0% $CHADS_2$=1: 0% $CHADS_2$=2: 1.4% $CHADS_2$=3: 4.4% $CHADS_2$=4: 13.5%	Mean 60 months	Low
Lip, 2010[15]	1,084	$CHADS_2$=0: 1.4% $CHADS_2$=1–2: 2.4% $CHADS_2$=3–6: 3.2%	1 year	Low
Sadanaga, 2010[106]	245	$CHADS_2$=0: 0% $CHADS_2$=1: 0.6% $CHADS_2$=2: 0.8% $CHADS_2$=3: 3.6% $CHADS_2$=4: 5.9% $CHADS_2$=5-6: 8.3%	Average 756 days	Low

Table 4. Thromboembolic events by $CHADS_2$ score and concomitant stroke prevention therapy (antiplatelet and/or anticoagulant) use (continued)

Study	No. of Patients	Results (Thromboembolic Event Rates)	Followup Period	Risk of Bias
Patients <u>on</u> therapy				
Connolly, 2009[27]	18,113	<u>Total Population</u> $CHADS_2$=0–1: 0.93* $CHADS_2$=2: 1.22* $CHADS_2$=3–6: 2.44* *% per year <u>Dabigatran 110 mg</u> $CHADS_2$=0–1: 1.06* $CHADS_2$=2: 1.43* $CHADS_2$=3–6: 2.12* <u>Dabigatran 150 mg</u> $CHADS_2$=0–1: 0.65* $CHADS_2$=2: 0.84* $CHADS_2$=3–6: 1.88* <u>Warfarin</u> $CHADS_2$=0–1: 1.05* $CHADS_2$=2: 1.38* $CHADS_2$=3–6: 2.68* *% per year	2 years	Low
Crandall, 2009[112]	343	$CHADS_2$=0: NR* $CHADS_2$=1: 1.29* $CHADS_2$=2: 1.54* $CHADS_2$=3: 2.07* $CHADS_2$=4: 2.41* $CHADS_2$=5: 2.68* $CHADS_2$=6: NR* *Reported as major cardiac events (stroke, MI, death)	Mean 8.9 years	High

Table 4. Thromboembolic events by $CHADS_2$ score and concomitant stroke prevention therapy (antiplatelet and/or anticoagulant) use (continued)

Study	No. of Patients	Results (Thromboembolic Event Rates)	Followup Period	Risk of Bias
Patients <u>on</u> therapy				
Masaki, 2009[113]	293	<u>Not on Warfarin</u> $CHADS_2$=0: 0% $CHADS_2$=1–2: 7.7% $CHADS_2$=3–4: 21.7% $CHADS_2$=5–6: 100% <u>On Warfarin</u> $CHADS_2$=0: 3.1% $CHADS_2$=1–2: 4.7% $CHADS_2$=3–4: 16.7% $CHADS_2$=5–6: 0%	703 days	Low
Morgan, 2009[115]	5,513	CHADS<2: On warfarin: 46.08* Not on warfarin: 44.5* CHADS≥2: On warfarin: 116.5* Not warfarin: 113.9* *Stroke rate per 1,000 patient-years NR by risk score	1,025 days	High
Poli, 2009[114]	662	$CHADS_2$=0–1: 0* $CHADS_2$=1–2: 0.7* $CHADS_2$=3–6: 3.0* *Per 100 patient-years	Mean 3.1 years, 2,365 patient-years	Low
Fang, 2008[118]	10,932	CHADS 0: 18.8%* CHADS 1-2: 61.2%* CHADS 3-6: 20.1%* *Risk of thromboembolism NR by risk score	Median 6 years	Low

Table 4. Thromboembolic events by $CHADS_2$ score and concomitant stroke prevention therapy (antiplatelet and/or anticoagulant) use (continued)

Study	No. of Patients	Results (Thromboembolic Event Rates)	Followup Period	Risk of Bias
Patients on therapy				
Rietbrock, 2008[116]	51,807	Control:* $CHADS_2$=0: 0.34% $CHADS_2$=1: 1.09% $CHADS_2$=2: 1.62% $CHADS_2$=3: 3.70% $CHADS_2$=4: 6.22% $CHADS_2$=5: 7.52% $CHADS_2$=6: 9.51% AF:* $CHADS_2$=0: 0.83% $CHADS_2$=1: 1.54% $CHADS_2$=2: 2.35% $CHADS_2$=3: 4.29% $CHADS_2$=4: 9.06% $CHADS_2$=5: 11.02% $CHADS_2$=6: 13.40% *Number of cases per 100 person-years	Control: 2.74 years (median) AF: 2.46 years (median)	Low
Ruiz Ortiz, 2008[128]	1,137	$CHADS_2$=0: 2.88* $CHADS_2$=1: 5.8* $CHADS_2$=2: 5.16* $CHADS_2$=3: 14.78* $CHADS_2$≥4: 22.02* *Per 100 patient-years	21 months (484 patient-years)	Low
Baruch, 2007[119]	7,329	$CHADS_2$=0–1: 0%* $CHADS_2$=1–2: 1.0%* $CHADS_2$=3–6: 2.3%* *Per patient-year	11,245 patient-years Mean 1.5 years per patient	Low

Table 4. Thromboembolic events by $CHADS_2$ score and concomitant stroke prevention therapy (antiplatelet and/or anticoagulant) use (continued)

Study	No. of Patients	Results (Thromboembolitic Event Rates)	Followup Period	Risk of Bias
Patients <u>off</u> therapy				
Friberg, 2012 [130]	182,678	<u>Unadjusted:</u> $CHADS_2$=0: 0.9* $CHADS_2$=1: 4.3* $CHADS_2$=2: 6.1* $CHADS_2$=3: 9.9* $CHADS_2$=4: 14.9* $CHADS_2$=5: 16.7* $CHADS_2$=6: 17.2* <u>Adjusted for aspirin:</u> $CHADS_2$=0: 0.9* $CHADS_2$=1: 4.9* $CHADS_2$=2: 6.8* $CHADS_2$=3: 11.1* $CHADS_2$=4: 16.8* $CHADS_2$=5: 18.9* $CHADS_2$=6: 19.4* *Per 100 patient-years	1.5 years	Low
Olesen, 2011[104]	73,538	$CHADS_2$=0: 1.24%* $CHADS_2$=1: 3.56%* $CHADS_2$=2: 5.4%* $CHADS_2$=3: 9.89%* $CHADS_2$=4: 13.7%* $CHADS_2$=5: 12.57%* $CHADS_2$=6: 17.17%* *Event rate for hospital admission and death due to thromboembolism per 100 person-years	10 years	Low

Table 4. Thromboembolic events by $CHADS_2$ score and concomitant stroke prevention therapy (antiplatelet and/or anticoagulant) use (continued)

Study	No. of Patients	Results (Thromboembolitic Event Rates)	Followup Period	Risk of Bias
Gage, 2001[13]	1,733	Unadjusted: $CHADS_2$=0: 1.2* $CHADS_2$=1: 2.8* $CHADS_2$=2: 3.6* $CHADS_2$=3: 6.4* $CHADS_2$=4: 8.0* $CHADS_2$=5: 7.7* $CHADS_2$=6: 44* Adjusted: $CHADS_2$=0: 1.9* $CHADS_2$=1: 2.8* $CHADS_2$=2: 4.0* $CHADS_2$=3: 5.9* $CHADS_2$=4: 8.5* $CHADS_2$=5: 12.5* $CHADS_2$=6: 18.5* *Per 100 patient-years	1733 patients were followed up for a mean (median) of 1.2 (1.0) years	Low
Patients on and off therapy				
Olesen, 2012[136]	6,438	Age <65 ($CHADS_2$=0): 0.23* Age 65–74 ($CHADS_2$=0): 2.05* Age ≥75 ($CHADS_2$=0): 3.99* *Per 100 person-years	Maximum 11 years.	High
Olesen, 2011[102]	132,372	No treatment:* $CHADS_2$=0: 1.6% $CHADS_2$=1: 4.0% $CHADS_2$=2–6: 8.4% Treatment (antiplatelet or anticoagulation):* $CHADS_2$=0: 1.4% $CHADS_2$=1: 2.8% $CHADS_2$=2–6: 6.0% *percentage of thromboembolic events per patient year	Maximum 12 years	High

Table 4. Thromboembolic events by $CHADS_2$ score and concomitant stroke prevention therapy (antiplatelet and/or anticoagulant) use (continued)

Study	No. of Patients	Results (Thromboembolitic Event Rates)	Followup Period	Risk of Bias
Ruiz Ortiz, 2010[110]	796	On OAC:* $CHADS_2$=0: 1.0 $CHADS_2$=1: 0.6 $CHADS_2$=2: 0.5 $CHADS_2$=3: 2.4 $CHADS_2$≥ 4: 2.9 No OAC:* $CHADS_2$=0: 4.1 $CHADS_2$=1: 7.1 $CHADS_2$=2: 5.1 $CHADS_2$=3: 12.5 $CHADS_2$≥4: 20.0 *events per 100 patient-years	Mean 2.4 years	Low

Abbreviations: AF=atrial fibrillation; $CHADS_2$=Congestive heart failure, Hypertension, Age ≥75, Diabetes mellitus, prior Stroke/transient ischemic attack (2 points); MI=myocardial infarction; No.=number; NR=not reported; OAC=oral anticoagulation

CHA_2DS_2-VASc Risk Tool

Ten studies directly examined CHA_2DS_2-VASc risk score and its predictive ability for thromboembolic events (Table 5).[15,102,104,105,109,129,130,132,134,135] One study examined the predictive value in elderly patients (mean age 74 years).[109] Five 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).[15,102,104,105,109] Five studies reported stroke outcomes by individual CHA_2DS_2-VASc score,[15,104,132,134,135] while one reported stroke outcomes by CHA_2DS_2-VASc score from 0 to 4 points.[129] Six studies examined stroke risk among patients not treated with oral anticoagulant therapy.[15,102,104,129,130,132]

Table 5. Thromboembolic events by CHA_2DS_2-VASc score and concomitant stroke prevention therapy (antiplatelet and/or anticoagulant) use

Study	No. of Patients	Results (Thromboembolic Event Rates)	Followup Period	Risk of Bias
Patients <u>on</u> therapy				
Olesen, 2012[132]	87,202	<u>1 year:</u> CHA_2DS_2-VASc=0: 1.59* <u>12 years:</u> CHA_2DS_2-VASc=0: 1.28* *Per 100 person-years	Maximum 12 years	Low
Olesen, 2012[129]	47,576	CHA_2DS_2-VASc=0: 0.76* CHA_2DS_2-VASc=1: 1.44* CHA_2DS_2-VASc=2: 2.89* CHA_2DS_2-VASc=3: 4.22* CHA_2DS_2-VASc=4: 4.93* *Rate per 100 person-years	12 years	Low
Potpara, 2012[135]	345	CHA_2DS_2-VASc=0: 0* *Per 100 patient-years	Mean 12.1 years; 4,166.5 patient-years	Unclear
Ruiz-Nodar, 2012[134]	590	<u>Continuous:</u> CHA_2DS_2-VASc=2: 3%* CHA_2DS_2-VASc=3: 11%* CHA_2DS_2-VASc=4: 16%* CHA_2DS_2-VASc=5: 20%* CHA_2DS_2-VASc=6: 22%* CHA_2DS_2-VASc=7: 15%* CHA_2DS_2-VASc=8: 40%* CHA_2DS_2-VASc=9: 50%* *Percent of major adverse cardiovascular events	1 year	Low

Table 5. Thromboembolic events by CHA_2DS_2-VASc score and concomitant stroke prevention therapy (antiplatelet and/or anticoagulant) use (continued)

Study	No. of Patients	Results (Thromboembolic Event Rates)	Followup Period	Risk of Bias
Poli, 2011[109]	662	CHA_2DS_2-VASc=0: 0* CHA_2DS_2-VASc=1: 2.8* CHA_2DS_2-VASc ≥2: 5.0* *Percent of patients with event during study	Mean 3.6 years	Low
Van Staa, 2011[105]	79,844	CHA_2DS_2-VASc=0: 0.5* CHA_2DS_2-VASc=1: 1.1* CHA_2DS_2-VASc ≥2: 4.6* *Number of cases per 100 person-years	Mean 4 years	High
Lip, 2010[15]	1,084	<u>Categorical:</u> CHA_2DS_2-VASc=0: 0.0%* CHA_2DS_2-VASc=1: 0.6%* CHA_2DS_2-VASc ≥2: 3.0%* <u>Continuous:</u> CHA_2DS_2-VASc=0: 0.0%* CHA_2DS_2-VASc=1: 0.6%* CHA_2DS_2-VASc=2: 1.6%* CHA_2DS_2-VASc=3: 3.9%* CHA_2DS_2-VASc=4: 1.9%* CHA_2DS_2-VASc=5: 3.2%* CHA_2DS_2-VASc=6: 3.6%* CHA_2DS_2-VASc=7: 8.0%* CHA_2DS_2-VASc=8: 11.1%* CHA_2DS_2-VASc=9: 100.0%* *Percentage of patients with event during study	1 year	Low

Table 5. Thromboembolic events by CHA_2DS_2-VASc score and concomitant stroke prevention therapy (antiplatelet and/or anticoagulant) use (continued)

Study	No. of Patients	Results (Thromboembolic Event Rates)	Followup Period	Risk of Bias
Patients <u>off</u> therapy				
Friberg, 2012[130]	182,678	<u>Unadjusted:</u> CHA_2DS_2-VASc=0: 0.3* CHA_2DS_2-VASc=1: 0.9* CHA_2DS_2-VASc=2: 2.9* CHA_2DS_2-VASc=3: 4.6* CHA_2DS_2-VASc=4: 6.7* CHA_2DS_2-VASc=5: 10.0* CHA_2DS_2-VASc=6: 13.6* CHA_2DS_2-VASc=7: 15.7* CHA_2DS_2-VASc=8: 15.2* CHA_2DS_2-VASc=9: 17.4* <u>Adjusted for aspirin:</u> CHA_2DS_2-VASc=0: 0.3* CHA_2DS_2-VASc=1: 1.0* CHA_2DS_2-VASc=2: 3.3* CHA_2DS_2-VASc=3: 5.3* CHA_2DS_2-VASc=4: 7.8* CHA_2DS_2-VASc=5: 11.7* CHA_2DS_2-VASc=6: 15.9* CHA_2DS_2-VASc=7: 18.4* CHA_2DS_2-VASc=8: 17.9* CHA_2DS_2-VASc=9: 20.3* *Per 100 patient-years	1.5 years	Low
Olesen, 2011[104]	73,538	<u>Categorical:*</u> CHA_2DS_2-VASc=0: 0.66 CHA_2DS_2-VASc=1: 1.45 CHA_2DS_2-VASc ≥2: 5.72 <u>Continuous:*</u> CHA_2DS_2-VASc=0: 0.66 CHA_2DS_2-VASc=1: 1.45 CHA_2DS_2-VASc=2: 2.92 CHA_2DS_2-VASc=3: 4.28 CHA_2DS_2-VASc=4: 6.46 CHA_2DS_2-VASc=5: 9.97 CHA_2DS_2-VASc=6: 12.52 CHA_2DS_2-VASc=7: 13.96 CHA_2DS_2-VASc=8: 14.10 CHA_2DS_2-VASc=9: 15.89 *Rate for hospital admission and death due to thromboembolism per 100 person-years	10 years	Low

Table 5. Thromboembolic events by CHA_2DS_2-VASc score and concomitant stroke prevention therapy (antiplatelet and/or anticoagulant) use (continued)

Study	No. of Patients	Results (Thromboembolic Event Rates)	Followup Period	Risk of Bias
Patients on and off therapy				
Olesen, 2011[102]	132,372	VKA:* CHA_2DS_2-VASc=0: 0.7% CHA_2DS_2-VASc=1: 1.1% CHA_2DS_2-VASc ≥2: 3.1% ASA:* CHA_2DS_2-VASc=0: 1.1% CHA_2DS_2-VASc=1: 1.8% CHA_2DS_2-VASc ≥2: 6.3% No antithrombotic:* CHA_2DS_2-VASc=0: 0.9% CHA_2DS_2-VASc=1: 1.7% CHA_2DS_2-VASc ≥2: 6.3% *Percentage per patient-year	12 years	High

Abbreviation: ASA=aspirin; 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; VKA=vitamin K antagonist

Framingham Risk Tool

Six studies reported the association of Framingham risk and stroke events among patients with AF (Table 6).[15,105,118,119,122,130] All studies reported the individual risk factors associated with Framingham risk. Three studies reported stroke outcomes in patients without oral anticoagulant therapy,[15,122,130] and one study where all patients were on oral anticoagulant therapy.[119]

Table 6. Thromboembolic events by Framingham risk score and concomitant stroke prevention therapy (antiplatelet and/or anticoagulant) use

Study	No. of Patients	Results (Thromboembolic Rates)	Followup Period	Risk of Bias
Patients on therapy				
Van Staa, 2011[105]	79,844	Low: 1.8* Moderate : 4.3* High: 9.5* *Per 100 patient-years	4 years	High
Fang, 2008[118]	10,932	Low: 0.81% (95% CI 0.66% to 0.99%)* Moderate: NR High: 3.9% (95% CI 3.4% to 4.5%)* *Annual thromboembolism rate	Median 6.0 years	Low
Baruch, 2007[119]	7,329	Low: 0.7%* Moderate: 1.4%* High: 2.7%* *Per patient-year	Mean 1.5 years	Low
Patients on and off therapy				
Friberg, 2012[130]	182,678	Low: 1.8* Moderate: 5.9* High: 11.8* *Event rate per 100 years at risk	1.5 years	Low
Lip, 2010[15]	1,084	Not on Anticoagulation at baseline:* Low: 1.2% Moderate: 3.2% High: 4.6% Not on Anticoagulation at baseline and 1 year:* Low: 1.0% Moderate: 1.2% High: 3.5% *Incidence of thromboembolic events	1 year	Low
Use of therapy uncertain (no VKA, but antiplatelet use NR)				
Wang, 2003[122]	705	NR by category	4.3 years	Low

Abbreviations: No.=number; NR=not reported; VKA=vitamin K antagonist

Imaging Risk Tool

Seven studies examined specific anatomical findings on imaging studies and the association with stroke risk in patients with AF (Table 7).[108,111,117,120,123,124,133] One study used MRI and magnetic resonance angiography (MRA) quantification of left atrial appendage (LAA) dimensions.[108] Four studies utilized transesophageal echocardiography to examine imaging

parameters or findings associated with stroke risk in patients with AF,[111,117,123,124] and two used both transesophageal echocardiography and transthoracic echocardiography.[120,133]

In the study examining MRI/MRA characteristics, 144 patients with nonvalvular AF not on warfarin underwent MRI/MRA prior to catheter ablation for AF.[108] 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).

Table 7. Thromboembolic events by echocardiographic criteria and concomitant stroke prevention therapy (antiplatelet and/or anticoagulant) use

Study	No. of Patients	Features Examined	Results	Risk of Bias
Patients on <u>and</u> off therapy				
Tamura, 2012[133]	179	LAA wall velocity	Relative risk 3.86 of recurrent stroke in patients with low TTE-LAWV (<8.7 cm/sec) compared to high TTE-LAWV	Low
Beinart, 2011[108]	144	LAA volume LAA depth LAA neck (short and long axes) Number of LAA lobes	LAA neck dimension (short x long axis): OR 3.59 per cm2 (95% CI 1.93-6.69, p<0.001)	Low
Nair, 2009[111]	226	Presence or absence of LA thrombus on TEE	No difference in stroke rates in patients with LA thrombus vs. those without LA thrombus (7% vs. 4%, p=NS)	Low

Table 7. Thromboembolic events by echocardiographic criteria and concomitant stroke prevention therapy (antiplatelet and/or anticoagulant) use (continued)

Study	No. of Patients	Features Examined	Results	Risk of Bias
Okuyama, 2008[117]	192	LAA spontaneous contrast LAA thrombus LAA peak flow velocity (cm/s) LAA peak flow velocity ≤20cm/s LAA area LAA wall velocity LAA intensity variation LAA intensity variation ≤9.2 dB	Decreased LAA intensity variation (HR 5.24; 95% CI 1.81 to16.4)	Low
Stollberger, 2004[120]	409	TTE: LV fractional shortening Reduced LV systolic function LA diameter Valvular abnormalities TEE: LAA thrombus Spontaneous echo contrast LAA size LAA length LAA width LAA area, mean	None significant in multivariate analysis	Low
Stoddard, 2003[123]	272	LA diameter LVEF LVEF<40% LA SEC Aortic plaque ≥5 mm Mobile PFO ≥grade 2 MV/AV strands Atrial septal aneurysm Mitral stenosis	LA thrombus (OR 7.7, 95% CI 2.7 to 21.6)	Low
Miyazaki, 2001[124]	89	LA dimension LV end-diastolic dimension LV fractional shortening Moderate to severe MR LAA velocity (cm/s) LAA size LA SEC LAA thrombus present	LAA thrombus (chi-square 5.5, p=0.019) LAA dysfunction (chi-square 4.0, p=0.045)	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

Four studies evaluated the predictor role of INR and its association with stroke risk in patients with AF.[115,121,125,131] One study considered the INR value on hospital admission,[121] one

considered the time in therapeutic range (TTR) of INR,[115] and one study considered both TTR and the standard deviation of transformed INR.[125] In 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.[115] 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). A second 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 in a multivariate model (OR 1.9; 95% CI 1.1 to 3.4).[121] 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.[125] 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 final study examined the thromboembolism rate in elderly Japanese patients (≥70 years old) with AF across INR values.[131] 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.

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 no 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 clinical 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 discrimination of the risk prediction tools in the selected population making cross study comparisons difficult.

A total of 10 studies directly investigated 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.[105,119,130] These studies showed similar performance of all three scores in the same population, with similar c-statistics ranging from 0.56-0.67. Three studies used the same population to assess the risk discrimination of $CHADS_2$ and CHA_2DS_2-VASc,[104,109,129] with c-statistics ranging from 0.60–0.89 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.[15,118,122] Only one study compared CHADS2-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.[130] These findings suggest that all three of these risk scores perform similarly when used in the same populations.

Table 8 provides a summary of available c-statistics for discrimination 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 0.52–0.82, the Framingham scores ranging from 0.62–0.69, and the CHA_2DS_2-VASc ranging from 0.52–0.89.

Table 8. C-statistics from studies comparing stroke risk scores of interest

Study	$CHADS_2$	Framingham	CHA_2DS_2-VASc
Friberg, 2012[130]	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)
Olesen, 2012[129]	Categorical: 0.63 (95% CI 0.62 to 0.65)	-	Continuous: 0.66 (95% CI 0.65 to 0.68)
Potpara, 2012[135]	Categorical: 0.58 (95% CI 0.38 to 0.79)	-	Categorical: 0.72 (95% CI 0.61 to 0.84)
Olesen, 2011[104]	*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)
Poli, 2011[109]	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)

Table 8. C-statistics from studies comparing stroke risk scores of interest (continued)

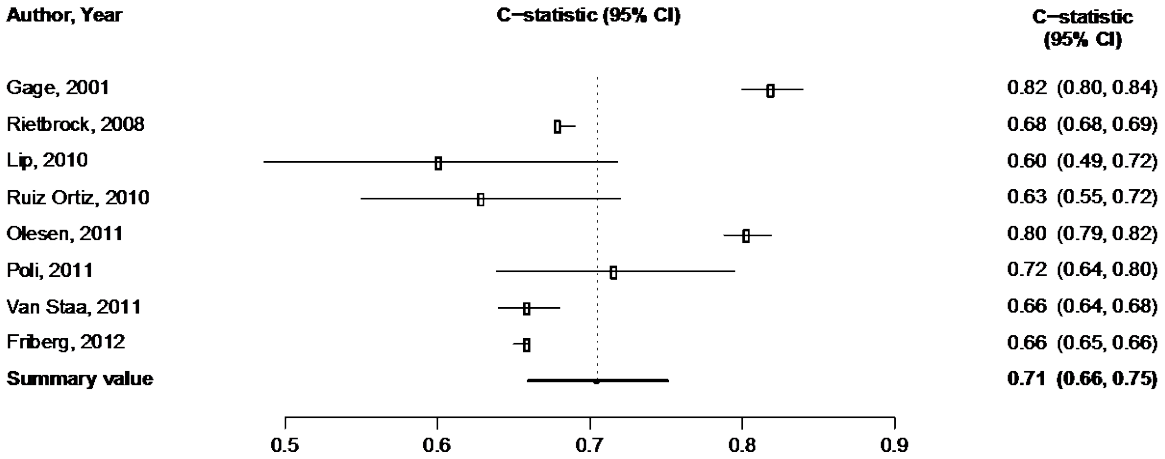
Study	$CHADS_2$	Framingham	CHA_2DS_2-VASc
Van Staa, 2011[105]	Continuous: 0.66 (95% CI 0.64 to 0.68) Categorical: 0.65 (95% CI 0.63 to 0.67)	Continuous: 0.65 (95% CI 0.63 to 0.68) Categorical: 0.62 (95% CI 0.60 to 0.64)	Continuous: 0.67 (95% CI 0.65 to 0.69) Categorical: 0.60 (95% CI 0.59 to 0.61)
Lip, 2010[15]	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)	-
Ruiz Ortiz, 2010[110]	Continuous: 0.63 (95% CI 0.55 to 0.72)	-	-
Poli, 2009[114]	Categorical: All patients: 0.68 On therapy: 0.52	-	-
Fang, 2008[118]	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	-
Rietbrock, 2008[116]	Continuous (Classic): 0.68 (95% CI 0.68 to 0.69) Continuous (Revised): 0.72 (95% CI 0.72 to 0.73)	-	-
Baruch, 2007[119]	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)
Wang, 2003[122]	Categorical: 0.62	Categorical: 0.66 (SD 0.03)	-
Gage, 2001[13]	Continuous: 0.82 (95% CI 0.80 to 0.84)	-	-

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) and categorical score (Figure 4), the Framingham categorical score (Figure 5), and the CHA_2DS_2-VASc continuous score (Figure 6)

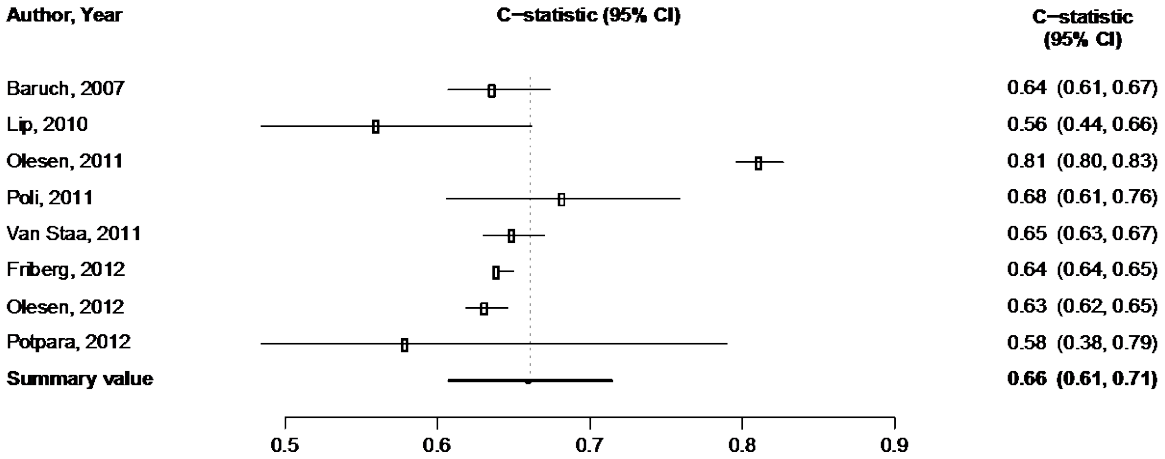
and categorical score (Figure 7). Meta-analysis could not be completed for other risk scores of interest.

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



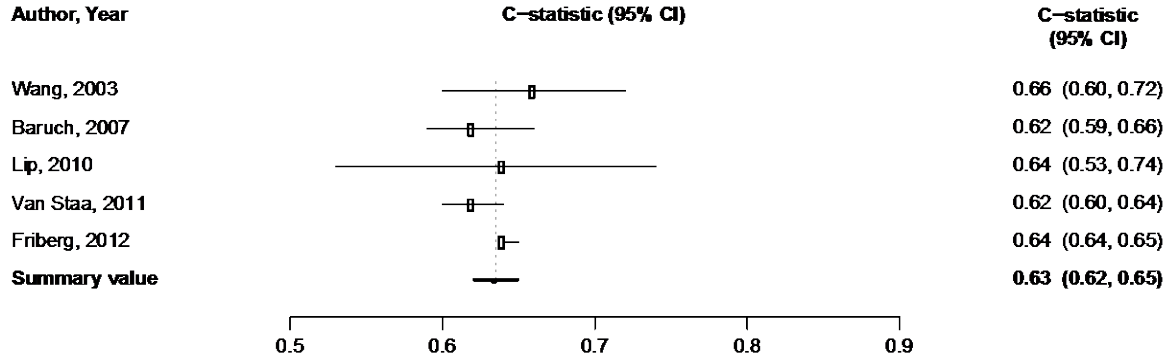
Abbreviations: $CHADS_2$=Congestive heart failure, Hypertension, Age ≥75, Diabetes mellitus, prior Stroke/transient ischemic attack (2 points); CI=confidence interval

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



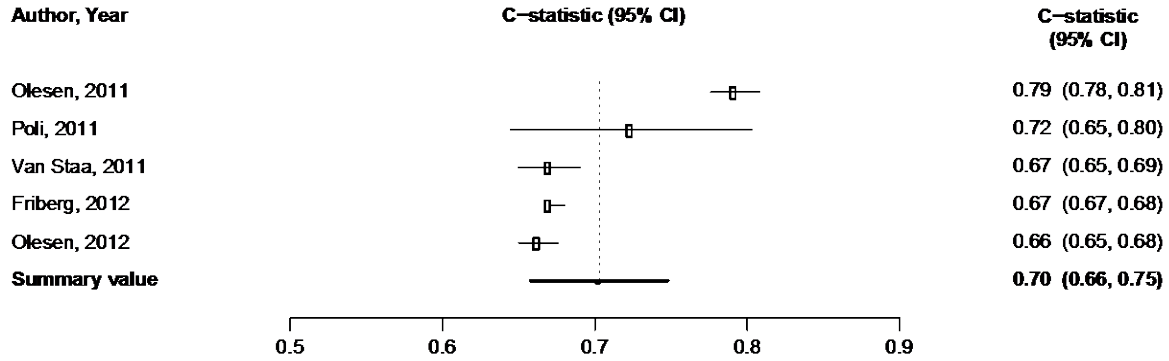
Abbreviations: $CHADS_2$=Congestive heart failure, Hypertension, Age ≥75, Diabetes mellitus, prior Stroke/transient ischemic attack (2 points); CI=confidence interval

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



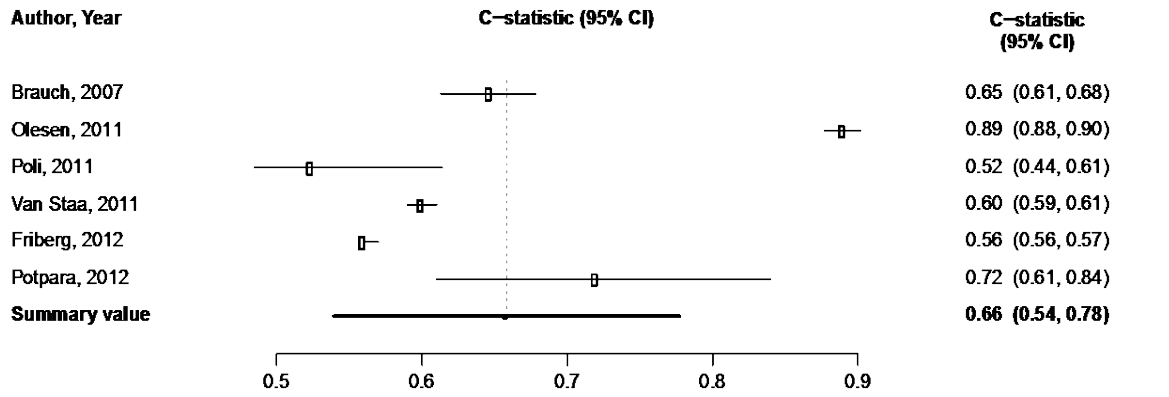
Abbreviation: CI=confidence interval

Figure 6. Summary estimate of c-statistics for discrimination 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 discrimination 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

These analyses demonstrated that the $CHADS_2$ continuous score and the CHA_2DS_2-VASc continuous score have comparable discrimination abilities for stroke risk (0.71 [95% CI 0.66 to 0.75], Q=471.8 [p<0.001], I^2=98.5; and 0.70 [95% CI 0.66 to 0.75], Q=205.4 [p<0.001], I^2=98.1, respectively; both modest risk prediction with low strength of evidence) and greater discrimination ability than other scores. These scores are not, however, statistically significantly different from either the $CHADS_2$ categorical score (0.66 [95% CI 0.61 to 0.71], Q=445.9 [p<0.001], I^2=98.4) or the CHA_2DS_2-VASc categorical score (0.66 [95% CI 0.54 to 0.78], Q=2333.9 [p<0.001], I^2=99.8). They do appear to be better predictors of risk than the Framingham categorical score (0.63 [95% CI 0.62 to 0.65], Q=6.6 [p=0.65], I^2=39.8) given our included studies. Although the 10 studies in Table 8 provide direct comparison evidence, our meta-analysis allows us to combine findings across studies and to synthesize seemingly inconsistent 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. Given the imprecision and inconsistency of the c-statistics in the categorical $CHADS_2$ and the CHA_2DS_2-VASc scores, there was insufficient strength of evidence for their discrimination abilities.

Strength of Evidence

Table 9 summarizes the strength of evidence for the thromboembolic risk discrimination abilities of the included tools. This summary table represents only those studies that evaluated the risk discrimination abilities of the tools using a c-statistic.

Table 9. Strength of evidence domains for discrimination of thromboembolic risk

Outcome	Number of Studies (Subjects)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
$CHADS_2$ (Categorical)	8 (380,669)	Observational/ Moderate	Inconsistent	Direct	Imprecise	**SOE=Insufficient**
$CHADS_2$ (Continuous)	8 (379,755)	Observational/ Moderate	Inconsistent	Direct	Precise	**SOE=Low** Modest risk discrimination ability (c-statistic=0.71; 95% CI 0.66 to 0.75)
CHA_2DS_2-VASc (Categorical)	6 (332,009)	Observational/ Moderate	Inconsistent	Direct	Imprecise	**SOE=Insufficient**
CHA_2DS_2-VASc (Continuous)	5 (371,911)	Observational/ Moderate	Inconsistent	Direct	Precise	**SOE=Low** Modest risk discrimination ability (c-statistic=0.70; 95% CI 0.66 to 0.75)
Framingham (Categorical)	5 (259,253)	Observational/ Moderate	Consistent	Direct	Precise	**SOE=Moderate** Limited risk discrimination ability (c-statistic=0.63; 95% CI 0.62 to 0.65)
Framingham (Continuous)	4 (262,151)	Observational/ Moderate	Consistent	Direct	Imprecise	**SOE=Low** Limited risk discrimination ability (c-statistic ranges between 0.64 and 0.69 across studies)
Imaging	0	NA	NA	NA	NA	**SOE=Insufficient**
INR	0	NA	NA	NA	NA	**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 AF, 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

- Comparison of risk scores between study populations was complicated by multiple factors. First, included studies used different approaches to calculating bleeding risk scores of interest due to unavailable data, such as genetic factors in $HEMORR_2HAGES$

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. Third, although studies consistently reported event rates and c-statistics, measures of calibration, strength of association, and diagnostic accuracy were inconsistently reported.

- Among AF patients on warfarin, 9 studies (6 good quality, 2 fair quality, 1 poor quality; 319,183 patients) compared different risk scores (Bleeding Risk Index [BRI], $HEMORR_2HAGES$, HAS-BLED, and ATRIA) 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. Limited evidence favors HAS-BLED based on two studies demonstrating that it has significantly higher discrimination (by c-statistic) for major bleeding events than other scores among patients on warfarin, but the majority of studies showed no statistically significant differences in discrimination, reducing the strength of evidence. One study showed that HAS-BLED had a significantly higher net reclassification improvement (NRI) than ATRIA for patients on warfarin, while another showed that HAS-BLED had a significantly higher NRI than three other scores in a mixed group of patients on and off warfarin (low strength of evidence).
- Among AF patients on warfarin, 1 study (good quality; 48,599 patients) compared $HEMORR_2HAGES$ and HAS-BLED in predicting intracranial hemorrhage (ICH). This study showed no statistically significant difference in discrimination between the two scores (low strength of evidence).
- Among AF patients on aspirin alone, 3 studies (2 good quality, 1 fair quality; 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 in discrimination (low strength of evidence).
- Among AF patients not on antithrombotic therapy, 6 studies (4 good quality, 2 fair quality; 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 in discrimination (low strength of evidence).

Description of Included Studies

An expert panel recently recommended that, following stroke risk assessment, bleeding risk for all patients with AF be assessed using an available scoring tool.[101] The factors comprising the bleeding risk scores of interest (Table 10), 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.

Seventeen studies described in 18 papers met our inclusion criteria (Appendix Table F-2).[16,102,103,121,125,130,131,134,137-146] Two articles reporting analyses based on the ATRIA study

cohort[121,137] are counted here as one study grouping due to overlapping patient populations; they address different research questions and are represented in separate rows of Appendix Table F-2 and in separate sections under "Detailed Synthesis," below. Apart from a shared focus on outpatient settings, the included studies varied in geographical location, study design, quality, and patient characteristics. Five studies analyzed prospective data (including data from RCTs),[16,103,130,138,143] while 12 analyzed retrospective data (including registries).[102,121,125,131,134,137,139-142,144-146] Ten studies were conducted in Europe,[16,102,103,125,130,134,142,144-146] four in the United States,[121,137,139-141] and one in Asia;[131] one study was multinational,[143] and another did not report geographical location.[138] Eleven studies were multicenter,[16,102,103,121,130,137-140,142,143,146] four were single-site,[131,141,144,145] and study site data were not reported for two studies.[125,134] Eleven studies were conducted primarily in the outpatient setting,[16,121,125,130,131,137-141,144,145] three did not report setting, and[103,134,143] three were conducted in the inpatient setting.[102,142,146] Of the 17 studies, 6 did not report funding source;[102,125,134,142,145,146] 3 used exclusively industry funding;[16,138,143] 2 used exclusively government funding;[139,144] 2 were unfunded;[103,141] 1 used funding exclusively from nongovernment, nonindustry sources;[131] and 3 used funding from multiple sources.[121,130,137,140] Eight studies were of good methodological quality,[16,121,130,137-139,141-143] 6 were of fair quality,[103,131,134,140,144,146] and 3 were of poor quality.[102,125,145]

Studies enrolled patients between 1995 and 2010. The number of patients included in studies ranged from fewer than 600[134] to 170,291,[130] with overlap in patient populations between some studies; altogether, the included studies analyzed data from approximately 250,000 unique patients. The mean age of study participants ranged from 65–80 years. The proportion of male patients ranged from approximately 40–60 percent. None of the studies presented data on ethnicity of subjects, and only one presented data on race (81% white).[141] Study followup duration ranged from 1–12 years. Each of the study populations included patients with paroxysmal, persistent, and permanent AF.

Regarding the outcomes assessed, 17 studies reported evaluated bleeding risk prediction scores with respect to major bleeding.[16,102,103,125,130,131,134,137-146] Two studies evaluated bleeding risk prediction scores with respect to intracranial hemorrhage (ICH) as a separate outcome (ICH was also included in definitions of major bleeding),[121,130] and one study reported these outcomes with respect to minor bleeding.[141] Clinical tools of interest included risk scores and INR indices (INR, time in therapeutic range [TTR], and standard deviation of transformed INR [SDT_{INR}]; Table 10).

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 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,[147] but it is a commonly reported statistic for characterizing a predictive model's discrimination. 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.

Table10. Description and interpretation of included bleeding risk scores

Bleeding Risk Score	Reference	Risk Factors Included	Interpretation
ATRIA	Fang, 2011[137]	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[148]	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[16]	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)
$HEMORR_2HAGES$	Gage, 2006[140]	Liver/renal disease, ethanol abuse, malignancy, age >75, low platelet count or function, re-bleeding 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: ATRIA=Anticoagulation and Risk Factors in Atrial Fibrillation; BRI=Bleeding Risk Index; CrCl=creatinine clearance; GI=gastrointestinal; HAS-BLED=Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (> 65 years), Drugs/alcohol concomitantly; $HEMORR_2HAGES$=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; INR=international normalized ratio; MI=myocardial infarction; TTR=time in therapeutic range

Detailed Synthesis

Major Bleeding

Overview

A total of 16 studies evaluated various risk scores for estimating major bleeding risk in patients with AF, including patients on warfarin, aspirin, and no antithrombotic therapy.[16,102,103,130,131,134,137-146] 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.[149] 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 studied quantitative meta-analysis was not possible for the studied risk scores.

Bleeding Risk Index (BRI)

The Bleeding Risk Index (BRI), also known as the Outpatient Bleeding Risk Index, was evaluated in seven included studies among patients with AF with and without anticoagulation.[103,137-141,146] 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 11). 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 strength of evidence for limited risk discrimination ability (Table 11).[137-140,146] 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,[140] while for patients not on antithrombotic therapy, c-statistics ranged from 0.50–0.65.[138,140,146]

Table 11. Summary of results for studies evaluating BRI among patients on warfarin

Study	Non Warfarin	Followup	Bleeding Event Rates	C-statistic[a]	Risk of Bias
Lip, 2012[146]	3,607	NR	NR	Categorical: 0.56 (95% CI 0.53 to 0.59) Continuous: 0.60 (95% CI 0.56 to 0.63)	Unclear
Fang, 2011[137]	3,063	Median 3.5 years	Low=0.39 events/100 patient-years Moderate=1.31 High=3.96	Categorical: 0.59 (95% CI 0.58 to 0.61) Continuous: 0.68 (95% CI 0.65 to 0.70)	Low
Lip, 2011[138]	3,665	Mean 499 days	Low=2.1% with bleeding event Moderate=3.9% High=4.0%	0.56 (95% CI 0.51 to 0.60)	Low
Poli, 2011[103]	3,302	Median 2.3 years	Low=0.95 events/100 patient-years Moderate=1.26 (BRI=1), 1.22 (BRI=2) High=1.74	NR	Low
Gage, 2006[140]	1,604	Mean 0.82 years	Low=1.1 events/100 patient-years Moderate=4.9 High=8.8	0.65 (SE 0.03)	Low

Table 11. Summary of results for studies evaluating BRI among patients on warfarin (continued)

Study	Non Warfarin	Followup	Bleeding Event Rates	C-statistic[a]	Risk of Bias
Shireman, 2006[139]	26,345	90 days	Low=0% with bleeding event Moderate=1% High=2.5%	0.61	Low
Aspinall, 2005[141]	543 with AF	Mean 1.02 years	Low=0% with bleeding event Moderate=2.3% High=11.1%	NR	Low

[a]C-statistics given are for categorical risk scores unless otherwise noted.
Abbreviations: AF=atrial fibrillation; BRI=Bleeding Risk Index; CI=confidence interval; N=number of participants; NR=not reported; SE=standard error

HEMORR$_2$HAGES

HEMORR$_2$HAGES was evaluated in eight included studies among patients with AF with and without anticoagulation.[16,130,137,138,140,142,143,146] Each of these eight 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[130,137,140,143,146] 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 12). 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 0.53–0.78, demonstrating moderate strength of evidence for limited risk discrimination ability (Table 12).[16,130,137,138,140,142,143,146] Six studies presented c-statistics for HEMORR$_2$HAGES in other populations; for patients on aspirin alone, c-statistics ranged from 0.60–0.83,[16,130,140] while for patients not on antithrombotic therapy, c-statistics ranged from 0.50–0.81.[16,130,138,140,142,146]

Table 12. Summary of results for studies evaluating HEMORR$_2$HAGES among patients on warfarin

Study	N on Warfarin	Followup	Bleeding Event Rates	C-statistic[a]	Risk of Bias
Apostolakis, 2012[143]	4,576	Mean 429 days	Low=1.4% with bleeding event Moderate=2.5% High=7.7% 0=1.0% with bleeding event 1=1.8% 2=2.1% 3=4.7% ≥4=7.6%	0.60 (95% CI 0.51 to 0.69)	Low
Friberg, 2012[130]	48,599	Mean 1.4 years	0=0.6% with bleeding event/yr 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%	0.63 (95% CI 0.61 to 0.64)	Low
Lip, 2012[146]	3,607	NR	NR	Categorical: 0.53 (95% CI 0.50 to 0.57) Continuous: 0.59 (95% CI 0.56 to 0.62)	Unclear
Fang, 2011[137]	3,063	Median 3.5 years	Low=0.72 events/100 patient-years Moderate=2.49 High=3.96	Categorical: 0.67 (95% CI 0.65 to 0.70) Continuous: 0.71 (95% CI 0.69 to 0.73)	Low
Lip, 2011[138]	3,665	Mean 499 days	Low=3.0% with bleeding event Moderate=6.1% High=2.0% (based on only 2.7% of population)	0.61 (95% CI 0.56 to 0.65)	Low
Olesen, 2011[142]	44,771	Mean 10 years	Low=3.06 events/100 patient-years Moderate=6.33 High=12.16	Categorical: 0.78 (95% CI 0.75 to 0.82) Continuous: 0.77 (95% CI 0.73 to 0.81)	High
Pisters, 2010[16]	1,706	Mean 1 year	NR	0.64 (95% CI 0.53 to 0.75)	Low
Gage, 2006[140b]	1,604	Mean 0.82 years	0=1.9 events/100 patient-years 1=2.5 2=5.3 3=8.4 4=10.4 ≥5=12.3	0.67 (SE 0.04)	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; N=number of participants; SE=standard error

HAS-BLED

HAS-BLED was evaluated in 10 included studies among patients with AF with and without anticoagulation.[16,130,131,134,138,142-146] Seven 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;[130,144,145] these studies were, in effect, evaluating a modified HAS-BLED. One study also excluded the "drugs" component of the HAS-BLED score.[130] 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 13). 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 0.58–0.80, demonstrating moderate strength of evidence for modest risk discrimination ability (Table 13).[16,130,138,142-146] Five studies presented c-statistics for HAS-BLED in other populations; for patients on aspirin alone, c-statistics ranged from 0.59–0.91,[16,130] while for patients not on antithrombotic therapy, c-statistics ranged from 0.60–0.81.[16,130,138,142,146]

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.[102] 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 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 13.

Table 13. Summary of results for studies evaluating HAS-BLED among patients on warfarin

Study	Non Warfarin	Followup	Bleeding Event Rates	C-statistic[a]	Risk of Bias
Apostolakis, 2012[143]	4,576	Mean 429 days	Low (<3)=1.3% with bleeding event High (≥3)=3.1%	0.65 (95% CI 0.56 to 0.73)	Low
Friberg, 2012[130]	48,599	Mean 1.4 years	0=1.1% with bleeding event 1=0.6% 2=1.8% 3=2.9% 4=3.4% ≥5=7.7%	0.61 (95% CI 0.59 to 0.62)	Low
Gallego, 2012[144]	965	Median 861 days	0=0.0% with bleeding event/year 1=0.7% 2=1.9% 3=2.4% 4=3.4% 5=5.7% 6=15.5% 7=0%	0.70 (95% CI 0.64 to 0.76)	Unclear
Lip, 2012[146]	3,607	NR	0=0.0% with bleeding event/year 1=1.2% 2=2.2% 3=5.9% 4=7.0% ≥5=19.4%	Categorical: 0.58 (95% CI 0.55 to 0.61) Continuous: 0.61 (95% CI 0.58 to 0.65)	Unclear
Naganuma, 2012[131]	845	Median 27 months	NR for patients on warfarin	NR	Low
Roldan, 2012[145]	937	Median 952 days	Low (<3)=2.0% with bleeding event High (≥3)=5.6%	Categorical: 0.68 (95% CI 0.65 to 0.71) Continuous: 0.71 (95% CI 0.68 to 0.74)	Unclear
			0=0.0% with bleeding event/year 1=0.8% 2=1.9% 3=5.7% 4=5.6% ≥5=16.48%		

Table 13. Summary of results for studies evaluating HAS-BLED among patients on warfarin (continued)

Study	Non Warfarin	Followup	Bleeding Event Rates	C-statistic[a]	Risk of Bias
Lip, 2011[138]	3,665	Mean 499 days	Low=0.9% with bleeding event Moderate=3.7% High=6.7% 0=0.9% with bleeding event 1=3.4% 2=4.1% 3=5.8% 4=8.9% 5=9.1% 6=0%	0.66 (95% CI 0.61 to 0.70)	Low
Olesen, 2011[142]	44,771	Mean 10 years	Low=2.66 events/100 patient-years Moderate=5.54 High=8.11	Categorical: 0.80 (95% CI 0.76 to 0.83) Continuous: 0.80 (95% CI 0.76 to 0.83)	High
Pisters, 2010[16b]	1,722	Mean 1 year	0=1.13 events/100 patient-years (includes patients off warfarin) 1=1.02 2=1.88 3=3.74 4=8.70 5=12.50 6=0.0 7-9=no patients	0.69 (95% CI 0.59 to 0.80)	Low

[a]C-statistics given are for categorical risk scores unless otherwise noted.
[b]Derivation study.
Abbreviations: 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; NR=not reported

ATRIA

ATRIA was evaluated in four included studies among patients with AF with and without anticoagulation.[137,143,145,146] 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 14). 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 0.55–0.69, but given the inconsistency and imprecision of the findings, there was insufficient evidence to determine the risk discrimination abilities (Table 14).[137,143,145,146] One study presented c-statistics for ATRIA among patients not on antithrombotic therapy: 0.59 (continuous) and 0.47 (categorical).[146]

Table 14. Summary of results for studies evaluating ATRIA among patients on warfarin

Study	N on Warfarin	Followup	Bleeding Event Rates	C-statistic[a]	Risk of Bias
Apostolakis, 2012[143]	4,576	Mean 429 days	Low=1.5% with bleeding event Moderate=2.9% High=3.9% 0=1.2% with bleeding event 1=1.2% 2=1.9% 3=2.2% 4=2.9% 5=3.6% 6=4.0% ≥7=0.0%	0.61 (95% CI 0.51 to 0.70)	Low
Lip, 2012[146]	3,607	NR	NR	Categorical: 0.55 (95% CI 0.52 to 0.59) Continuous: 0.60 (95% CI 0.56 to 0.63)	Unclear
Roldan, 2012[145]	937	Median 952 days	0=1.1% with bleeding event/year 1=2.0% 2=2.4% 3=1.9% 4=9.1% ≥5=6.5%	Categorical: 0.59 (95% CI 0.55 to 0.62) Continuous: 0.68 (95% CI 0.65 to 0.71)	Unclear
Fang, 2011[137b]	3,063	Median 3.5 years	Low=0.83 events/100 patient-years Moderate=2.41 High=5.32 0=0.48 events/100 patient-years 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	Categorical: 0.69 (95% CI 0.66 to 0.71) Continuous: 0.74 (95% CI 0.72 to 0.76)	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; NR=not reported

INR

One included study evaluated the use of two INR-related statistics, TTR (% time in therapeutic INR range of 2.0–3.0) and SDT_{INR} (standard deviation of transformed INR values), in terms of impact on diagnostic thinking with respect to estimating the likelihood of major bleeding in patients with AF on warfarin.[125] This study presented hazard ratios (HRs) associated with a 1 standard deviation (SD) change in each risk variable. The 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).

Another included study evaluated the relationship between patient-years within an INR range and incidence of major bleeding events among patients with AF on warfarin.[131] This study indicated that major bleeding incidence increased with increasing INR, but the study was not designed to evaluate the predictive accuracy of this risk factor. Major bleeding event rates per patient-year were 1.7 for INR <1.49, 1.8 for INR 1.50–1.99, 1.5 for INR 2.00–2.49, 3.4 for INR 2.50–2.99, and 20.0 for INR >3.00.

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 2 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 $HEMORR_2HAGES$ 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. For these reasons, we 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 discrimination only. Table 15 provides a summary of available c-statistics for the risk scores of interest among AF patients on warfarin. Tables 16 and 17 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 18.

Among patients on warfarin, the four risk scores—BRI, $HEMORR_2HAGES$, HAS-BLED, and ATRIA—were evaluated in studies where direct comparison with one or more of the other three scores was possible (Table 15). 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 two cases; in one study HAS-BLED had a statistically significantly higher c-statistic than BRI,[138] while in another the categorical HAS-BLED had a statistically significantly higher c-statistic than the categorical ATRIA (Table 15).[145] Neither of these two studies was the derivation study for any bleeding risk score. Among patients on aspirin alone or no antithrombotic therapy, no study appeared to show any significant between-score differences in c-statistics (Tables 16 and 17).

Four studies provided data on NRI as a means for comparing bleeding risk scores (Table 18). Within studies, NRI for patients differed significantly between risk scores in only two cases. In one study,[145] HAS-BLED had a statistically significant positive NRI compared with ATRIA among patients on warfarin. In another study,[146] HAS-BLED had a statistically significant positive NRI in separate, two-way comparisons with BRI, $HEMORR_2HAGES$, 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. 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 newer antithrombotic agents, and AF patients off of anticoagulation therapy).

Table 15. C-statistics from studies comparing scores of interest for discrimination of major bleeding risk among patients on warfarin[a]

Study	BRI	HEMORR$_2$HAGES	HAS-BLED	ATRIA
Apostolakis, 2012[143d]	-	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)
Friberg, 2012[130d]	-	0.63 (95% CI 0.61 to 0.64)	0.61 (95% CI 0.59 to 0.62)	-
Lip, 2012[146g]	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)
Roldan, 2012[145h]	-	-	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)
Fang, 2011[137d,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)
Lip, 2011[138d]	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)	-
Olesen, 2011[142d]	-	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[16d,e]	-	0.64 (95% CI 0.53 to 0.75)	0.69 (95% CI 0.59 to 0.80)	-
Gage, 2006[140b,c]	0.65 (SE 0.03)	0.67 (SE 0.04)	-	-

[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: 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, Re-bleeding risk (2 points), Hypertension (uncontrolled), Anemia, Genetic factors, Excessive fall risk, Stroke; SE=standard error

Table 16. C-statistics from studies comparing scores of interest for discrimination of major bleeding risk among patients on aspirin alone[a]

Study	BRI	HEMORR$_2$HAGES	HAS-BLED
Friberg, 2012[130e]	-	0.60 (95% CI 0.59 to 0.61)	0.59 (95% CI 0.58 to 0.60)
Pisters, 2010[16d,e]	-	0.83 (95% CI 0.68 to 0.98)	0.91 (95% CI 0.83 to 1.00)
Gage, 2006[140b,c]	0.69 (SE 0.05)	0.72 (SE 0.05)[b]	-

[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, Re-bleeding risk (2 points), Hypertension (uncontrolled), Anemia, Genetic factors, Excessive fall risk, Stroke; SE=standard error

Table 17. C-statistics from studies comparing scores of interest for discrimination of major bleeding risk among patients off antithrombotic therapy[a]

Study	BRI	HEMORR$_2$HAGES	HAS-BLED	ATRIA
Friberg, 2012[130e]	-	0.69 (95% CI 0.67 to 0.70)	0.66 (95% CI 0.65 to 0.68)	-
Lip, 2012[146f]	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)
Lip, 2011[138d]	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)	-
Olesen, 2011[142d]	-	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[16d,e]	-	0.81 (95% CI 0.00 to 1.00)	0.85 (95% CI 0.00 to 1.00)	-
Gage, 2006[140b,c]	0.65 (SE 0.03)	0.66 (SE 0.04)	-	-

[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, Re-bleeding risk (2 points), Hypertension (uncontrolled), Anemia, Genetic factors, Excessive fall risk, Stroke; SE=standard error

Table 18. 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[143]	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)		
Lip, 2012[146a]	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[145]	HAS-BLED	+13.6% compared with ATRIA (continuous) (p=0.04) +19.6% compared with ATRIA (categorical) (p=0.02)	-	-
Fang, 2011[137b]	ATRIA	+50.5% compared with BRI (p=NR)	+28.9% compared with HEMORR$_2$HAGES (p=NR)	-

[a]Population used to calculate NRI included both patients on warfarin and patients not taking warfarin.
[b]Derivation study for ATRIA.
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, Re-bleeding risk (2 points), Hypertension (uncontrolled), Anemia, Genetic factors, Excessive fall risk, Stroke; NR=not reported; SE=standard error

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

Although the 95% confidence intervals 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 potential benefit of the HAS-BLED score albeit it with low strength of evidence/limited confidence.

Intracranial Hemorrhage

Overview

Most available studies for KQ 2 included ICH within the outcome "major bleeding," but two studies presented this outcome separately. One of these studies evaluated both HAS-BLED and HEMORR$_2$HAGES,[130] and the other evaluated INR.[121]

HEMORR$_2$HAGES

HEMORR$_2$HAGES was evaluated in one included study of patients with AF with and without anticoagulation.[130] 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 one included study of patients with AF with and without anticoagulation.[130] This study compared HAS-BLED with one other risk score of interest, HEMORR$_2$HAGES. Of note, this study 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.

This 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).

INR

A single study conducted among patients with AF presenting with stroke evaluated the incidence of ICH by INR at the time of stroke.[121] 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 discrimination 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 newer 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.[101]

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.[141]

BRI

A single study provided event rate data for incidence of minor bleeding by BRI risk category among patients on warfarin.[141] 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 19 summarizes the strength of evidence for the bleeding risk discrimination abilities of the included tools. This summary table represents only those studies that evaluated the risk discrimination abilities of the tools using a c-statistic.

Table 19. Strength of evidence domains for discrimination of bleeding risk[a]

Outcome	Number of Studies (Subjects)	Domains Pertaining to Strength of Evidence (SOE)				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Summary c-Statistic (Patients on Warfarin)						
BRI	5 (47,684)	Observational/ Moderate	Consistent	Direct	Precise	**SOE=Moderate** Limited risk discrimination ability (c-statistic ranging from 0.56 to 0.65)
$HEMORR_2HAGES$	8 (318,246)	Observational/ Moderate	Consistent	Direct	Imprecise	**SOE=Moderate** Limited risk discrimination ability (c-statistic ranging from 0.53 to 0.78)
HAS-BLED	8 (313,294)	Observational/ Moderate	Consistent	Direct	Imprecise	**SOE=Moderate** Modest risk discrimination ability (c-statistic ranging from 0.58 to 0.80)
ATRIA	4 (15,732)	Observational/ Moderate	Inconsistent	Direct	Imprecise	**SOE=Insufficient**
Comparative Risk Discrimination Abilities						
Major bleeding events among patients with AF on warfarin	9 (319,183)	Observational/ Moderate	Consistent	Direct	Imprecise	**SOE=Low** Favors HAS-BLED
Intracranial hemorrhage among patients with AF on warfarin	1 (48,599)	Observational/ Moderate	NA	Direct	Precise	**SOE=Low** No difference
Major bleeding events among patients with AF on aspirin alone	3 (177,538)	Observational/ Moderate	Inconsistent	Direct	Imprecise	**SOE=Low** No difference
Major bleeding events among patients with AF not on antithrombotic therapy	6 (310,607)	Observational/ Moderate	Consistent	Direct	Imprecise	**SOE=Low** No difference

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

Abbreviations: 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, Re-bleeding 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:

In patients with nonvalvular AF?

In specific subpopulations of patients with nonvalvular AF?

Key Points

- Based on 4 retrospective studies (1 good quality, 2 fair quality, and 1 poor quality) involving 170,642 patients, warfarin reduces the risk of non-fatal and fatal ischemic stroke compared with aspirin (moderate strength of evidence); on the other hand, based on 3 studies (1 good quality, 1 fair quality, and 1 poor quality) involving 99,876 patients, warfarin is associated with increased annual rates of severe bleeding complications compared with aspirin (moderate strength of evidence).
- In patients not eligible for warfarin, the combination of aspirin+clopidogrel is more effective than aspirin alone for preventing any stroke. This conclusion is based on 1 large good quality trial involving 7,554 patients that showed lower rates of stroke for combination therapy, but the strength of evidence was rated as only moderate because a much smaller study (593 patients) did not find any difference. In the large RCT, the combination of aspirin+clopidogrel was associated with higher rates of major bleeding than aspirin alone (high strength of evidence).
- Based on 1 large retrospective, good quality study involving 54,636 patients, warfarin reduces the risk of non-fatal and fatal ischemic stroke compared with clopidogrel monotherapy, with no differences in major bleeding (moderate strength of evidence).
- Based on 1 large, good-quality RCT of 6,706 patients, warfarin is superior to aspirin plus clopidogrel for the prevention of stroke or systemic embolism and reduction in minor bleeding, although this did not result in a difference in all-cause mortality (high strength of evidence for all 3 outcomes). There was moderate strength of evidence that warfarin increases hemorrhagic stroke risk, and that there is no difference between therapies for MI or death from vascular causes. A retrospective, good-quality study of 53,778 patients confirmed the stroke outcome findings.
- Adding clopidogrel to warfarin shows a trend toward a benefit on stroke prevention (low strength of evidence) and is associated with increased risk of non-fatal and fatal bleeding compared with warfarin alone (moderate strength of evidence). These findings are based on 1 good-quality retrospective study involving 52,349 patients
- Triple therapy with warfarin+aspirin+clopidogrel substantially increases the risk of non-fatal and fatal bleeding (moderate strength of evidence) and also shows a trend toward increased ischemic stroke (low strength of evidence) compared with warfarin alone. These findings are based on 1 good-quality retrospective study involving 52,180 patients
- A Factor IIa inhibitor (dabigatran) at a 150 mg dose is superior to warfarin in reducing the incidence of the composite outcome of stroke (including hemorrhagic) or systemic embolism, with no significant difference in the occurrence of major bleeding (high

strength of evidence for both outcomes) or all-cause mortality (moderate strength of evidence). However, dabigatran increases MI risk (moderate strength of evidence). These findings are based on 1 large good-quality RCT involving 12,098 patients from the larger RE-LY trial of 18,113 patients.

- A Factor IIa inhibitor (dabigatran) at a 110 mg dose is noninferior to warfarin for the composite outcome of stroke or systemic embolism and is associated with a reduction in major bleeding when compared with warfarin (high strength of evidence for both outcomes), but there is no difference in all-cause mortality (moderate strength of evidence). Dabigatran increases MI risk, although this finding did not reach statistical significance (low strength of evidence). The rates of ICH are significantly lower with both dabigatran doses (150 mg and 110 mg) compared with warfarin (high strength of evidence). These findings are based on 1 large good-quality RCT involving 12,037 patients from the larger RE-LY trial of 18,113 patients. Of note, the 150 mg dabigatran dose is FDA approved and marketed in the United States; the 110 mg dose is not.
- The Xa inhibitor apixaban is superior to aspirin in reducing the incidence of stroke or systemic embolism, with similar major bleeding risk, in patients who are not suitable for oral anticoagulation (high strength of evidence for both outcomes). These findings are based on 1 good-quality RCT involving 5,599 patients.
- The Xa inhibitor apixaban is superior in reducing the incidence (separately) of (1) stroke or systemic embolism (high strength of evidence), (2) major bleeding (high strength of evidence), and (3) all-cause mortality (moderate strength of evidence) when compared with warfarin. These findings are based on similar findings from 1 good-quality RCT involving 18,201 patients and one small, fair-quality RCT involving 222 Japanese patients.
- The Xa inhibitor rivaroxaban is noninferior to warfarin in preventing stroke or systemic embolism (moderate strength of evidence), with similar rates of major bleeding (moderate strength of evidence) and all-cause mortality (high strength of evidence). These findings are based on 1 large, good-quality RCT involving 14,264 patients and a second good-quality RCT involving 1,280 Japanese patients.
- Percutaneous left atrial appendage (LAA) closure shows trends toward a benefit over warfarin for all strokes and all-cause mortality (low strength of evidence for both outcomes). Although LAA with percutaneous closure results in less frequent major bleeding than warfarin (low strength of evidence), it is also associated with a higher rate of adverse safety events (moderate strength of evidence). These findings are based on 1 good-quality RCT involving 707 patients. LAA occluding devices are currently investigational, pending approval by the FDA.
- Based on a two substudies of the ROCKET-AF and ARISTOTLE trials for rivaroxaban and apixaban respectively, patients with renal impairment benefitted equally for stroke prevention from the new anticoagulant agents compared with warfarin. Results were also similar in a substudy of the AVERROES (Apixaban Versus Acetylsalicylic acid [ASA] to Prevent Strokes in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment) trial comparing apixaban with aspirin and demonstrating equal benefit in stroke prevention for patients with renal impairment (low strength of evidence).
- Patients with different INR control and with prior stroke seem to benefit equally for stroke prevention from the new anticoagulant agents when compared with warfarin or

aspirin (low strength of evidence). This finding is based on four studies of patients at centers with different INR control, and seven studies of patients with prior stroke.

Description of Included Studies

We identified 43 relevant studies (Appendix Table F-3). The majority (28) were multicenter,[14,27,28,102,121,150-172] 14 were single-center,[110,173-185] and in 1 the study site was unclear.[186] A total of 22 RCTs,[27,28,150-152,154-156,158-161,163,166-168,171,172,176,177,180,181] 12 retrospective studies,[102,121,153,162,165,170,174,175,182-184,186] 8 prospective cohorts,[14,110,157,164,173,178,179,185] and 1 case-control study[169] were included in our analyses. Eight studies enrolled only inpatients,[102,155,157,160,161,165,168,181] 17 included only outpatients,[27,28,110,121,152-154,156,167,169,171,175-177,180,185,186] 5 included both inpatients and outpatients,[164,166,170,178,179,182] and 12 studies included patients from unclear settings.[14,150,151,158,159,162,163,172-174,183,184] The number of patients included in studies ranged from 30[180] to 132,372,[102] with a total of 447,175 patients.

In regards to funding, 19 studies were sponsored by industry,[27,28,150-156,158-160,163,166,169,171,172,175,180] 3 by government,[121,167,186] 3 received funding from nongovernment, nonindustry sources,[161,165,168] 5 received funding from multiple sources including government, industry, nongovernment and nonindustry,[162,164,170,174,182]and 13 had either no sponsorship or this information was unclear.[14,102,110,157,173,176-179,181,183-185] Sixteen studies enrolled consecutive patients,[28,110,152,155,160,164,168,173,178-185] and one used a convenience sample.[27] The remaining studies either did not report the enrollment approach, or the approach used was unclear.[14,102,121,150,151,153,154,156-159,161-163,165-167,169-172,174-177,186]

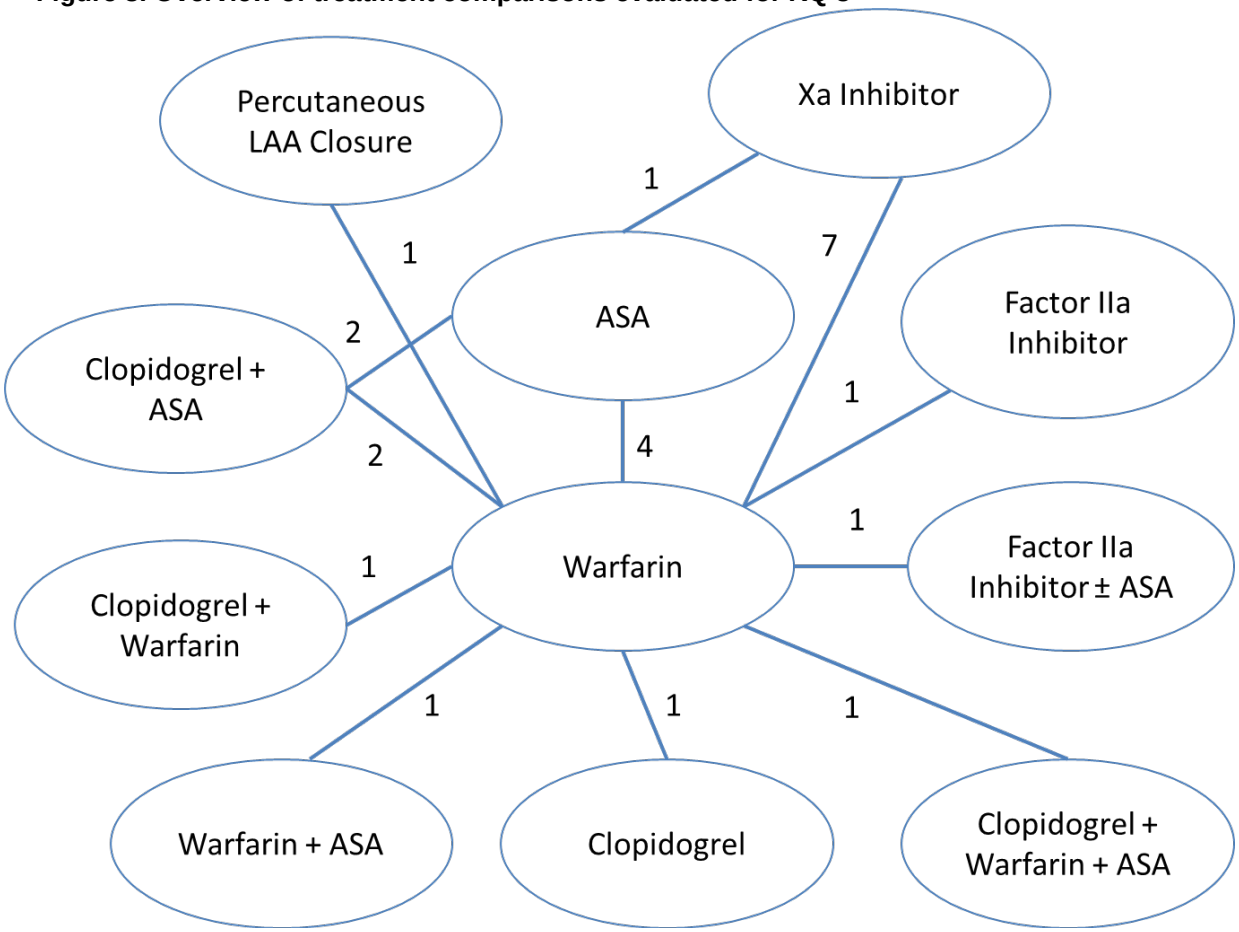
The mean age of included patients varied from 62.6[181] to 77.2[165] years. Only three studies reported the overall mean $CHADS_2$ score, which varied from 2.1[156] to 3.5.[28] Three studies included only patients with persistent AF,[154,162,181] while three studies included only patients with permanent AF.[110,157,176] In two studies, only patients with prior stroke were enrolled.[121,168] Among the studies in which comorbidities were reported these varied widely, 6.6–40 percent of the population had diabetes mellitus, 15.4–90.5 percent had systemic hypertension, 14–62.5 percent had congestive heart failure, 9–67.4 percent had coronary artery disease, and 6.2–17 percent had a history of prior MI.

Among the multicenter studies, three were performed exclusively in the UK,[161,162,169] six in Europe,[102,153,157,164,166,168] five in Asia,[14,151,167,171,172] four in the United States,[121,158,165,170] two in both the United States and Europe,[155,160] and the remaining in multiple continents.[27,28,150,152,154,156,159,163] Among the single-center studies, one was conducted in the United States,[175] one in the UK[176] three in Asia,[173,174,184] and seven in Europe.[110,177-183,185]

Twenty-one studies were considered of good quality,[27,28,121,150,152-156,158-161,163,164,168,170-172,176,179] 15 of fair quality,[110,151,165,166,169,173,174,177,178,180,181,183-186] and 7 were of poor quality.[14,102,157,162,167,175,182]

Figure 8 represents the treatment comparisons evaluated for this KQ.

Figure 8. Overview of treatment comparisons evaluated for KQ 3



Abbreviations: ASA=aspirin; KQ=Key Question; LAA=left atrial appendage. Numbers refer to numbers of comparisons.

As Figure 8 shows, most comparisons were explored in only a limited number of studies, although many of these were good-quality RCTs involving over 5,000 patients. The comparisons of Xa inhibitor versus warfarin and aspirin versus warfarin were the only comparisons for which we identified more than two studies.

We also describe results from 17 substudies[187-203] of the 43 included studies in the relevant subsections under "Detailed Synthesis," below; see Appendix E for details of the relationship between primary publications and substudy reports.

Relationship to Previous Systematic Reviews

Our systematic review builds on two prior meta-analyses by Hart and colleagues.[19,20]. Their 1999 meta-analysis included the classic clinical trials of AFASAK I and II (Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulation Study, I and II), SPAF I, II (Stroke Prevention in Atrial Fibrillation, I and II), EAFT (European Atrial Fibrillation Trial), ESPS II (European Stroke Prevention Study II), and LASAF (Low-Dose Aspirin, Stroke, and Atrial Fibrillation Pilot Study), demonstrating the superiority of warfarin (relative risk reduction of 36%) over aspirin.[20] This meta-analysis included 16 RCTs with a total of 9,874 patients. Adjusted-dose warfarin was reported to reduce the risk of stroke by 62 percent (95% CI 48% to 72%) compared with aspirin, with a reduced stroke risk of 22 percent (95% CI 2% to 38%). Absolute risk reduction was 2.7

percent per year (primary prevention) and 8.4 percent per year (secondary prevention) for adjusted-dose warfarin, and 1.5 percent and 2.5 percent per year, respectively, for aspirin.

From 1999-2007, there were 13 additional RCTs that included 18,140 additional patients with nonvalvular AF. Hart and colleagues reviewed these additional trials in 2007 using long-term (≥12 weeks) use of antithrombotic agents in patients with nonvalvular AF and addressing five outcomes: all stroke (ischemic and hemorrhagic), ischemic stroke, intracranial hemorrhage, all-cause mortality, and major extracranial hemorrhage.[19] Included in the 2007 meta-analysis were the SPORTIF II, III, V (Stroke Prevention using an ORal Thrombin Inhibitor in atrial Fibrillation, II, III, and IV) and ACTIVE-W (Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events-W) trials, focusing on comparisons of adjusted-dose warfarin with a combination of clopidogrel plus aspirin and warfarin therapy compared with all antiplatelet therapies. The superiority of adjusted-dose warfarin was clearly established by consistent results from eight of the RCTs included in the 2007 meta-analysis. All stroke was reduced by 38 percent (95% CI 18% to 51%) in the 3,647 patients included in those 8 trials. These earlier trials included participants typically younger (mean of 70 years of age) than those seen in current clinical practice (typically late 70s and early 80s), leaving a gap in the evidence on the safety and efficacy of adjusted-dose warfarin in the very elderly.

Stroke risk was confirmed to be reduced by approximately 60 percent when using adjusted-dose warfarin, and risk of death reduced by 25 percent when compared with no antithrombotic therapy in patients with nonvalvular AF.[19,20] When compared with antiplatelet agents, adjusted-dose warfarin reduced stroke by approximately 40 percent. The best estimate of stroke reduction by antiplatelet drugs was reported to be approximately 20 percent. No major benefit of adding clopidogrel to aspirin in patients with nonvalvular AF was found.[19] Whether specific antiplatelet agents and their combinations are more or less efficacious in patients with nonvalvular AF was not clear. No evidence favored one dosage of aspirin over another.

Recommendations suggest that choice of antithrombotic agents should be based on each patient's individual stroke and bleeding risks, including factors such as access to anticoagulation monitoring and patient preferences. Low-risk patients did not benefit substantially from warfarin, and the risk stratification scores were noted to reliably identify these patients. Recommendations of adjusted-dose warfarin for high-risk patients with nonvalvular AF were validated, with antiplatelet medications for low-risk patients or for those with contraindications to warfarin.

We now update the findings above with literature through 2012. In this updated review, we are now able to evaluate studies that stratify patients previously classified as low-risk by $CHADS_2$ criteria into further subgroups to tailor anticoagulation recommendations based on more specific criteria. Also, we evaluate newer antithrombotic agents for use in stroke prevention in patients with nonvalvular AF.

Detailed Synthesis

Nineteen 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. An additional 24 unique studies (and 15 substudies of included RCTs) 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.

As described above, for most comparisons we identified only one or two studies per comparison of interest. The data for these comparisons therefore were deemed inappropriate for meta-analysis. Although we identified four studies for the Xa inhibitors versus warfarin comparison, the specific Xa inhibitors and the trials differed substantially, and a quantitative synthesis of these data was also considered inappropriate. We therefore describe results for outcomes of interest qualitatively below.

Aspirin Versus Warfarin

We identified one good-quality retrospective study involving 98,460 patients[153] and one poor-quality retrospective study involving 601 patients[162] that compared aspirin with warfarin. Two additional retrospective studies[169,184] 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,[169] and a fair-quality observational study that compared the efficacy of warfarin, antiplatelet therapy, and no therapy in 815 Taiwanese patients with nonvalvular AF.[184] A fifth retrospective study[186] also evaluated aspirin versus warfarin, but study investigators were not able to distinguish patients who were on a combination of warfarin+aspirin and counted these patients as warfarin only. This final study was therefore excluded from our analysis and not synthesized with the other four.

Ischemic Stroke

In one study,[153] treatment with aspirin was associated with increased risk of non-fatal and fatal ischemic stroke when compared with warfarin (HR 1.83; 95% CI 1.73 to 1.94). Similarly, in the second study,[162] there were increased rates of stroke among patients receiving aspirin compared with warfarin (3.57% per patient-year in the aspirin group vs. 1.64% per patient-year in the warfarin group). The third study[169] showed that warfarin use was associated with a three percent decreased risk of ischemic stroke compared with no use of any antithrombotic therapy. On the other hand, treatment with aspirin was not associated with a decreased risk of ischemic stroke. Finally, the study by Yang and colleagues[184] demonstrated that rates of non-ischemic stroke did not differ between treatment with warfarin, aspirin, and no therapy (2.9% with warfarin vs. 3.7% with aspirin vs. 5.8% with no therapy; p=0.395). There was moderate strength of evidence that warfarin therapy reduced stroke as compared with aspirin.

Bleeding

In one study,[153] the risk of non-fatal and fatal bleeding was lower in the aspirin group (HR 0.93; 95% CI 0.88 to 0.98). Similarly, in the second study,[162] annual rates of severe bleeding complications were higher in the warfarin group (1.90% per patient-year in the aspirin group vs. 2.6% per patient-year in the warfarin group). Overall bleeding rates were also higher in the warfarin group (4.7% per patient-year in the aspirin group vs. 9.0% per patient-year in the warfarin group). A third study[184] reported similar rates of any bleeding with warfarin (0.4% major bleeding), aspirin (0.2% major bleeding), and no therapy (0.7% major bleeding; p=0.196). There was moderate strength of evidence that warfarin increased rates of bleeding compared with aspirin.

All-Cause Mortality

One study[162] reported rates of all-cause mortality and found that they were lower among patients receiving warfarin (7.3% per patient-year in the warfarin group vs. 13.3% per patient-year in the aspirin group). There was insufficient evidence to determine the impact of warfarin and aspirin on all-cause mortality.

Strength of Evidence

Table 20 summarizes the strength of evidence for outcomes of interest for this comparison.

Table 20. Strength of evidence domains for preventing thromboembolic events—aspirin vs. warfarin

Outcome	Number of Studies (Subjects)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Ischemic stroke	4 (170,642)	Observational/ Moderate	Consistent	Direct	Precise	**SOE=Moderate** 4 retrospective studies showing consistent reduction in stroke with warfarin
Bleeding	3 (99,876)	Observational/ Moderate	Consistent	Direct	Precise	**SOE=Moderate** Warfarin associated with increased rates of bleeding
All-cause mortality	1 (601)	Observational/ High	NA	Direct	Imprecise	**SOE=Insufficient**

Abbreviations: ASA=aspirin; CI=confidence interval; NA=not applicable; SOE=strength of evidence

Warfarin+Aspirin Versus Warfarin Alone

One good-quality retrospective cohort study compared warfarin+aspirin (18,345 patients) with warfarin monotherapy (50,919 patients).[153] This study demonstrated increased risks of both stroke and bleeding in the combination arm compared with warfarin monotherapy.

Ischemic Stroke

In this study, the combination of warfarin+aspirin was associated with statistically significant increased risk of non-fatal and fatal ischemic stroke when compared with warfarin monotherapy (HR 1.27; 95% CI 1.14 to 1.40) (moderate strength of evidence).

Bleeding

In this study, the risk of non-fatal and fatal bleeding was almost twice as high among patients on combined warfarin+aspirin therapy as among patients receiving warfarin monotherapy (HR 1.83; 95% CI 1.72 to 1.96) (moderate strength of evidence).

Strength of Evidence

Table 21 summarizes the strength of evidence for outcomes of interest for this comparison.

Table 21. Strength of evidence domains for preventing thromboembolic events—warfarin+aspirin vs. warfarin alone

Outcome	Number of Studies (Subjects)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Ischemic stroke	1 (69,264)	Observational/ Moderate	NA	Direct	Precise	**SOE=Moderate** Increased with warfarin+ASA (HR 1.27 (95% CI 1.14 to 1.40)
Bleeding	1 (69,264)	Observational/ Moderate	NA	Direct	Precise	**SOE=Moderate** Increased with warfarin+ASA (HR 1.83 (95% CI 1.72 to 1.96)

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

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.[156,158] Both reported intention-to-treat (ITT) analyses. Given the size and quality of the larger RCT of 7,554 patients,[156] the findings of the smaller study involving 593 patients[158] are presented here, but our findings and strength of evidence rating are based mainly on the larger RCT.

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).[156] 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).[158] Based on the large study, but reflecting the inconsistent findings, there was moderate strength of evidence 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),[156] 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).[158] Based on the large study, but reflecting the inconsistent findings, there was low strength of evidence that combined therapy lowered the risk of ischemic stroke.

Hemorrhagic Stroke

Rates of hemorrhagic stroke were similar between the groups in both studies (moderate strength of evidence).

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)[156] (moderate strength of evidence).

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 to1.92; p<0.001)[156] (high strength of evidence). The smaller study did not report rates of major bleeding.[158]

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)[156] (high strength of evidence). 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),[156] 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).[158] Based on the larger study, but reflecting the inconsistent and imprecise findings, there was low strength of evidence 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).[156]The small study involving 593 patients found 2% extracranial bleeding in the clopidogrel+aspirin group vs. 1% in the aspirin alone group (p=0.51),[158] Given the consistent findings, there was high strength of evidence that combined therapy increased extracranial bleeding.

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;[156] 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[158]) (moderate strength of evidence).

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;[156] 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[158]), reducing the strength of evidence (low strength of evidence).

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);[156] 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[158]), reducing the strength of evidence (low strength of evidence).

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).[158] Given the small size of the study and the imprecision of the findings, there was insufficient strength of evidence to determine the impact of combined therapy on hospitalization.

Strength of Evidence

Table 22 summarizes the strength of evidence for outcomes of interest for this comparison.

Table 22. Strength of evidence domains for preventing thromboembolic events—clopidogrel+aspirin vs. aspirin alone

Outcome	Number of Studies (Subjects)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Any stroke	2 (8,147)	RCT/Low	Inconsistent	Direct	Precise	**SOE=Moderate** Lower rates with combined therapy (HR 0.72; 95% CI 0.62 to 0.83)
Ischemic stroke	2 (8,147)	RCT/Low	Inconsistent	Direct	Imprecise	**SOE=Low** Lower rates with combined therapy (HR 0.68; 95% CI 0.57 to 0.80)
Hemorrhagic stroke	2 (8,147)	RCT/Low	Consistent	Direct	Imprecise	**SOE=Moderate** Similar between therapies in both studies
Systemic embolism	1 (7,554)	RCT/Low	NA	Direct	Imprecise	**SOE=Moderate** Similar between therapies (HR 0.96; 95% CI 0.66 to 1.40)
Major bleeding	1 (7,554)	RCT/Low	NA	Direct	Precise	**SOE=High** Clopidogrel+ASA associated with higher rates (HR 1.57; 95% CI 1.29 to 1.92)

Table 22. Strength of evidence domains for preventing thromboembolic events—clopidogrel+aspirin vs. aspirin alone (continued)

Outcome	Number of Studies (Subjects)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Minor bleeding	1 (7,554)	RCT/Low	NA	Direct	Precise	**SOE=High** Clopidogrel+ASA associated with higher rates (HR 2.42; 95% CI 2.03 to 2.89)
Intracranial bleeding	2 (8,147)	RCT/Low	Inconsistent	Direct	Imprecise	**SOE=Low** Higher rate with clopidogrel+ASA (HR 1.87; 95% CI 1.19 to 2.94)
Extracranial bleeding	2 (8,147)	RCT/Low	Inconsistent	Direct	Imprecise	**SOE=High** Higher rate with clopidogrel+ASA (HR 1.51; 95% CI 1.21 to 1.88)
All-cause mortality	2 (8,147)	RCT/Low	Consistent	Direct	Imprecise	**SOE=Moderate** No 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 (8,147)	RCT/Low	Inconsistent	Direct	Imprecise	**SOE=Low** No 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)	RCT/Low	Inconsistent	Direct	Imprecise	**SOE=Low** No 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 (593)	RCT/Low	NA	Direct	Imprecise	**SOE=Insufficient**

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

Clopidogrel Versus Warfarin

One good-quality retrospective cohort study compared clopidogrel (3,717 patients) with warfarin (50,919 patients).[153]

Ischemic Stroke

This study demonstrated that treatment with clopidogrel was associated with increased risk of non-fatal and fatal ischemic stroke when compared with warfarin (HR 1.86; 95% CI 1.52 to 2.27) (moderate strength of evidence).

Bleeding

This study found that the risk of non-fatal and fatal bleeding was similar between groups (HR 1.06; 95% CI 0.87 to1.29) (moderate strength of evidence).

Strength of Evidence

Table 23 summarizes the strength of evidence for outcomes of interest for this comparison.

Table 23. Strength of evidence domains for preventing thromboembolic events—clopidogrel vs. warfarin

Outcome	Number of Studies (Subjects)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Ischemic stroke	1 (54,636)	Observational/ Moderate	NA	Direct	Precise	**SOE=Moderate** Increased risk with clopidogrel (HR 1.86; 95% CI 1.52 to 2.27)
Bleeding	1 (54,636)	Observational/ Moderate	NA	Direct	Precise	**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

Clopidogrel+Aspirin Versus Warfarin

Two studies compared clopidogrel+aspirin with warfarin in ITT analyses.[153,163] One study was a good-quality retrospective analysis involving 2,859 patients on clopidogrel+aspirin treatment and 50,919 patients on warfarin monotherapy.[153] 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.[163]

Stroke or Systemic Embolism

In both studies, treatment with clopidogrel+aspirin was associated with increased risk of non-fatal and fatal ischemic stroke when compared with warfarin (HR 1.56; 95% CI 1.17 to 2.10;[153] and HR 1.72; 95% CI 1.24 to 2.37; p=0.001[163]) (high strength of evidence).

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).[163] (moderate strength of evidence).

Major Bleeding

The RCT reported no 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).[163] The other large retrospective study reported that the risk of non-fatal and fatal bleeding was higher in the clopidogrel+aspirin group (HR 1.66; 95% CI 1.34 to 2.04).[153] Given the inconsistent findings, but the similar rates found in the RCT, there was low strength of evidence 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)[163] (high strength of evidence).

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 (p=0.08)[163] (insufficient strength of evidence).

All-Cause Mortality

All-cause mortality was reported by the RCT, and there was no 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)[163] (high strength of evidence).

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)[163] (moderate strength of evidence).

Myocardial Infarction

Within the RCT,[163] MI occurred at rates of less than one percent per year in both groups and was not significantly different between the treatments. Rates of MI were not reported in the other study[153] (moderate strength of evidence).

Strength of Evidence

Table 24 summarizes the strength of evidence for outcomes of interest for this comparison.

Table 24. Strength of evidence domains for preventing thromboembolic events—clopidogrel+aspirin vs. warfarin

Outcome	Number of Studies (Subjects)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Stroke or systemic embolism	2 (60,484)	RCT+ Observational/ Low	Consistent	Direct	Precise	**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 (6,706)	RCT/Low	NA	Direct	Imprecise	**SOE=Moderate** Increased risk with warfarin (HR 0.34 [95% CI 0.12 to 0.93])
Major bleeding	2 (60,484)	RCT+ Observational/ Low	Inconsistent	Direct	Imprecise	**SOE=Low** Similar rates between therapies (HR 1.10; 95% CI 0.83 to 1.45),
Minor bleeding	1 (6,706)	RCT/Low	NA	Direct	Precise	**SOE=High** Increased risk with clopidogrel+ASA (HR 1.23; 95% CI 1.09 to 1.39)
Intracranial bleeding	1 (6,706)	RCT/Low	NA	Direct	Imprecise	**SOE=Insufficient**
All-cause mortality	1 (6,706)	RCT/Low	NA	Direct	Precise	**SOE=High** No difference (HR 1.01; 95% CI 0.81 to 1.26)
Death from vascular causes	1 (6,706)	RCT/Low	NA	Direct	Imprecise	**SOE=Moderate** No difference (HR 1.14; 95% CI 0.88 to 1.48)
Myocardial infarction	1 (6,706)	RCT/Low	NA	Direct	Imprecise	**SOE=Moderate** No 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

Warfarin+Clopidogrel Versus Warfarin Alone

One good-quality retrospective study compared warfarin+clopidogrel (1,430 patients) with warfarin monotherapy (50,919 patients).[153] While the risk of ischemic stroke was similar across the two treatments, the risk of bleeding was greatly increased in patients receiving clopidogrel+warfarin compared with those receiving warfarin monotherapy.

Ischemic Stroke

In the one included study, there was a trend toward benefit of warfarin+clopidogrel for non-fatal and fatal ischemic stroke (HR 0.70; 95% CI 0.35 to 1.40) (low strength of evidence).

Bleeding

The risk of non-fatal 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 strength of evidence).

Strength of Evidence

Table 25 summarizes the strength of evidence for outcomes of interest for this comparison.

Table 25. Strength of evidence domains for preventing thromboembolic events—warfarin+clopidogrel vs. warfarin alone

Outcome	Number of Studies (Subjects)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Ischemic stroke	1 (52,349)	Observational/ Moderate	NA	Direct	Imprecise	**SOE=Low** Trend toward benefit of warfarin+ clopidogrel (HR 0.70; 95% CI 0.35 to 1.40)
Bleeding	1 (52,349)	Observational/ Moderate	NA	Direct	Precise	**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

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).[153]

Ischemic Stroke

The rates of non-fatal 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 strength of evidence).

Bleeding

Triple therapy was associated with a large and statistically significant increased risk of non-fatal and fatal bleeding (HR 3.70; 95% CI 2.89 to 4.76) (moderate strength of evidence).

Strength of Evidence

Table 26 summarizes the strength of evidence for outcomes of interest for this comparison.

Table 26. Strength of evidence domains for preventing thromboembolic events—warfarin alone vs. warfarin+aspirin+clopidogrel

Outcome	Number of Studies (Subjects)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Ischemic stroke	1 (52,180)	Observational/ Moderate	NA	Direct	Imprecise	**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)	Observational/ Moderate	NA	Direct	Precise	**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

Factor IIa Inhibitor (Dabigatran 150 mg and 110 mg) Versus Warfarin

One large, good-quality, noninferiority RCT of 18,113 patients (RE-LY) compared a Factor IIa inhibitor (dabigatran) with warfarin in nonvalvular AF patients in ITT analyses.[27] Patients receiving dabigatran were randomized to one of two doses (110 mg and 150 mg). Patients receiving the 110 mg dose had rates of stroke and systemic embolism that were similar to those associated with warfarin, but lower rates of major hemorrhage. Patients who received 150 mg of dabigatran had lower rates of stroke and systemic embolism than patients in the warfarin group, but similar rates of major hemorrhage.

Stroke or Systemic Embolism

Dabigatran at a 110 mg dose was noninferior 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) (high strength of evidence for no difference). Dabigatran at 150 mg 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 strength of evidence that dabigatran reduced risk).

Ischemic or Uncertain Stroke

The rates of ischemic or uncertain stroke were not different between dabigatran 110 mg and warfarin (1.34% per year for dabigatran 110 mg vs. 1.20% per year for warfarin; RR 1.11; 95% CI 0.89 to 1.40; p=0.35) (moderate strength of evidence). Dabigatran 150 mg was associated with lower rates of ischemic or uncertain stroke when compared with warfarin (0.92% per year for dabigatran 150 mg vs. 1.20% per year for warfarin; RR 0.76; 95% CI 0.60 to0.98; p=0.03) (moderate strength of evidence).

Hemorrhagic Stroke

Both doses of dabigatran were associated with lower rates of hemorrhagic stroke when compared with warfarin (0.12% per year for dabigatran 110 mg 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 150 mg versus 0.38% per

year for warfarin; RR 0.26; 95% CI 0.14 to 0.49; p<0.001) (high strength of evidence that dabigatran reduced risk with both doses).

Major Bleeding

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

Minor Bleeding

Overall, the rates of minor bleeding were higher in the warfarin group compared with both doses of dabigatran (13.16% per year for dabigatran 110 mg 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 150 mg vs. 16.37% per year for warfarin; RR 0.91; 95% CI 0.85 to 0.97; p=0.005) (moderate strength of evidence that dabigatran reduced risk with the 150 mg dose and high strength of evidence that dabigatran reduced risk at the lower 110 mg dose). Gastrointestinal bleeding was more common with higher dose dabigatran than with warfarin.

Intracranial Bleeding

Both doses of dabigatran were associated with lower rates of intracranial bleeding (0.23% per year for dabigatran 110 mg 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 150 mg vs. 0.74% per year for warfarin; RR 0.40; 95% CI 0.27 to 0.60; p<0.001) (high strength of evidence that dabigatran reduced risk with both doses).

A substudy[201] of the RE-LY trial[27] analyzed intracranial hemorrhages occurring during anticoagulation in all three groups (warfarin, dabigatran 110 mg, and dabigatran 150 mg). 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 150 mg, and dabigatran 110 mg, 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 150 mg, and 41% dabigatran 110 mg). Fewer fatal intracranial hemorrhages occurred among those assigned to dabigatran 150 mg and 110 mg (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 150 mg, and dabigatran 110 mg, 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 150 mg (0.09% per year, n=11; RR, 0.26; 95% CI 0.13 to 0.50) and dabigatran 110 mg (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 significant differences between treatment arms. Fatal spontaneous intracerebral bleeding occurred in 19 patients assigned to warfarin versus 7 patients each with dabigatran 150 mg and 110 mg ($p<0.01$ 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 150 mg (RR, 0.65; 95% CI 0.39 to 1.1; P=0.10) and dabigatran 110 mg (RR, 0.27; 95% CI 0.12 to 0.55; $p<0.001$), respectively. The rate of subdural hematomas was significantly higher with dabigatran 150 mg compared with the 110 mg 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 150 mg, and dabigatran 110 mg respectively ($p<0.05$ for dabigatran 110 mg compared with warfarin).

All-Cause Mortality

All-cause mortality did not differ between warfarin and either dose of dabigatran (3.75% per year for dabigatran 110 mg 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 150 mg vs. 4.13% per year for warfarin; RR 0.88; 95% CI 0.77 to 1.00; p=0.051) (moderate strength of evidence of no difference with both doses).

Death From Vascular Causes

Death from vascular causes was lower with the higher dose of dabigatran (moderate strength of evidence) but there was no difference at the lower dose (moderate strength of evidence) (2.43% per year for dabigatran 110 mg 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 150 mg vs. 2.69% per year for warfarin; RR 0.85; 95% CI 0.72 to 0.99; p=0.04).

Myocardial Infarction

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 110 mg 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 150 mg vs. 0.53% per year for warfarin; RR 1.38; 95% CI 1.00 to 1.91; p=0.048) (moderate strength of evidence of increased risk with 150 mg dabigatran and low strength of evidence at the 110 mg dose).

Hospitalization

Hospitalization rates were lower with dabigatran 110 mg (high strength of evidence), and there was no difference between the higher dose and warfarin (19.4% per year for dabigatran 110 mg 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 150 mg vs. 20.8% per year for warfarin; RR 0.97; 95% CI 0.92 to 1.03; p=0.34) (high strength of evidence).

Adverse Events

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

Strength of Evidence

Table 27 summarizes the strength of evidence for outcomes of interest for these comparisons.

Table 27. Strength of evidence domains for preventing thromboembolic events—Factor IIa inhibitor (dabigatran 150 mg and 110 mg) vs. warfarin

Outcome	Number of Studies (Subjects)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Factor IIa Inhibitor (Dabigatran 150 mg) vs. Warfarin						
Stroke or systemic embolism	1 (12,098)	RCT/Low	NA	Direct	Precise	**SOE=High** Dabigatran reduced risk (RR 0.66; 95% CI 0.53 to 0.82)
Ischemic or uncertain stroke	1 (12,098)	RCT/Low	NA	Direct	Imprecise	**SOE=Moderate** Dabigatran reduced risk (RR 0.76; 95% CI 0.60 to 0.98)
Hemorrhagic stroke	1 (12,098)	RCT/Low	NA	Direct	Precise	**SOE=High** Dabigatran reduced risk (RR 0.26; 95% CI 0.14 to 0.49)
Major bleeding	1 (12,098)	RCT/Low	NA	Direct	Precise	**SOE=High** No difference (RR 0.93; 95% CI 0.81 to 1.07)
Minor bleeding	1 (12,098)	RCT/Low	NA	Direct	Imprecise	**SOE=Moderate** Dabigatran reduced risk (RR 0.91; 95% CI 0.85 to 0.97)
Intracranial bleeding	1 (12,098)	RCT/Low	NA	Direct	Precise	**SOE=High** Dabigatran reduced risk (RR 0.40; 95% CI 0.27 to 0.60)
All-cause mortality	1 (12,098)	RCT/Low	NA	Direct	Imprecise	**SOE=Moderate** No difference (RR 0.88; 95% CI 0.77 to 1.00)
Death from vascular causes	1 (12,098)	RCT/Low	NA	Direct	Imprecise	**SOE=Moderate** Dabigatran reduced risk (RR 0.85; 95% CI 0.72 to 0.99)
Myocardial infarction	1 (12,098)	RCT/Low	NA	Direct	Imprecise	**SOE=Moderate** Dabigatran increased risk (RR 1.38; 95% CI 1.00 to 1.91)

Table 27. Strength of evidence domains for preventing thromboembolic events—Factor IIa inhibitor (dabigatran 150 mg and 110 mg) vs. warfarin (continued)

Outcome	Number of Subjects	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Factor IIa Inhibitor (Dabigatran 150 mg) vs. Warfarin						
Hospitalization	1 (12,098)	RCT/Low	NA	Direct	Precise	**SOE=High** No difference (RR 0.97; 95% CI 0.92 to 1.03)
Adverse events	1 (12,098)	RCT/Low	NA	Direct	Imprecise	**SOE=Moderate** Dyspepsia more common with dabigatran (11.3% of patients with dabigatran 150 mg vs. 5.8% with warfarin, p<0.001). No differences in liver function or other adverse events between therapies.
Factor IIa Inhibitor (Dabigatran 110 mg) vs. Warfarin						
Stroke or systemic embolism	1 (12,037)	RCT/Low	NA	Direct	Precise	**SOE=High** No difference (RR 0.91; 95% CI 0.74 to 1.11)
Ischemic or uncertain stroke	1 (12,037)	RCT/Low	NA	Direct	Imprecise	**SOE=Moderate** No difference (RR 1.11; 95% CI 0.89 to 1.40)
Hemorrhagic stroke	1 (12,037)	RCT/Low	NA	Direct	Precise	**SOE=High** Dabigatran reduced risk (RR 0.31; 95% CI 0.17 to 0.56)
Major bleeding	1 (12,037)	RCT/Low	NA	Direct	Precise	**SOE=High** Dabigatran reduced risk (RR 0.80; 95% CI 0.69 to 0.93)
Minor bleeding	1 (12,037)	RCT/Low	NA	Direct	Precise	**SOE=High** Dabigatran reduced risk (RR 0.79; 95% CI 0.74 to 0.84)
Intracranial bleeding	1 (12,037)	RCT/Low	NA	Direct	Precise	**SOE=High** Dabigatran reduced risk (RR 0.31; 95% CI 0.20 to 0.47)
All-cause mortality	1 (12,037)	RCT/Low	NA	Direct	Imprecise	**SOE=Moderate** No difference (RR 0.91; 95% CI 0.80 to 1.03)

Table 27. Strength of evidence domains for preventing thromboembolic events—Factor IIa inhibitor (dabigatran 150 mg and 110 mg) vs. warfarin (continued)

Outcome	Number of Subjects	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Factor IIa Inhibitor (Dabigatran 110 mg) vs. Warfarin						
Death from vascular causes	1 (12,037)	RCT/Low	NA	Direct	Imprecise	**SOE=Moderate** No difference (RR 0.90; 95% CI 0.77 to 1.06)
Myocardial infarction	1 (12,037)	RCT/Low	NA	Direct	Imprecise	**SOE=Low** Dabigatran increased risk, although the difference did not reach statistical significance (RR 1.35; 95% CI 0.98 to 1.87)
Hospitalization	1 (12,037)	RCT/Low	NA	Direct	Precise	**SOE=High** Dabigatran reduced risk (RR 0.92; 95% CI 0.87 to 0.97)
Adverse events	1 (12,037)	RCT/Low	NA	Direct	Imprecise	**SOE=Moderate** Dyspepsia more common with dabigatran (11.8% of patients with dabigatran 110 mg vs. 5.8% with warfarin, p<0.001). No differences in liver function or other adverse events between therapies.

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

Factor IIa Inhibitor (Dabigatran) ± Aspirin Versus Warfarin

One good-quality RCT (PETRO) involving 502 patients evaluated different doses of the Factor IIa inhibitor dabigatran with and without concomitant aspirin at different doses and compared with warfarin alone.[160]

Thromboembolic Events

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

Major Bleeding

Major hemorrhages were limited to the group treated with 300 mg dabigatran twice daily+aspirin (4 of 64), and the rate was statistically different compared with the group treated with dabigatran 300 mg twice daily without aspirin (0 of 105; $p<0.02$). There was 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 versus 14 of 105; p=0.0003) between 300 mg dabigatran twice daily+aspirin and 300 mg dabigatran twice daily without aspirin. The frequency of bleeding in the group treated with 50 mg 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 300 mg twice daily and 150 mg twice daily groups versus the 50 mg 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 300 mg (23%) and 150 mg (18%) dabigatran groups compared with the 50 mg groups (7%).

Myocardial Infarction

Seven patients reported angina, of which two were classified as having acute coronary syndrome, one treated with 50 mg dabigatran twice daily+81 mg aspirin and the other treated with 300 mg dabigatran twice daily+81 mg 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.

Xa Inhibitors (Apixaban and Rivaroxaban) Versus Warfarin

Seven studies compared various factor Xa inhibitors with warfarin. One good-quality RCT (ARISTOTLE) involving 18,201 patients compared apixaban with warfarin;[150] one good-quality RCT involving 1,146 patients compared edoxaban with warfarin;[154] another good-quality RCT including 536 Japanese patients[172] compared different edoxaban doses with warfarin; one good-quality RCT (ROCKET-AF) involving 14,264 patients compared rivaroxaban (20 mg once daily) with warfarin;[28] another good-quality RCT (J-ROCKET AF) involving 1,280 Japanese patients compared a lower dose of rivaroxaban (15 mg once daily) with warfarin;[171] one good-quality RCT (AMADEUS) involving 4,576 patients compared idraparinux with warfarin;[159] and one fair-quality RCT (ARISTOTLE-J) compared apixaban (either 2.5 mg twice daily or 5.0 mg twice daily) with warfarin in 222 Japanese patients.[151].

Although each of these RCTs compared a novel Xa inhibitor with warfarin, they differed in significant ways, making a quantitative synthesis of the findings inappropriate. Specifically, the ROCKET AF and ARISTOTLE studies were both Phase III trials of oral anticoagulants. The study by Wietz and colleagues,[154] however, was a Phase II trial. The corresponding Phase III study (ENGAGE-AF) will be completed in early 2013,[204] and at that time a synthesis of its findings with the ROCKET AF and ARISTOTLE studies would be appropriate. Also, in the AMADAEUS trial, treatment was given subcutaneously and once a week, having a very different pharmacokinetics and pharmacodynamics profile from the oral anticoagulants. 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. We therefore do not combine the data from these four trials through meta-analysis, but instead describe their impact on the outcomes of interest qualitatively below.

Stroke or Systemic Embolism

Five studies explored the impact of Xa inhibitors versus warfarin on stroke or systemic embolism. In one study,[150] 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 to0.95; p=0.01). In a second study, [28] 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). Similar to the ITT analysis of the ROCKET trial,[28] the ITT results of the J ROCKET-AF trial[171] did not show a significant difference in primary efficacy outcome of stroke or non-CNS systemic embolism between rivaroxaban and warfarin. In the ITT population analysis including 30-day followup, the primary efficacy outcome occurred at a rate of 2.38 percent per year and 2.91 percent per year in patients receiving rivaroxaban and warfarin, respectively (HR 0.82; 95% CI 0.46 to1.45). In the on-treatment analysis of the ITT population, the primary efficacy outcome occurred at a rate of 1.26 percent per year and 2.60 percent per year in patients receiving rivaroxaban and warfarin, respectively (HR 0.48; 95% CI 0.23 to1.00). However, prespecified per-protocol analyses showed a strong trend for a reduction in the rate of stroke/systemic embolism with lower dose of rivaroxaban (15 mg once daily) compared to warfarin in Japanese patients in the primary per-protocol population analysis (HR, 0.49; 95% CI 0.24 to1.00; p=0.050). In the on-treatment analysis, there were no statistically significant differences in the composite of adjudicated stroke, non-CNS systemic embolism, and vascular death (HR 0.65; 95% CI 0.34 to1.22), or of the composite of adjudicated stroke, non-CNS systemic embolism, MI, and vascular death (HR 0.74; 95% CI 0.41 to 1.34). All-cause stroke occurred at a lower rate in patients treated with rivaroxaban than with warfarin (HR 0.46; 95% CI 0.22 to 0.98), as did primary ischemic stroke (HR 0.40; 95% CI 0.17 to 0.96). In the fourth study,[159] 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). Finally, in the ARISTOTLE-J study,[151] there were no strokes or systemic embolisms in either apixaban dose group, but the warfarin group had two ischemic strokes and one subarachnoid hemorrhage in the ITT population.

There was high strength of evidence that apixaban reduced risk of stroke or systemic embolism compared with warfarin. There was moderate strength of evidence that there was no difference in stroke risk between rivaroxaban and warfarin.

Ischemic or Uncertain Stroke

One study[150] 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 strength of evidence). One other study reported this outcome in the on-treatment population for rivaroxaban compared to warfarin;[28] it showed no 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 difference between rivaroxaban and warfarin was rated to have moderate strength of evidence.

Hemorrhagic Stroke

Four studies evaluated rates of hemorrhagic stroke.[28,150,159,171] In one study,[150] 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 second study,[159] hemorrhagic stroke occurred in 0.2 percent of patients in both the idraparinux and warfarin groups. In the ROCKET AF trial,[28] 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). In the J-ROCKET AF study,[171] the occurrence of primary hemorrhagic stroke was similar in both treatment arms in the per-protocol analyses (HR 0.73; 95% CI 0.16 to 3.25). There was high strength of evidence that apixaban reduced risk of hemorrhagic stroke compared with warfarin. Given on-treatment (rather than intention-to-treat) and imprecise findings, there was low strength of evidence of a benefit of rivaroxaban in reducing hemorrhagic stroke.

Any Stroke or TIA

In one study,[154] any stroke or TIA were observed in 0.4, 0.8, 0.4, 1.1, and 1.6 percent of patients in the edoxaban 30 mg daily, 30 mg twice daily, 60 mg daily, 60 mg twice daily, and warfarin treatment groups, respectively.

Systemic Embolism

Four studies specifically reported the impact of therapy on systematic embolism separated out from stroke. In one study,[150] 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 30 mg daily, 30 mg twice daily, 60 mg daily, 60 mg twice daily, and warfarin treatment groups, respectively,[154] and in the other, there was no difference between the groups (0% of patients in the idraparinux group vs. 0.1% in the warfarin group).[159] Among those in the on-treatment population of the ROCKET trial,[28] 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 strength of evidence that there was no difference between apixaban and warfarin arms. There was moderate strength of evidence that rivaroxaban reduced risk.

Major Bleeding

Five studies reported on the impact of Xa inhibitors versus warfarin on the outcome of major bleeding. In one study,[150] 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). In another study, in the safety, as-treated population,[28] there was no 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). The observed rate of major bleeding events in the J-ROCKET AF study[171] in the on-treatment population was 3.00 percent per year in the rivaroxaban arm compared with 3.59 percent per year in the warfarin arm (HR 0.85; 95% CI 0.50 to 1.43), and observed rates also tended to be lower with rivaroxaban for all individual components of the major bleeding outcome, although none of the differences was statistically significant. By contrast, in a fourth study,[154] major bleeding events were observed in 0, 2.0, 0.4, 3.3, and 0.4 percent of patients in the edoxaban 30 mg daily, 30 mg twice daily, 60 mg daily, 60 mg twice daily, and warfarin treatment groups, respectively. Compared with warfarin, the incidence of major bleeding was significantly higher with edoxaban doses of 30 mg twice daily or 60 mg twice daily. With the 30 mg or 60 mg daily edoxaban regimens, the incidence of major bleeding was similar to that in patients randomized to warfarin. Finally, in the fifth study[159] 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.[191] There was high strength of evidence that apixaban reduced risk of major bleeding compared with warfarin, and there was moderate strength of evidence that there was no difference between rivaroxaban and warfarin.

Major, Nonmajor Clinically Relevant, and Minor Bleeding

In one study,[172] the mean incidence of all bleeding events in patients who received at least one dose of the study drug for edoxaban 30, 45, and 60 mg, and warfarin was 18.5, 22.4, 27.7, and 20.0 percent, respectively. There were no statistically significant differences among the edoxaban groups and no significant differences from the warfarin group.

The J-ROCKET AF Study[171] confirmed the noninferiority of rivaroxaban to warfarin in respect to the composite of major bleeding and nonmajor clinically relevant bleeding events in the on-treatment group (18.04% patients per year in the rivaroxaban group compared with 16.42% patients per year in the warfarin group; HR 1.11; 95% CI 0.87 to1.42). Nonmajor

clinically relevant bleeding event rates were 15.42 percent per year in rivaroxaban-treated patients compared with 12.99 percent per year in warfarin-treated patients (HR 1.20; 95% CI 0.92 to1.56), and this difference was also not statistically significant.

Intracranial Bleeding

Four studies 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;[150] rivaroxaban: HR 0.67; 95% CI 0.47 to 0.93; p=0.02[28]). In the J-ROCKET AF study,[171] intracranial hemorrhages were observed in 0.8 percent of patients in the rivaroxaban group and in 1.6 percent of patients in the warfarin group. These results were not tested for statistical significance. In the fourth study,[159] rates of intracranial bleeding were higher with idraparinux than with warfarin in its ITT population (1.1% vs. 0.4%; HR 2.58; 95% CI 1.18 to 5.64; p=0.014). There was high strength of evidence that apixaban reduced risk of intracranial bleeding compared with warfarin, and moderate strength of evidence that rivaroxaban did the same.

All-Cause Mortality

Four studies reported all-cause mortality. In one,[150] 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 ARISTOTLE-J study[151] there were no deaths in any of the treatment arms. 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,[28] 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). In the fourth study,[159] there was no 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). There was moderate strength of evidence that apixaban reduced risk of all-cause mortality, and high strength of evidence that there was no difference between rivaroxaban and warfarin for this outcome.

Death From Cardiovascular Causes

Three studies assessed death from cardiovascular causes.[28,150,154] All 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;[150] and death from cardiovascular causes occurring in 0.9, 1.6, 0, 0, and 0.8 percent of patients in the edoxaban 30 mg daily, 30 mg twice daily, 60 mg daily, 60 mg twice daily, and warfarin treatment groups, respectively[154]). 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). There was high strength of evidence of no difference between treatment arms for apixaban and edoxaban, and moderate strength of evidence for of no difference between treatment arms for rivaroxaban based on the on-treatment findings.

Myocardial Infarction

Four studies reported rates of MI across therapies. There were no significant differences across treatment groups in any of the four studies. Specifically, in one study,[150] 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,[154] MI occurred in 0.9, 0.4, 0.9, 0, and 0 percent of patients in the edoxaban 30 mg daily, 30 mg twice daily, 60 mg daily, 60 mg twice daily, and warfarin treatment groups, respectively. In the third study,[28] 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). And similarly, in the fourth study,[159] the rates of MI were similar between groups (0.8% for idraparinux vs. 0.6% for warfarin). There was moderate strength of evidence that there was no difference between apixaban or rivaroxaban and warfarin in rates of MI.

Hospitalization

One study[154] 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 30 mg daily, 30 mg twice daily, 60 mg daily, 60 mg twice daily, and warfarin treatment groups, respectively**.**

Adverse Events

Studies evaluating apixaban, edoxaban, and rivaroxaban specifically looked at adverse events.[150,154,171] In one,[150] 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,[154] there were 11.1, 13.5, 11.5, 22.2, and 18.4 percent drug-related treatment-emergent adverse events in the edoxaban 30 mg daily, 30 mg twice daily, 60 mg daily, 60 mg 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 differences in the incidence of abnormal hepatic function tests across treatment groups. In the J-ROCKET AF Study,[171] elevations of hepatic enzyme activity and total bilirubin during the study were similar in the rivaroxaban and warfarin treatment groups, and there was no indication of severe liver damage. There was moderate strength of evidence that there was no difference between apixaban and warfarin for adverse events.

Strength of Evidence

Table 28 summarizes the strength of evidence for outcomes of interest for these comparisons.

Table 28. Strength of evidence domains for preventing thromboembolic events—Xa inhibitors (apixaban and rivaroxaban) vs. warfarin

Outcome	Number of Studies (Subjects)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Xa Inhibitor (Apixaban) vs. Warfarin						
Stroke or systemic embolism	2 (18,423)	RCT/Low	Consistent	Direct	Precise	**SOE=High** Apixaban reduced risk (HR 0.79; 95% CI 0.66 to 0.95)
Ischemic stroke	1 (18,201)	RCT/Low	NA	Direct	Precise	**SOE=High** No difference (HR 0.92; 95% CI 0.74 to 1.13)
Hemorrhagic stroke	1 (18,201)	RCT/Low	NA	Direct	Precise	**SOE=High** Apixaban reduced risk (HR 0.51; 95% CI 0.35 to 0.75)
Systemic embolism	2 (18,423)	RCT/Low	Consistent	Direct	Imprecise	**SOE=Moderate** No difference (HR 0.87; 95% CI 0.44 to 1.75)
Major bleeding	2 (18,423)	RCT/Low	Consistent	Direct	Precise	**SOE=High** Apixaban reduced risk (HR 0.69; 95% CI 0.60 to 0.80)
Intracranial bleeding	1 (18,201)	RCT/Low	NA	Direct	Precise	**SOE=High** Apixaban reduced risk (HR 0.42; 95% CI 0.30 to 0.58)
All-cause mortality	2 (18,423)	RCT/Low	Consistent	Direct	Precise	**SOE=Moderate** Apixaban reduced risk (HR 0.89; 95% CI 0.80 to 0.998)
Death from cardiovascular causes	1 (18,201)	RCT/Low	NA	Direct	Precise	**SOE=High** No difference (HR 0.89; 95% CI 0.76 to 1.04)
Myocardial infarction	1 (18,201)	RCT/Low	NA	Direct	Imprecise	**SOE=Moderate** No difference (HR 0.88; 95% CI 0.66 to 1.17)
Adverse events	2 (18,423)	RCT/Low	Consistent	Direct	Imprecise	**SOE=Moderate** Adverse events occurred in almost equal proportions of patients in the apixaban and the warfarin therapy arms

Table 28. Strength of evidence domains for preventing thromboembolic events—Xa inhibitors (apixaban and rivaroxaban) vs. warfarin (continued)

Outcome	Number of Subject (Subjects)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Xa Inhibitor (Rivaroxaban) vs. Warfarin						
Stroke or systemic embolism	2 (15,544)	RCT/Low	Inconsistent	Direct	Precise	**SOE=Moderate** No difference (HR 0.88; 95% CI 0.74 to 1.03)
Ischemic stroke	1 (14,264)	RCT/Low	NA	Direct	Precise	**SOE=Moderate** No difference in on-treatment analyses (HR 0.94; 95% CI 0.75 to 1.17)
Hemorrhagic stroke	2 (15,544)	RCT/Low	Inconsistent	Direct	Imprecise	**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 (14,264)	RCT/Low	NA	Direct	Precise	**SOE=Moderate** Rivaroxaban reduced risk in on-treatment analyses (HR 0.23; 95% CI 0.09 to 0.61)
Major bleeding	2 (15,544)	RCT/Low	Consistent	Direct	Precise	**SOE=Moderate** No difference in 2 studies in on-treatment analyses (HR 1.04 [95% CI 0.90 to 1.20] in one study; HR 0.85 [95% CI 0.50 to 1.43] in other study)
Intracranial bleeding	2 (15,544)	RCT/Low	Consistent	Direct	Precise	**SOE=Moderate** Rivaroxaban reduced risk in on-treatment analyses (HR 0.67; 95% CI 0.47 to 0.93)

Table 28. Strength of evidence domains for preventing thromboembolic events—Xa inhibitors (apixaban and rivaroxaban) vs. warfarin (continued)

Outcome	Number of Subject (Subjects)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Xa Inhibitor (Rivaroxaban) vs. Warfarin						
All-cause mortality	1 (14,264)	RCT/Low	NA	Direct	Precise	**SOE=High** No difference (HR 0.92; 95% CI 0.82 to 1.03)
Death from cardiovascular causes	1 (14,264)	RCT/Low	NA	Direct	Precise	**SOE=Moderate** No difference in on-treatment analyses (HR 0.89; 95% CI 0.73 to 1.10)
Myocardial infarction	1 (14,264)	RCT/Low	NA	Direct	Precise	**SOE=Moderate** No difference in on-treatment analyses (HR 0.81; 95% CI 0.63 to 1.06)

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

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.[152] 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) (high strength of evidence).

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) (high strength of evidence).

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 strength of evidence).

Major Bleeding

There were no 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) (high strength of evidence).

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 strength of evidence).

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 strength of evidence).

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 strength of evidence).

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 strength of evidence).

Myocardial Infarction

There were no 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 strength of evidence).

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) (high strength of evidence).

Adverse Events

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

Strength of Evidence

Table 29 summarizes the strength of evidence for outcomes of interest for this comparison.

Table 29. Strength of evidence domains for preventing thromboembolic events—Xa inhibitor (apixaban) vs. aspirin

Outcome	Number of Studies (Subjects)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Stroke or systemic embolism	1 (5,599)	RCT/Low	NA	Direct	Precise	**SOE=High** Apixaban reduced risk (HR 0.45; 95% CI 0.32 to 0.62)
Ischemic stroke	1 (5,599)	RCT/Low	NA	Direct	Precise	**SOE=High** Apixaban reduced risk (HR 0.37; 95% CI 0.25 to 0.55)
Hemorrhagic stroke	1 (5,599)	RCT/Low	NA	Direct	Imprecise	**SOE=Moderate** Trend toward a reduction in risk with apixaban (HR 0.67; 95% CI 0.24 to 1.88)
Major bleeding	1 (5,599)	RCT/Low	NA	Direct	Precise	**SOE=High** No difference (HR 1.13; 95% CI 0.74 to 1.75)
Minor bleeding	1 (5,599)	RCT/Low	NA	Direct	Precise	**SOE=Moderate** Apixaban increased risk (HR 1.20; 95% CI 1.00 to 1.53)
Intracranial bleeding	1 (5,599)	RCT/Low	NA	Direct	Imprecise	**SOE=Low** Trend toward a reduction in risk with apixaban (HR 0.85; 95% CI 0.38 to 1.90)
All-cause mortality	1 (5,599)	RCT/Low	NA	Direct	Imprecise	**SOE=Low** Trend toward a reduction in risk with apixaban (HR 0.79; 95% CI 0.62 to 1.02)
Death from vascular causes	1 (5,599)	RCT/Low	NA	Direct	Imprecise	**SOE=Moderate** No difference (HR 0.87; 95% CI 0.66 to 1.17)
Myocardial infarction	1 (5,599)	RCT/Low	NA	Direct	Imprecise	**SOE=Moderate** No difference (HR 0.86; 95% CI 0.50 to 1.48)

Table 29. Strength of evidence domains for preventing thromboembolic events—Xa inhibitor (apixaban) vs. aspirin (continued)

Outcome	Number of Studies (Subjects)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Hospitalization	1 (5,599)	RCT/Low	NA	Direct	Precise	**SOE=High** Apixaban reduced risk (HR 0.79; 95% CI 0.69 to 0.91)
Adverse events	1 (5,599)	RCT/Low	NA	Direct	Imprecise	**SOE=Moderate** No differences in liver function or other adverse events between therapies

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

Percutaneous Left Atrial Appendage (LAA) 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.[155]

Composite of Stroke, Cardiovascular Death, and Systemic Embolism

The primary outcome in the trial 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, 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 strength of evidence that there was no difference between treatment arms.

All Strokes

The rate of all strokes was lower in the LAA group, although the difference did not reach statistical significance (RR 0.71; 95% CI 0.35 to 1.64). There was low strength of evidence that there was toward a benefit of LAA.

Major Bleeding

Major bleeding was less frequent in the LAA group than in the warfarin group (3.5% vs. 4.1%) (low strength of evidence).

All-Cause Mortality

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) demonstrating a trend toward a benefit of LAA (low strength of evidence).

Adverse Events

The primary composite outcome for safety 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 rate 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 strength of evidence).

Strength of Evidence

Table 30 summarizes the strength of evidence for outcomes of interest for this comparison.

Table 30. Strength of evidence domains for preventing thromboembolic events—percutaneous LAA closure vs. warfarin

Outcome	Number of Studies (Subjects)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Ischemic stroke	1 (707)	RCT/Low	NA	Direct	Imprecise	**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 difference between therapies
All strokes	1 (707)	RCT/Low	NA	Direct	Imprecise	**SOE=Low** Trend toward a benefit of LAA (RR 0.71; 95% CI 0.35 to 1.64)
Major bleeding	1 (707)	RCT/Low	NA	Direct	Imprecise	**SOE=Low** Less frequent with LAA (3.5% vs. 4.1%)
All-cause mortality	1 (707)	RCT/Low	NA	Direct	Imprecise	**SOE=Low** Trend toward a benefit of LAA (RR 0.62; 95% CI 0.34 to 1.24)
Adverse events	1 (707)	RCT/Low	NA	Direct	Imprecise	**SOE=Moderate** Higher rate with LAA (RR 1.69; 95% CI 1.01 to 3.19)

Abbreviations: CI=confidence interval; LAA=left atrial appendage; NA=not applicable; RCT=randomized controlled trial; RR=relative risk; SOE=strength of evidence

Results in Specific Subgroups of Interest

Thirty-three 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. Below we describe these studies and the qualitative synthesis of their findings.

Patients Not Eligible for Warfarin Use

Only two studies have specifically looked at effectiveness of therapy in patients who were considered unsuitable for warfarin therapy.[152,156] The ACTIVE-A trial[156] was designed to determine whether the combination of clopidogrel (75 mg daily) plus aspirin (75 to 100 mg 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 (5 mg orally twice daily) was compared with aspirin (81–324 mg daily) in the AVERROES trial, a randomized, double-blind, and multicenter study.[152] This trial enrolled about 5,600 patients. The primary efficacy outcome was the composite of stroke or systemic embolism, and secondary outcomes included the composite of: stroke, systemic embolism, MI, or vascular death (major vascular events). The study was terminated early by the data safety and monitoring board (DSMB) due to the superiority of apixaban over aspirin. This finding was more or less expected, since an oral anticoagulant was compared with aspirin, which is known to be less effective than VKAs for the prevention of stroke in patients with AF. However, the most impressive results were the similar rates of bleeding between aspirin and apixaban, which illustrates that often times the risk of bleeding associated with aspirin is underestimated. Finally, apixaban was better tolerated than aspirin, leading to a lower rate of drug discontinuation than aspirin during the course of the trial. This finding also highlights that aspirin has side effects which are sometimes underappreciated in clinical practice.

In summary, despite the established rules, risk scores, and formal contraindications that exist to guide oral anticoagulation therapy in patients with AF, decisionmaking on VKA's eligibility in clinical practice seems to be very complex and does not necessarily rely on known factors or on data collected in clinical trials. Thus, there are a substantial number of AF patients who are not considered to be eligible to VKAs, but who are at high risk for ischemic events, and for whom an alternative strategy for stroke prevention is needed.

Patients With AF and Renal Impairment

One substudy[188] of the ROCKET AF study[28] 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 15 mg/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.

One substudy[200] of the AVERROES trial[152] compared apixaban 5 mg twice daily (2.5 mg twice daily in selected patients) with aspirin 81–324 mg 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[203] of the ARISTOTLE trial[150] compared apixaban 5 mg 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 (2.5 mg twice daily). In both sensitivity analyses, the interaction between treatment and renal function remained statistically significant for major bleeding.

Patients With Paroxysmal Versus Sustained AF

One substudy[195] of the ACTIVE W RCT[163] 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).

Patients With AF Undergoing Cardioversion

Four studies (including a subgroup analysis[192] of the RE-LY trial[27]) explored stroke prevention in AF patients undergoing cardioversion.[166,180,181,192] One very small study[180] compared aspirin plus clopidogrel versus warfarin in the prevention of thromboembolic events in a group of patients with non-high-risk AF. Thirty patients (11 women, 45 to 75 years of age) with non-high-risk permanent (n=12) or persistent AF awaiting cardioversion (n=18) underwent transesophageal echocardiography to exclude left heart thrombi and were then randomly assigned to receive warfarin (INR 2–3 for 3 weeks) or aspirin (100 mg/day alone for 1 week) plus clopidogrel (75 mg/day added to aspirin for 3 weeks). Seven of nine patients receiving warfarin and seven of nine patients receiving aspirin+clopidogrel and undergoing electrical cardioversion achieved sinus rhythm. No thromboembolic or hemorrhagic events occurred in either arm throughout the 3-week treatment and a further 3-month followup.

A second study[166] was an RCT comparing the safety and efficacy of enoxaparin administered subcutaneously with intravenous unfractionated heparin (UFH) followed by the oral anticoagulant phenprocoumon in 496 patients scheduled for cardioversion of AF of >48 hours and ≤1 year's duration. Patients were stratified to cardioversion with (n=431) and without (n=65) guidance by transesophageal echocardiogram (TEE). The study aimed to demonstrate noninferiority of enoxaparin compared with UFH+phenprocoumon with regard to the incidence of embolic events, all-cause death, and major bleeding complications. Of 496 randomized patients, 428 were analyzed per protocol. Enoxaparin was noninferior to UFH+phenprocoumon with regard to the incidence of the composite primary outcome in an intention-to-treat analysis (7 of 248 patients vs. 12 of 248 patients, respectively; p=0.013) and in a per-protocol analysis (7 of

216 patients vs. 12 of 212 patients, respectively; p=0.016). Analyzing the events separately, none of them (cerebral embolic infarct, minor and major hemorrhagic events, and death) were statistically different between the groups. There was also no significant difference between the two groups in the number of patients reverted to sinus rhythm.

A third study[181] was an RCT comparing the difference in the rate of thromboembolic events of TEE-guided early cardioversion with short-term low molecular weight heparin (LMWH) use in patients with nonvalvular persistent AF. The study group consisted of 172 consecutive patients with nonvalvular AF. Before TEE, 90 patients received LMWH (dalteparin 2 × 5,000 U) and 82 patients received standard heparin (UFH; 5,000 U bolus followed by infusion to raise APTT to 1.5 times control). TEE was performed, and the left atrium and LAA were examined thoroughly for the presence of thrombus. One patient from each group was excluded due to detection of a left atrial thrombus by TEE. Immediately after TEE, cardioversion was attempted and warfarin was initiated. All patients received warfarin for one month after cardioversion. In the LMWH group, 89 of 90 patients (98.9%) were successfully cardioverted. Cardioversion was successful in 97.5 percent of the patients in the UFH group. None of the patients experienced thromboembolic events during the 4 weeks after cardioversion.

The fourth study[192] was a subgroup analysis of the RE-LY trial[27] evaluating patients that were submitted to cardioversion therapy during the trial. Data from before, during, and 30 days after cardioversion were analyzed. A total of 1,983 cardioversions were performed in 1,270 patients: 647, 672, and 664 in the dabigatran 110 mg, dabigatran 150 mg, and warfarin groups, respectively. For dabigatran 110 mg, dabigatran 150 mg, and warfarin, TEE was performed before 25.5, 24.1, and 13.3 percent of cardioversions, respectively, of which 1.8, 1.2, and 1.1 percent, respectively, were positive for left atrial thrombi. Continuous treatment with study drug for ≥3 weeks before cardioversion was lower in dabigatran 110 mg (76.4%) and dabigatran 150 mg (79.2%) compared with warfarin (85.5%; p<0.01 for both). Stroke and systemic embolism rates at 30 days were 0.77, 0.3, and 0.6 percent in dabigatran 110 mg, dabigatran 150 mg, and warfarin, respectively (dabigatran 110 mg vs. warfarin, p=0.71; dabigatran 150 mg vs., p=0.40) and similar in patients with and without TEE. Major bleeding rates were 1.7, 0.6, and 0.6 percent, respectively (dabigatran 110 mg vs. warfarin, p=0.06; dabigatran 150 mg vs. warfarin, p=0.99).

Patients With AF After Stroke

Seven studies explored stroke prevention treatment in patients with AF who had previously suffered a stroke[164,168,178,193,197-199]

The Heparin in Acute Embolic Stroke Trial (HAEST)[168] was a multicenter RCT on the effect of LMWH (dalteparin 100 IU/kg subcutaneously twice a day) or aspirin (160 mg 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[197] of the ROCKET AF study[28] 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 20 mg 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[178] 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[164] 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 follow-up 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 follow-up (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[193] was conducted of the outcomes of the RE-LY trial[27] 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 110 mg dabigatran group, 1,233 from the 150 mg 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 110 mg dabigatran (relative risk [RR] 0.84; 95% CI 0.58 to 1.20) and 51 (2.07% per year) on 150 mg dabigatran (RR 0.75, 95% CI 0.52 to 1.08). The rate of major bleeding was significantly lower in patients on 110 mg dabigatran (RR 0.66; 95% CI 0.48 to 0.90) and similar in those on 150 mg 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 (110 mg group compared with warfarin group, interaction p=0.038). By these results, the effects of 110 mg dabigatran and 150 mg 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, 150 mg dabigatran reduced stroke or systemic embolism and 110 mg dabigatran was noninferior.

A prespecified subgroup analysis[198] of AVERROES[152] 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 5 mg twice daily (n=2,808) or aspirin 81–324 mg 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[199] from the ARISTOTLE trial[150] 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.

Patients With AF and Different Thromboembolic Risks

Eight studies explored the comparative safety and effectiveness of stroke prevention therapy in patients with different thromboembolic risks.[14,102,110,174,183,187,194,202]

An observational study[102] 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 post hoc analysis[14] was performed to determine the relationship of risk levels (quantified using the $CHADS_2$) and thromboembolic events in patients with nonvalvular AF. A total of 509 patients with nonvalvular AF were analyzed, and the $CHADS_2$ score of 0 was classified as low risk, 1–2 a moderate risk, and ≥3 high risk. Warfarin was given to 263 patients (mean INR at enrollment, 1.86), antiplatelets (aspirin or ticlopidine) to 163 patients, and no antithrombotic therapy to 83. The event rate increased as the risk level estimated with $CHADS_2$ score increased in patients in the non-warfarin group, although the difference did not reach the significance level (p=0.11). In contrast, the event rate differed significantly between the three different risk level groups of patients receiving warfarin (p=0.015), but paradoxically the event rate of the low-risk group was higher than that of the moderate-risk group (3.9% vs. 1.9%). Surprisingly, the event rate was 7.7 percent per year for high-risk patients receiving warfarin. INR levels at the time of enrollment did not differ among the three groups of warfarin-treated patients (low risk, 1.82 ± 0.81; moderate risk, 1.92 ± 0.87; high risk, 1.78 ± 0.70). The unpredictable results shown above could be attributed to the fact that patients with hypertrophic cardiomyopathy but without any clinical risk factors for thromboembolism were defined as low risk, but they actually experienced thromboembolic events frequently. When patients with hypertrophic cardiomyopathy were excluded from the analyses, the event rates increased in patients receiving warfarin as the risk level increased (p=0.033).

A prospective cohort study[110] 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 (non-significant.). This study demonstrated that oral anticoagulants appeared safe and effective in patients with $CHADS_2$≥1.

Another observational study[174] compared warfarin versus aspirin therapy for the prevention of stroke in AF patients with $CHADS_2$ score=1. Among 1,502 patients (mean 62.4 ± 13.8 years old, male 65.4%) who were treated for nonvalvular AF without previous stroke, the number of patients with $CHADS_2$ score=1 was 422 (62.9 ± 10.7 years old, male 290 [68.7%]) and their antithrombotic therapies were as follows: warfarin (n=143), aspirin (n=124), other antiplatelet

(n=45), and no antithrombotic therapy (none: n=110). During followup, the incidence of ischemic stroke was significantly lower in warfarin (6 patients, 4.2%) than in aspirin (16 patients, 12.9%, p=0.008) than none (23 patients, 20.9%, p <0.001) without differences in all-cause mortality. There was no difference in the incidence of major bleeding between patients on warfarin (2.1%) and aspirin (0.8%, p=NS), but minor bleeding was more common in patients on warfarin (10.5%) than in on aspirin (2.4%, p=0.007).

In ACTIVE W,[163] oral anticoagulation was more efficacious than combined clopidogrel plus aspirin in preventing vascular events in patients with AF. A subanalysis of ACTIVE W[194] 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[187] of the RE-LY trial[27] 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 150 mg 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 110 mg twice daily and warfarin. The rates of intracranial bleeding with dabigatran 150 mg or 110 mg 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[183] 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[202] of the ARISTOTLE trial[150] compared apixaban 5 mg 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.

Patients With AF According to INR Control

Four studies evaluated treatment safety and effectiveness according to center-based INR control.[121,167,169,184] In the first study,[121] 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 study[167] analyzed the efficacy and safety of conventional and low-intensity warfarin therapy in a prospective, randomized, multicenter trial. The study population consisted of patients with nonvalvular AF who had a stroke or TIA. The patients were randomly allocated into a conventional-intensity group (INR 2.2–3.5) and a low-intensity group (INR 1.5–2.1). A total of 115 patients were enrolled (mean age 66.7/66.5 years): Fifty-five and 60 patients were allocated into the conventional- and low-intensity groups, respectively. The trial was stopped when major hemorrhagic complications occurred in 6 patients of the conventional-intensity group and the frequency (6.6% per year) was significantly higher than that in the low-intensity group (0% per year, p=0.01, Fisher's exact test). All of the 6 patients with major bleeding were elderly (mean age 74 years, mean INR before the major hemorrhage 2.8). The annual rate of ischemic stroke was low in both groups and similar (1.1% per year in the conventional-intensity group vs. 1.7% per year in the low-intensity groups, p=NS).

A third observational study included an analysis of warfarin subgroups according to INR control compared with no therapy.[169] 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.

Another observational study of fair quality[184] including 815 patients compared the effects of two different intensities of warfarin therapy (INR values <2 versus INR >2) and showed higher bleeding rates in the group with INR >2 (p<0.001), with no significant differences in the frequencies of ischemic stroke between the two groups (HR 1.93; 95% CI 0.80 to 4.70; p=0.146).

Elderly Patients With AF

Eleven studies specifically explored the safety and effectiveness of stroke prevention therapies in the elderly.[157,161,165,175-177,179,182,185,189,190]

A single-center, retrospective, observational study[175] 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[157] 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[161] 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 (75 mg 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[176] of primary thromboprophylaxis for AF included patients aged >80 and <90 randomized to receive dose-adjusted warfarin (INR 2.0–3.0) or aspirin 300 mg. 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[177] recruited patients over 75 years of age without previous stroke or systemic embolism. Patients were randomized into three groups, (A) aspirin 100 mg/day, (B) fixed-dose warfarin 1 mg/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[179] 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[165] 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[189] of the BAFTA trial[161] 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[182] 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[27] randomized 18,113 patients to receive dabigatran 110 or 150 mg 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[190] assessed the impact of age on the findings and found that there was a significant treatment-by-age interaction, such that dabigatran 110 mg 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 150 mg 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.

Finally, 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.[185].

Patients With AF Undergoing Drug-Eluting Stent Implantation

One prospective cohort study[173] analyzed outcomes in 622 AF patients who underwent drug-eluting stent (DES) implantation. Among them, 142 patients (TT group) continued triple antithrombotic therapy comprising aspirin, clopidogrel, and warfarin after discharge; 355 patients (DT group) had dual antiplatelet therapy; 125 patients (WS group) were discharged with warfarin and a single antiplatelet agent. Primary outcome was defined as the occurrence of major adverse cardiac and cerebral events (MACCE) including death, MI, target vessel revascularization, stent thrombosis, or stroke at 12 months. The TT group had a significant reduction in stroke and MACCE (8.8% vs. 20.1% vs. 14.9%; p=0.010) as compared with either the DT or WS group. Warfarin use (HR 0.49; 95% CI 0.31 to 0.77; p=0.002) and baseline $CHADS_2$ score ≥2 (HR 2.09; 95% CI 1.27 to 3.45; p=0.004) were independent predictors of MACCE. Importantly, the incidence of major bleeding was comparable among the three groups (2.9% vs. 1.8% vs.2.5%; p=0.725), although the overall bleeding rate was increased in the TT group. Analyzing the events separately in two ways of comparison (all three therapies and therapies with warfarin versus therapy without warfarin), the only event that achieved statistically significance was stroke in the comparison of therapy with warfarin (DT and TT) versus dual antiplatelet therapy without warfarin (less stroke in warfarin group).

Patients With AF and Myocardial Infarction

One substudy of the RE-LY trial[27] evaluated the use of therapies for stroke prevention in AF patients with MI.[196] 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 110 mg group, 1,915 (31%) in the dabigatran 150 mg 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[170] 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 (adjusted HR 1.22; 95% CI 1.03 to 1.46 for aspirin+clopidogrel vs. aspirin alone; adjusted 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).

Key Question 4. Anticoagulation Strategies in Patients Undergoing Invasive Procedures

KQ 4. What are the comparative safety and effectiveness of available strategies for anticoagulation in patients with nonvalvular AF who are undergoing invasive procedures?

Key Points

- The included studies of oral anticoagulation after percutaneous coronary intervention (PCI) with stenting (3 good-quality retrospective studies; 689 patients) were relatively small and reached different conclusions regarding the effectiveness of triple therapy (warfarin+aspirin+clopidogrel) compared with other combinations of therapies for both bleeding and ischemic outcomes (insufficient strength of evidence for all outcomes assessed).
- Studies of bridging therapies (7 retrospective studies; 2 good quality, 4 fair quality, 1 poor quality; 2,797 patients) were hampered by the variety of procedures (radiofrequency ablation [RFA], other surgeries) and strategies assessed and provided inconclusive findings (insufficient strength of evidence for all outcomes assessed).
- Two studies investigating the safety of dabigatran versus warfarin in the periprocedural period (RFA) reported higher bleeding rates among patients using dabigatran, while the single study comparing dabigatran with warfarin in patients undergoing PCI found no differences in bleeding or ischemic complications (3 studies; 2 good quality, 1 poor quality; 5,037 patients; insufficient strength of evidence).

Description of Included Studies

Thirteen studies were included in our analysis (Appendix Table F-4),[205-217] of which seven were prospective cohort studies,[205,208-211,213,214] five were retrospective cohort studies,[206,207,212,215,216] and one was a prospective observational study within an RCT.[217] These studies assessed oral anticoagulation after PCI with stenting,[205-207] bridging therapies,[208-214] or dabigatran in the periprocedural setting.[215-217] We analyze each of these groups separately in the "Detailed Synthesis" section, below.

The numbers of patients analyzed varied from 104–4,591, although all studies but one[217] enrolled fewer than 703 patients. Seven studies were single-center,[205,206,208-210,212,215] five were multicenter,[207,213,214,216,217] and one did not report the number of sites.[211] Studies were conducted

in the United States,[211,212,215,216] South America,[208] Asia,[209] and Europe;[205-207,210,213,214] one study was conducted in multiple continents.[217] Studies were conducted between the years 1999 and 2011. Seven were rated as good quality,[205-207,209,211,216,217] four as fair quality,[208,210,213,214] and two as poor quality.[212,215] Two studies were government funded,[209,214] two were sponsored by industry,[210,217] one received funding from both government and industry,[213] and eight received no funding or the funding source was unclear or not reported.[205-208,211,212,215,216] Subjects ranged in age from a mean of 55–78.6 years; a total of 8,523 subjects were enrolled.

Detailed Synthesis

Overview

Our analysis was limited by the small number of included studies, the variability of the clinical context studied, and the variability of the anticoagulation strategies employed. For the purposes of this analysis, the studies are grouped according to indication studied, in particular according to whether they assessed anticoagulation post-PCI with stenting, bridging therapies, or dabigatran in the periprocedural setting. The main findings are summarized in Table 31.

Table 31. Summary of findings for KQ 4

Study	N	Comparators	Outcomes	Results
OAC After PCI With Stenting				
Maegdefessel, 2008[205]	159	Clopidogrel+ASA (n=103) Clopidogrel+ASA+LMWH (n=42) Clopidogrel+ASA+OAC (n=14)	Followup: 1.4 years Major bleeding MI Ischemic stroke CV mortality	Major bleeding: 2 vs. 0 vs. 0 events MI: 4 vs. 0 vs. 0 events Ischemic stroke: 9 vs. 4 vs. 0 CV mortality: 3 vs. 5 vs. 1

Table 31. Summary of findings for KQ 4 (continued)

Study	N	Comparators	Outcomes	Results
OAC After PCI With Stenting				
Manzano-Fernandez, 2008[206]	104	Clopidogrel+ASA (n=53) Clopidogrel+ASA+OAC (n=51)	Followup: 12 months Early major bleeding (within 48 hours post-PCI) Late major bleeding (after 48 hours post-PCI) Composite outcome: MACE (CV mortality, MI, revascularization, stent thrombosis)	Early major bleeding: 5.3% vs. 11.3% (p=0.33) Late major bleeding: 3.8% vs. 21.6% (p=0.006); HR 7.1 (95% CI 1.5 to 32.4) Composite: 21.0% vs. 25.5% (p=0.53)
Ruiz-Nodar, 2008[207]	426	Antipplatelet agents only (n=184) Antiplatelet therapy+OAC (n=242)	Followup: 594 days Composite outcome: MACE (death, MI, TVR) Composite outcome: MACE+major bleeding+stroke Major bleeding Minor bleeding Death MI	Composite (MACE): 38.7% vs. 26.5% (p=0.01) Composite (MACE+major bleeding+stroke): 39.2% vs. 26.8% (p=0.014) Major bleeding: 9.0 vs. 14.9%(p=0.19) Minor bleeding: 9.0% vs. 12.6% (p=0.32) Death: 27.8% vs. 17.8% (p=0.02) MI: 10.4% vs. 6.5% (p=0.14)
Bridging Therapies				
Kiviniemi, 2012[214]	414	Uninterrupted OAC without additional anticoagulation (n=196) Uninterrupted OAC with additional anticoagulation (n=218)	Followup: In-hospital Composite: MACCE (death, MI, TVR, stent thrombosis, stroke) Death MI TVR Stent thrombosis Stroke TIMI major bleeding Access site complications	Composite: 4.1% vs. 3.2% (p=0.79) Death: 1.0% vs. 1.8% (p=0.69) MI: 1.5% vs. 1.4% (p=1.0) TVR: 1.5% vs. 0.5% (p=0.35) Stent thrombosis: 1.5% vs. 0.5% (p=0.35) Stroke: 0.5% vs. 0% (p=0.47) TIMI major bleeding 1.0% vs. 3.7% (p=0.11) Access site complications: 5.1% vs. 11% (p=0.032)

Table 31. Summary of findings for KQ 4 (continued)

Study	N	Comparators	Outcomes	Results
Lahtela, 2012[213]	451	Uninterrupted OAC (n=290) Stop OAC and add bridging therapy with LMWH (n=161)	Followup: 30 days Composite outcome: MACCE (death, MI, TVR, stent thrombosis, stroke) Death MI Re-revascularization Stent thrombosis Stroke All bleeding events Major bleeding Access site bleeding	Composite: 3.8% vs. 6.2% (p=0.25) Death: 2.1% vs. 2.5% (p=0.73) MI: 1.0% vs. 1.9% (p=0.67) Re-revascularization: 0.7% vs. 2.5% (p=0.19) Stent thrombosis: 2.1% vs. 1.2% (p=0.72) Stroke: 0.3% vs. 0% (p=1.0) All bleeding: 12.% vs. 18.6% (p=0.07) Major bleeding: 1.4% vs. 2.5% (p=0.25) Access site bleeding: 5.5% vs. 11.2% (p=0.030)
Saad, 2011[208]	140	Enoxaparin 1 mg/kg (n=55) Warfarin (n=49)	Followup: 16 months Minor bleeding Major bleeding CV mortality All-cause mortality Systemic embolism	Minor bleeding: 4(5.7%) vs. 2 (2.8%) Major bleeding: 1 (1.4%) vs. 1 (1.4%) CV mortality: None All-cause mortality: None Systemic embolism: None
Kwak, 2010[209]	104	Enoxaparin 1 mg/kg (n=70) Warfarin (n=70)	Followup: In-hospital Major bleeding Minor bleeding Ischemic stroke	Major bleeding: 2 (3.6%) vs. 6 (12.2%) events (p=0.14) Minor bleeding: 8 (14.5%) vs. 3 (6.1%) (p=0.28) Ischemic stroke: None
Bunch, 2009[212]	630	Aspirin (n=123) Warfarin (n=507)	Followup: 12 months Death Stroke TIA	Death: 0 vs. 5 (1.0%; p=0.59) Stroke: 0 vs. 4 (0.8%; p=0.24) TIA: None
Hammerstingl, 2009[210]	703	Patients at low risk of thromboembolic events: Enoxaparin 1 mg/kg once a day (n=345) Patients at high risk of thromboembolic events: Enoxaparin 1 mg/kg twice daily (n=358)	Followup: 30 days Composite outcome: stroke/TIA, arterial embolism Major bleeding Minor bleeding	Composite: No events Major bleeding: 1 (0.29%) vs. 2 (0.56%) Minor bleeding: 25 (7.25%) vs. 35 (9.78%)

Table 31. Summary of findings for KQ 4 (continued)

Study	N	Comparators	Outcomes	Results
Wazni, 2007[211]	355	Enoxaparin 1 mg/kg twice daily (n=105) Enoxaparin 0.5 mg/kg twice daily (n=100) Warfarin (INR 2-3.5) (n=150)	Followup: 3 months Ischemic stroke Minor bleeding Major bleeding	Ischemic stroke: 1 (1.0%) vs. 2 (2.0%) vs. 0 (p=0.12) Minor bleeding: 23 (21.9%) vs. 19 (19.0%) vs. 8 (5.3%) (p<0.001) Major bleeding: 9 (8.6%) vs. 0 vs. 0 (p<0.001)
Dabigatran in the Periprocedural Setting				
Healey, 2012[217]	4,591	Dabigatran 110 mg twice daily (n=1,487) Dabigatran 150 mg twice daily (n=1,546) Warfarin (n=1,558)	Followup: 30 days Minor bleeding Major bleeding Fatal bleeding Transfusion CV death Stroke Systemic embolism MI Composite outcome: CV death, ischemic stroke, non-CNS embolism, and pulmonary embolism	Minor bleeding: 8.1% vs. 9.0% vs. 7.8% Major bleeding: 3.8% vs. 5.1% vs. 4.6% Fatal bleeding: 0.2% vs. 0.1% vs. 0.1% Transfusion: 3.3% vs. 3.5% vs. 4.0% CV death: 0.6% vs. 0.5% vs. 0.5% Stroke: 0.5% vs. 0.5% vs. 0.6% Systemic embolism: 0.1% vs. 0.1% vs. 0.1% MI: 0.1% vs. 0.5% vs. 0.3% Composite: 1.2% vs. 1.5% vs. 1.2% All comparisons p=NS
Lakkireddy, 2012[216]	290	Dabigatran 150 twice daily withheld morning of procedure (n=145) Uninterrupted warfarin (n=145)	Followup: 30 days Major bleeding Minor bleeding Groin hematoma Total bleeding Embolic complications (CVA/TIA) Composite outcome: Total bleeding+embolic complications	Major bleeding: 6% vs. 1% (p=0.019) Minor bleeding: 8% vs. 6% (p=0.35) Groin hematoma: 4% vs. 3% (p=0.75) Total bleeding: 14% vs. 6% (p=0.031) Embolic complications: 2% vs. 0% (p=0.25) Composite: 16% vs. 6% (p=0.009)
Snipelisky, 2012[215]	156	Dabigatran (n=31) Warfarin (n=125)	Followup: 1 week Major complications Minor complications	Major complications: 0% vs. 0% Minor complications: 19.4% vs. 16.8% (p=0.74)

Abbreviations: ASA=aspirin; CI=confidence interval; CNS=central nervous system; CV=cardiovascular; CVA=cerebrovascular accident; HR=hazard ratio; INR=international normalized ratio; KQ=Key Question; LMWH=low molecular weight heparin; MACCE=major adverse cardiac and cerebrovascular events; MACE=major adverse cardiac events; MI=myocardial infarction; N=number of participants; NS=not statistically significant; OAC=oral anticoagulation; PCI=percutaneous coronary intervention; TIA=transient ischemic attack; TIMI=Thrombolysis In Myocardial Infarction trial; TVR=target vessel revascularization

Oral Anticoagulation After PCI With Stenting

Three studies compared antiplatelet therapy plus oral anticoagulation with antiplatelet therapy alone after PCI with stenting.[205-207] All were cohort studies subject to the biases inherent in the clinical decision of anticoagulation strategy implemented at the discretion of the physician. The strategies compared differed across studies, making cross-study analysis difficult. One study compared dual therapy with aspirin plus clopidogrel with "triple therapy," defined as either aspirin plus clopidogrel plus LMWH, or as aspirin plus clopidogrel plus oral anticoagulation.[205] A second study compared triple therapy (dual antiplatelet therapy plus warfarin) with dual therapy (clopidogrel plus aspirin).[206] Finally, the third study compared a strategy of antiplatelet agents alone with antiplatelet agents plus oral anticoagulation;[207] however, the antiplatelet agents used were not consistent. Given the known association of both bleeding and protection against thromboembolic events with each of the agents considered, it was deemed inappropriate to combine any of these treatment strategies for analysis.

In general, these studies enrolled an older patient population (mean age 69–71) with a high proportion of patients with diabetes (33–54%), hypertension (82–91%), and hyperlipidemia (>50%), reflecting the demographics of a patient population with AF and coronary disease. The median $CHADS_2$ score was 2, with an IQR of 2–3, indicating that a vast majority of patients had a $CHADS_2$ score of at least 2.

Major Bleeding

One study[206] reported major bleeding within 48 hours of PCI and found no significant difference in the occurrence of early major bleeding between the two treatment arms (5.8% for triple therapy vs. 11.3% for dual therapy, p=0.33). In the same study, triple therapy was associated with a significantly higher rate of major bleeding (21.6% for triple therapy vs. 3.8% for dual therapy, p=0.006) during the first 6 months of followup.

At followup at 1.4 years, one study[205] reported two major bleeding events in the dual antiplatelet therapy group and none in the triple therapy arms. The third study[207] reported a nonsignificant increase of major (14.9% vs. 9.0%, p=0.19) and minor (12.6% vs. 9.0%) bleeding among patients discharged on triple therapy compared with those on dual antiplatelet therapy (insufficient strength of evidence).

Mortality

Two studies compared the effect of triple therapy versus dual antiplatelet therapy on mortality.[205,207] One[205] reported three cardiovascular deaths in the dual antiplatelet therapy group, five cardiovascular deaths among patients receiving triple therapy with LMWH, and one cardiovascular death among patients receiving triple therapy with oral anticoagulant. The second study[207] reported a statistically significantly higher rate of all-cause mortality among patients discharged on dual antiplatelet therapy compared with those on triple therapy (10.4% vs. 6.5%; HR 3.43; 95% CI 1.61 to 7.54; p=0.002) (insufficient strength of evidence).

Myocardial Infarction

Two studies compared the effect of triple therapy versus dual antiplatelet therapy on myocardial infarction.[205,207] One[205] reported four myocardial infarction events in the dual antiplatelet therapy group and none in the triple therapy arms. The other[207] reported a nonsignificant increase in the rate of myocardial infarction events (10.4% vs. 6.5%) among

patients discharged on dual antiplatelet therapy compared with those on triple therapy (insufficient strength of evidence).

Composite Outcomes

Two studies compared the effect of triple therapy versus dual antiplatelet therapy on the composite outcome of death, myocardial infarction, and revascularization or stent thrombosis.[206,207] One[206] found no significant difference in the rate of the composite endpoint between the two treatment arms (25.5% triple therapy vs. 21.0% dual therapy, p=0.53). The other[207] reported a statistically significantly higher rate of the composite outcome among patients discharged on dual antiplatelet therapy compared with those on triple therapy (38.7% vs. 26.5%; HR 4.9; 95% CI 2.17 to 11.1; p=0.01). Similarly, in this same study, a significant increase in the secondary safety endpoint (any major adverse cardiovascular event, major bleeding, and/or stroke) was observed among patients treated with dual therapy compared with triple therapy (39.2% vs. 26.8%, p=0.014).

Bridging Therapies

Seven studies assessed bridging therapies during cardiac and non-cardiac procedures.[208-214] Three studies compared a bridging strategy involving LMWH with a strategy not employing LMWH;[208,209,211] Across the studies, the surgical procedures (RFA,[208,209,211,212] minor and major surgery[210] and PCI[213,214]) varied, as did the comparator arms. These studies reported on shorter term, periprocedural outcomes.

Two trials compared a strategy of "bridging" peri-RFA with enoxaparin versus continuous oral anticoagulation.[208,209] The only demographic data available for both studies were on the age of the population, which appears to have differed significantly across the two studies (mean age 73–76 years in one study[208] and 55–56 years in the other[209]) and sex (~83% male in one study,[208] 74% male in the other[209]). Other risk factors for thromboembolism and bleeding were inconsistently reported between the two studies.

Two studies compared performance of PCI on uninterrupted oral anticoagulation versus using a variety of bridging strategies. In the first,[213] comparison was made between those undergoing PCI with continuous oral anticoagulation, including those who received additional periprocedural heparin, versus those in whom oral anticoagulation was stopped. There were trends toward lower bleeding events in those maintained on uninterrupted oral anticoagulation; however, the use of radial procedures was markedly higher in this arm (43.4% vs. 13.7%; p<0.0001), which may have accounted for this observation. Interestingly, once propensity matching was performed, no differences were observed in any bleeding or ischemic endpoint, suggesting that these treatment strategies appeared to be equivalent in this small, underpowered study.

A second study assessed the impact of giving additional anticoagulation to patients undergoing PCI while already therapeutic on oral anticoagulants.[214] This study suggested that additional anticoagulation administered during the procedure may increase risk of bleeding (3.7% vs. 1.0%; p=0.11) while not impacting ischemic events (3.2 vs. 4.1%; p=0.79). Major access site complications were lower (5.1% vs. 11.0%; p=0.032) in patients who did not receive additional anticoagulation.

These two studies should be interpreted with caution. Decisions about anticoagulation were not randomized, and therefore the findings are potentially confounded by the multiple differences between the populations in the comparison groups. Furthermore, given the small

number of ischemic events, the safety of this approach to minimizing ischemic events remains to be established and would require studies of a different order of magnitude.

Major and Minor Bleeding

Major and minor bleeding events were reported by six of the seven bridging studies. In one study,[208] one patient experienced a major bleeding complication (1.4%) in the LMWH group versus none in the oral anticoagulation group at 16±8 months followup. In the same study, minor bleeding complications occurred at a higher rate in the LMWH group than in the oral anticoagulation group (5.7% vs. 2.8%). Similarly, in another study[211] patients in the LMWH group exhibited higher rates of major bleeding than those in the oral anticoagulation group (9 vs. 0 patients, $p < 0.001$). In another study,[209] the in-hospital bleeding complication rate was not statistically different in the oral anticoagulation group than in the LMWH group (18.4% vs. 18.2%, $p=1.000$), and the major bleeding rate was higher in the oral anticoagulation group (12.2%) than in the LMWH group (3.6%) but did not reach statistical significance ($p=0.1444$). In contrast, when bridging therapy was compared with uninterrupted oral anticoagulation in the setting of PCI[213] bleeding trended higher with the bridging strategy (18.6% vs. 12.1%, $p=0.07$). In the study that assessed bridging anticoagulation during other operative procedures, only three major bleeding events were reported in the entire cohort (n=703).[210] As described above, in the study assessing the impact of giving additional anticoagulation to patients undergoing PCI while already therapeutic on oral anticoagulants,[214] additional anticoagulation administered during the procedure increased the risk of bleeding (3.7% vs. 1.0%, $p=0.11$).

Despite these commonalities, the differences in procedures and bleeding definitions in these trials, as well as the relative rarity of serious bleeding and ischemic complications, make definitive conclusions premature and point to the need for much larger studies powered to detect differences in the risk of relatively rare events (insufficient strength of evidence).

Mortality

There were no deaths reported in one report.[208] Two reports failed to comment on death explicitly,[209,210] although one indicated no post-discharge thrombotic or bleeding complications.[209] One study reported five deaths in patients treated with warfarin post-RFA compared with none in those treated with aspirin; however, there was no attempt to correct for preprocedural differences in these patients, and the difference was not statistically significant ($p=0.59$).[212] Finally, in one study,[213] there were six and four deaths in the oral anticoagulation and bridging therapy arms, respectively; the difference between the two arms was not statistically significant (insufficient strength of evidence).

Myocardial Infarction

Myocardial infarction events were not reported as an outcome in any of the included studies except in the PCI setting, in which case the rate was identical for the two strategies evaluated (oral anticoagulation vs. bridging therapy, 1.0% vs. 1.9%)[213] (insufficient strength of evidence).

Other Thromboembolic Outcomes

In three studies,[208-210] none of the patients experienced ischemic stroke, peripheral embolism, or other thromboembolic complications during followup. In one study,[211] one patient in the LMWH full-dose group and two patients in the LMWH lower dose group developed ischemic stroke, but no patient developed ischemic stroke in the oral anticoagulation group ($p=0.12$). In

another study,[212] there were four CVA/TIA events in patients treated with warfarin compared with aspirin; however, there were multiple baseline differences between groups for which no statistical modeling/correction was attempted.

Use of Dabigatran in the Periprocedural Setting

More recently, three studies have investigated the safety of dabigatran in the periprocedural period in patients with AF.[215-217] Two of these evaluated the use of dabigatran versus warfarin during RFA.[215,216] While one of these reported no major complications,[215] both studies report higher major and minor bleeding rates in patients receiving dabigatran (16.8% warfarin vs. 19.4% dabigatran,[215] and 6% warfarin vs. 14% dabigatran[216]). In a subanalysis (n=4,951) of a larger study (RE-LY) of patients undergoing a variety of invasive procedures, Healey et al.[217] reported no significant differences in the incidence of bleeding or ischemic complications in patients treated with either 110 or 150 mg twice daily of dabigatran compared with warfarin.

Strength of Evidence

Table 32 summarizes the strength of evidence for the various comparisons and outcomes of interest.

Table 32. Strength of evidence domains for anticoagulation strategies in patients undergoing invasive procedures

Outcome	Number of Studies (Subjects)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
OAC After PCI With Stenting						
Major bleeding	3 (689)	Observational/ Moderate	Inconsistent	Direct	Imprecise	**SOE=Insufficient**
Mortality	2 (585)	Observational/ Moderate	Inconsistent	Direct	Imprecise	**SOE=Insufficient**
Myocardial Infarction	2 (585)	Observational/ Moderate	Inconsistent	Direct	Imprecise	**SOE=Insufficient**
Bridging Therapies						
Major and minor bleeding	6 (2,167)	Observational/ High	Inconsistent	Direct	Imprecise	**SOE=Insufficient**
Mortality	5 (1,932)	Observational/ High	Inconsistent	Direct	Imprecise	**SOE=Insufficient**
Other thomboembolic outcomes	5 (1,932)	Observational/ High	Inconsistent	Direct	Imprecise	**SOE=Insufficient**
Use of Dabigatran in Periprocedural Setting						
Major and minor bleeding	3 (5,037)	Observational/ High	Inconsistent	Direct	Imprecise	**SOE=Insufficient**

Abbreviations: CI=confidence interval; OAC=oral anticoagulation; PCI=percutaneous coronary intervention; SOE=strength of evidence

Key Question 5. Strategies for Switching Between Warfarin and Novel Oral Anticoagulants

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 AF?

Key Points

- There is currently no safety or effectiveness evidence to answer this question based on the absence of any peer-reviewed published studies in this area (insufficient strength of evidence for all outcomes of interest).

Description of Included Studies

There is no independent, peer-reviewed, published evidence that answers this question. In lieu of such evidence, we describe briefly below:

- Guidance given on this topic in the study protocol for one major RCT;
- Relevant information from package inserts for rivaroxaban and dabigatran; and
- Four unpublished trials that may provide evidence soon.

Detailed Synthesis

The RE-LY study protocol[218] advised providers to stop warfarin on the day of randomization and begin the assigned drug (dabigatran) when the INR fell below 2.0 (if randomized to dabigatran) or below 3.0 (if randomized to warfarin).

Manufacturers (Janessen/Bayer, Boehringer Ingelheim) have included the following information in their package inserts for rivaroxaban and dabigatran:

- "Discontinue warfarin and start Xarelto® [rivaroxaban] as soon as the INR is below 3.0 to avoid periods of inadequate anticoagulation."[219]
- "Discontinue warfarin and start Pradaxa® [dabigatran] when the INR is below 2.0."[220]

These statements do not reference any published evidence.

Finally, although we did not identify any relevant studies within the published literature, our search of ClinicalTrials.gov identified four clinical trials (two ongoing, two recently completed) that may provide data regarding optimal switching strategies between warfarin and other novel oral anticoagulants for patients with AF. These are described briefly in Table 33.

Table 33. Ongoing and recently completed trials relevant to KQ 5

ClinicalTrials.gov Identifier	Brief Description
NCT01578044	Scheduled to be completed in January 2013 and funded by the Department of Veterans Affairs, targets an enrollment of 50 patients. This study includes qualitative interviews with patients (n~30) and pharmacists (n~20) to better understand reasons that patients are not compliant with the drug. This study also proposes to develop interventions for patient adherence to dabigatran based on the qualitative data obtained.
NCT0159082	Seeks to determine the proper dabigatran drug dosing in hemodialysis patients with atrial fibrillation through evaluating pharmacokinetics in 10 patients. This study opens for enrollment July 2012 with an estimated completion date of December 2012, and is funded by the Canadian Capital District Health Authority. All participants will receive a single dose of dabigatran etexilate 100 mg at the start of their 4-hour dialysis session. Blood sampling will be conducted during and up to 48 hours after hemodialysis.
NCT01507051	Funded by Bayer Pharmaceuticals, had a target enrollment of 96 patients and was completed in November 2009. The study objective was to investigate the pharmacodynamics when switching from warfarin to rivaroxaban in a randomized, parallel-group (Treatments A, B, and C), placebo-controlled (Treatment B), and single-blind (Treatments A and B) design. The first two groups (A, B) received warfarin for approximately 1 week to maintain an INR of 2.0–3.0. The first group (A) then received rivaroxaban for 4 days, the second group (B) received placebo. On the last day, all subjects in groups A and B received vitamin K to neutralize the effects of warfarin. The third group (C) did not undergo prior treatment with warfarin but received rivaroxaban for 4 days. Although completed in 2009, we did not identify publications based on the findings of this study.
NCT01400646	Sponsored by Janssen Research & Development, LLC was completed in May 2012 with an enrollment of 46 subjects. This was a single-center, open-label, sequential, two-treatment period study in healthy adult volunteers to explore the pharmacodynamic changes specifically in regard to blood coagulation in healthy volunteers taking oral rivaroxaban followed by warfarin. Subjects transitioned from rivaroxaban 20 mg once daily to warfarin dosed to a therapeutic level as measured by the INR range of 2.0–3.0. Subjects were given rivaroxaban 20 mg/day for 5 days followed by rivaroxaban 20 mg/day + warfarin 10 mg/day for ≥2 to ≤4 days of concomitant therapy, then warfarin 0–15 mg/day for 4 days (Treatment Period 1). A 14-day washout period separated Treatment Periods 1 and 2. Treatment Period 2 consisted of warfarin 10 mg/day for ≥2 to ≤4days, then warfarin 0–15 mg/day for 4 days.

Abbreviations: INR=international normalized ratio; KQ=Key Question

Key Question 6. Stroke Prevention After a Hemorrhagic Event

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 AF?

Key Points

- There is currently no safety or effectiveness evidence to answer this question based on the absence of any peer-reviewed published studies in this area (insufficient strength of evidence for all outcomes of interest).

Description of Included Studies

There is no evidence to describe that answers this question.

Detailed Synthesis

Although we did not identify any relevant studies within the published literature, future substudy analyses likely to be reported from three major RCTs (RE-LY,[27] ROCKET-AF,[28,197] and ARISTOLE[150]) may provide data regarding optimal anticoagulation management strategies for patients with AF who have had prior bleeding events.

Discussion

Key Findings and Strength of Evidence

In this comparative effectiveness review (CER), we reviewed 92 unique studies represented by 122 publications and involving over 1,164,900 patients that evaluated stroke and bleeding prediction tools and stroke prevention strategies in patients with nonvalvular atrial fibrillation (AF). The current evidence base was greatest for the comparative safety and effectiveness of stroke prevention therapies and tools for predicting thromboembolic and bleeding risk; however, the evidence was very limited or nonexistent regarding AF patients undergoing invasive procedures, switching among anticoagulant therapies, and starting or restarting anticoagulant therapy in patients with previous major bleeding events.

KQ 1. Predicting Thromboembolic Risk

Our review included 37 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, and imaging tools, as well as international normalized ratio (INR) monitoring for patients treated with warfarin. 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 $CHADS_2$ and CHA_2DS_2-VASc continuous 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 only one advanced imaging study utilizing magnetic resonance angiography (MRA)/magnetic resonance imaging (MRI) was reviewed and therefore 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 regards to stability of covariates, concomitant medications, stroke inducing procedures, etc.

Table 34 summarizes the strength of evidence for the thromboembolic risk discrimination abilities of the included tools. This summary table represents only those studies that evaluated the risk discrimination 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 34. Summary of strength of evidence and c-statistic estimates for KQ 1 (discrimination of thromboembolic risk)

Tool	Number of Studies (Subjects)	Strength of Evidence and Effect Estimate[a]
$CHADS_2$ (Categorical)	8 (380,669)	**SOE=Insufficient**
$CHADS_2$ (Continuous)	8 (379,755)	**SOE=Low** Modest risk discrimination ability (c-statistic=0.71; 95% CI 0.66 to 0.75)
CHA_2DS_2-VASc (Categorical)	6 (332,009)	**SOE=Insufficient**
CHA_2DS_2-VASc (Continuous)	5 (371,911)	**SOE=Low** Modest risk discrimination ability (c-statistic=0.70; 95% CI 0.66 to 0.75)
Framingham (Categorical)	5 (259,253)	**SOE=Moderate** Limited risk discrimination ability (c-statistic=0.63; 95% CI 0.62 to 0.65)
Framingham (Continuous)	4 (262,151)	**SOE=Low** Limited risk discrimination ability (c-statistic ranges between 0.64 and 0.69 across studies)
Imaging	0	**SOE=Insufficient**
INR	0	**SOE=Insufficient**

[a]All strength of evidence ratings of "Insufficient" are shaded.

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; SOE=strength of evidence

KQ 2. Predicting Bleeding Events

Seventeen 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. Four different bleeding risk scores were evaluated in these studies, all based on clinical parameters, including ATRIA, 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, 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 35 summarizes the strength of evidence for the bleeding risk discrimination abilities of the included tools. This summary table represents only those studies that evaluated the risk discrimination 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 35. Summary of strength of evidence and c-statistic estimates for KQ 2 (discrimination of bleeding risk)

Tool	Number of Studies (Subjects)	Strength of Evidence and Effect Estimate[a]
Summary c-statistic		
BRI	5 (47,684)	**SOE=Moderate** Limited risk discrimination ability (c-statistic ranging from 0.56 to 0.65)
$HEMORR_2HAGES$	8 (318,246)	**SOE=Moderate** Limited risk discrimination ability (c-statistic ranging from 0.53 to 0.78)
HAS-BLED	8 (313,294)	**SOE=Moderate** Modest risk discrimination ability (c-statistic ranging from 0.58 to 0.80)
ATRIA	4 (15,732)	**SOE=Insufficient**
Comparative Risk Discrimination Abilities		
Major bleeding events among patients with AF on warfarin	9 (319,183)	**SOE=Low** Favors HAS-BLED
Intracranial hemorrhage among patients with AF on warfarin	1 (48,599)	**SOE=Low** No difference
Major bleeding events among patients with AF on aspirin alone	3 (177,538)	**SOE=Low** No difference
Major bleeding events among patients with AF not on antithrombotic therapy	6 (310,607)	**SOE=Low** No difference

[a]All strength of evidence ratings of "Insufficient" are shaded.

Abbreviations: 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, Re-bleeding 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 43 studies comparing the safety and effectiveness of specific anticoagulation therapies, antiplatelet therapies, and procedural interventions for preventing thromboembolic events. Among these studies, several new agents were evaluated including Factor IIa inhibitors (dabigatran) and novel Xa inhibitors (apixaban, edoxaban, rivaroxaban, idraparinux). Dabigatran, apixaban, and rivaroxaban have been approved by the FDA; edoxaban and idraparinux are currently investigational. Of the dabigatran doses discussed in this report, the

150 mg dose is FDA-approved and marketed in the United States; the 110 mg dose is not. Although the number of studies for any specific comparison of interest was limited, the included RCTs were often very large, of good quality, and considered definitive in the field. These trials were, however, limited to comparing novel therapies with warfarin or aspirin and have not involved head-to-head comparison among the newer agents. Based on these trials though, it has been 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 novel antithrombotics (apixaban, rivaroxaban, dabigatran) were non-inferior or superior to warfarin for stroke prevention. LAA occlusion devices are currently investigational, pending FDA approval.

Based on these recent studies, these novel antithrombotics have been incorporated into the stroke prevention guidelines in Europe. In these guidelines, there has been a shift away from both warfarin and aspirin, particularly for those patients with lower risk of stroke, for whom aspirin is becoming less favored. In these European guidelines, for those patients with low to moderate risk (CHA2DS2-VASc=1) of thromboembolic event, these novel anticoagulants are recommended or aspirin; and for those with an even lower risk of thromboembolic event (CHA2DS2-VASc=0), it is recommended that these patients receive no anticoagulants or aspirin, with no anticoagulants recommended over aspirin.[17]

While novel antithrombotics have shown significant benefit for prevention of thromboembolic complications of atrial fibrillation, they are not without risk. Dabigatran with or without aspirin has been associated with a higher risk of MI than warfarin. Further study is needed to determine if dabigatran itself leads to increased risk, or if warfarin is somehow protective against MI. Dabigatran has also been associated with a higher rate of dyspepsia and other GI symptoms than warfarin.

Table 36 summarizes the strength of evidence 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 36. Summary of strength of evidence and effect estimates for KQ 3 (interventions for preventing thromboembolic events)

Outcome	Number of Studies (Subjects)	SOE and Magnitude of Effect[a] (95% CI)
ASA vs. Warfarin		
Ischemic stroke	4 (170,642)	**SOE=Moderate** 4 retrospective studies showing consistent reduction in stroke with warfarin
Bleeding	3 (99,876)	**SOE=Moderate** Warfarin associated with increased rates of bleeding
All-cause mortality	1 (601)	**SOE=Insufficient**

Table 36. Summary of strength of evidence and effect estimates for KQ 3 (interventions for preventing thromboembolic events) (continued)

Outcome	Number of Subjects (Studies)	SOE and Magnitude of Effect[a] (95% CI)
Warfarin+ASA vs. Warfarin Alone		
Ischemic stroke	1 (69,264)	**SOE=Moderate** Increased with warfarin + ASA (HR 1.27; 95% CI 1.14 to 1.40)
Bleeding	1 (69,264)	**SOE=Moderate** Increased with warfarin + ASA (HR 1.83; 95% CI 1.72 to 1.96)
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=High** Clopidogrel+ASA associated with higher rates (HR 1.57; 95% CI 1.29 to 1.92)
Minor bleeding	1 (7,554)	**SOE=High** Clopidogrel+ASA associated with higher rates (HR 2.42; 95% CI 2.03 to 2.89)
Intracranial bleeding	2 (8,147)	**SOE=Low** Higher rates with clopidogrel+ASA (HR 1.87; 95% CI 1.19 to 2.94)
Extracranial bleeding	2 (8,147)	**SOE=High** Higher rates with clopidogrel+ASA (HR 1.51; 95% CI 1.21 to 1.88)
All-cause mortality	2 (8,147)	**SOE=Moderate** No 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 (8,147)	**SOE=Low** No 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 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 (593)	**SOE=Insufficient**
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** 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 (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=High** Increased risk with clopidogrel+ASA (HR 1.23; 95% CI 1.09 to 1.39)
Intracranial bleeding	1 (6,706)	**SOE=Insufficient**

Table 36. Summary of strength of evidence and effect estimates for KQ 3 (interventions for preventing thromboembolic events) (continued)

Outcome	Number of Subjects (Studies)	SOE and Magnitude of Effect[a] (95% CI)
All-cause mortality	1 (6,706)	**SOE=High** No difference (HR 1.01; 95% CI 0.81 to 1.26)
Death from vascular causes	1 (6,706)	**SOE=Moderate** No difference (HR 1.14; 95% CI 0.88 to 1.48)
Myocardial infarction	1 (6,706)	**SOE=Moderate** No difference (myocardial infarction 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		
Stroke or systemic embolism	1 (12,098)	**SOE=High** Dabigatran reduced risk (RR 0.66; 95% CI 0.53 to 0.82)
Ischemic or uncertain stroke	1 (12,098)	**SOE=Moderate** Dabigatran reduced risk (RR 0.76; 95% CI 0.60 to 0.98)
Hemorrhagic stroke	1 (12,098)	**SOE=High** Dabigatran reduced risk (RR 0.26; 95% CI 0.14 to 0.49)
Major bleeding	1 (12,098)	**SOE=High** No difference (RR 0.93; 95% CI 0.81 to 1.07)
Minor bleeding	1 (12,098)	**SOE=Moderate** Dabigatran reduced risk (RR 0.91; 95% CI 0.85 to 0.97)
Intracranial bleeding	1 (12,098)	**SOE=High** Dabigatran reduced risk (RR 0.40; 95% CI 0.27 to 0.60)
All-cause mortality	1 (12,098)	**SOE=Moderate** No difference (RR 0.88; 95% CI 0.77 to 1.00)
Death from vascular causes	1 (12,098)	**SOE=Moderate** Dabigatran reduced risk (RR 0.85; 95% CI 0.72 to 0.99)
Myocardial infarction	1 (12,098)	**SOE=Moderate** Dabigatran increased risk (RR 1.38; 95% CI 1.00 to 1.91)
Hospitalization	1 (12,098)	**SOE=High** No difference (RR 0.97; 95% CI 0.92 to 1.03)
Adverse events	1 (12,098)	**SOE=Moderate** Dyspepsia more common with dabigatran (11.3% of patients with dabigatran 150 mg vs. 5.8% with warfarin, p<0.001). No differences in liver function or other adverse events between therapies.
Factor IIa Inhibitor (Dabigatran 110 mg) vs. Warfarin		
Stroke or systemic embolism	1 (12,037)	**SOE=High** No difference (RR 0.91; 95% CI 0.74 to 1.11)

Table 36. Summary of strength of evidence and effect estimates for KQ 3 (interventions for preventing thromboembolic events) (continued)

Outcome	Number of Subjects (Studies)	SOE and Magnitude of Effect[a] (95% CI)
Ischemic or uncertain stroke	1 (12,037)	**SOE=Moderate** No difference (RR 1.11; 95% CI 0.89 to 1.40)
Hemorrhagic stroke	1 (12,037)	**SOE=High** Dabigatran reduced risk (RR 0.31; 95% CI 0.17 to 0.56)
Major bleeding	1 (12,037)	**SOE=High** Dabigatran reduced risk (RR 0.80; 95% CI 0.69 to 0.93)
Minor bleeding	1 (12,037)	**SOE=High** Dabigatran reduced risk (RR 0.79; 95% CI 0.74 to 0.84)
Intracranial bleeding	1 (12,037)	**SOE=High** Dabigatran reduced risk (RR 0.31; 95% CI 0.20 to 0.47)
All-cause mortality	1 (12,037)	**SOE=Moderate** No difference (RR 0.91; 95% CI 0.80 to 1.03)
Death from vascular causes	1 (12,037)	**SOE=Moderate** No difference (RR 0.90; 95% CI 0.77 to 1.06)
Myocardial infarction	1 (12,037)	**SOE=Low** Dabigatran increased risk, although the difference did not reach statistical significance (RR 1.35; 95% CI 0.98 to 1.87)
Hospitalization	1 (12,037)	**SOE=High** Dabigatran reduced risk (RR 0.92; 95% CI 0.87 to 0.97)
Adverse events	1 (12,037)	**SOE=Moderate** Dyspepsia more common with dabigatran (11.8% of patients with dabigatran 110 mg vs. 5.8% with warfarin, p<0.001). No differences in liver function or other adverse events between therapies.
Xa Inhibitor (Apixaban) vs. Warfarin		
Stroke or systemic embolism	2 (18,423)	**SOE=High** Apixaban reduced risk (HR 0.79; 95% CI 0.66 to 0.95)
Ischemic stroke	1 (18,201)	**SOE=High** No difference (HR 0.92; 95% CI 0.74 to 1.13)
Hemorrhagic stroke	1 (18,201)	**SOE=High** Apixaban reduced risk (HR 0.51; 95% CI 0.35 to 0.75)
Systemic embolism	2 (18,423)	**SOE=Moderate** No difference (HR 0.87; 95% CI 0.44 to 1.75)
Major bleeding	2 (18,423)	**SOE=High** Apixaban reduced risk (HR 0.69; 95% CI 0.60 to 0.80)
Intracranial bleeding	1 (18,201)	**SOE=High** Apixaban reduced risk (HR 0.42; 95% CI 0.30 to 0.58)
All-cause mortality	2 (18,423)	**SOE=Moderate** Apixaban reduced risk (HR 0.89; 95% CI 0.80 to 0.998)
Death from cardiovascular causes	1 (18,201)	**SOE=High** No difference (HR 0.89; 95% CI 0.76 to 1.04)
Myocardial infarction	1 (18,201)	**SOE=Moderate** No difference (HR 0.88; 95% CI 0.66 to 1.17)
Adverse events	2 (18,423)	**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	2 (15,544)	**SOE=Moderate** No difference (HR 0.88; 95% CI 0.74 to 1.03)

Table 36. Summary of strength of evidence and effect estimates for KQ 3 (interventions for preventing thromboembolic events) (continued)

Outcome	Number of Subjects (Studies)	SOE and Magnitude of Effect[a] (95% CI)
Ischemic stroke	1 (14,264)	**SOE=Moderate** No difference in on-treatment analyses (HR 0.94; 95% CI 0.75 to 1.17)
Hemorrhagic stroke	2 (15,544)	**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 (14,264)	**SOE=Moderate** Rivaroxaban reduced risk in on-treatment analyses (HR 0.23; 95% CI 0.09 to 0.61)
Major bleeding	2 (15,544)	**SOE=Moderate** No difference in 2 studies in on-treatment analyses (HR 1.04 [95% CI 0.90 to 1.20] in one study; HR 0.85 [95% CI 0.50 to 1.43] in other study)
Intracranial bleeding	2 (15,544)	**SOE=Moderate** Rivaroxaban reduced risk in on-treatment analyses (HR 0.67; 95% CI 0.47 to 0.93)
All-cause mortality	1 (14,264)	**SOE=High** No difference (HR 0.92; 95% CI 0.82 to 1.03)
Death from cardiovascular causes	1 (14,264)	**SOE=Moderate** No difference in on-treatment analyses (HR 0.89; 95% CI 0.73 to 1.10)
Myocardial infarction	1 (14,264)	**SOE=Moderate** No difference in on-treatment analyses (HR 0.81; 95% CI 0.63 to 1.06)
Xa Inhibitor (Apixaban) vs. ASA		
Stroke or systemic embolism	1 (5,599)	**SOE=High** Apixaban reduced risk (HR 0.45; 95% CI 0.32 to 0.62)
Ischemic stroke	1 (5,599)	**SOE=High** Apixaban reduced risk (HR 0.37; 95% CI 0.25 to 0.55)
Hemorrhagic stroke	1 (5,599)	**SOE=Moderate** Trend toward a reduction in risk with apixaban (HR 0.67; 95% CI 0.24 to 1.88)
Major bleeding	1 (5,599)	**SOE=High** No difference (HR 1.13; 95% CI 0.74 to 1.75)
Minor bleeding	1 (5,599)	**SOE=Moderate** Apixaban increased risk (HR 1.20; 95% CI 1.00 to 1.53)
Intracranial bleeding	1 (5,599)	**SOE=Low** Trend toward a reduction in risk with apixaban (HR 0.85; 95% CI 0.38 to 1.90)
All-cause mortality	1 (5,599)	**SOE=Low** Trend toward a reduction in risk with apixaban (HR 0.79; 95% CI 0.62 to 1.02)
Death from vascular causes	1 (5,599)	**SOE=Moderate** No difference (HR 0.87; 95% CI 0.66 to 1.17)
Myocardial infarction	1 (5,599)	**SOE=Moderate** No difference (HR 0.86; 95% CI 0.50 to 1.48)
Hospitalization	1 (5,599)	**SOE=High** Apixaban reduced risk (HR 0.79; 95% CI 0.69 to 0.91)
Adverse events	1 (5,599)	**SOE=Moderate** No differences in liver function or other adverse events between therapies
Percutaneous LAA Closure vs. Warfarin		
Ischemic stroke	1 (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 difference between therapies

Table 36. Summary of strength of evidence and effect estimates for KQ 3 (interventions for preventing thromboembolic events) (continued)

Outcome	Number of Subjects (Studies)	SOE and Magnitude of Effect[a] (95% CI)
All strokes	1 (707)	**SOE=Low** Trend toward a benefit of LAA (RR 0.71; 95% CI 0.35 to 1.64)
Major bleeding	1 (707)	**SOE=Low** Less frequent with LAA (3.5% vs. 4.1%)
All-cause mortality	1 (707)	**SOE=Low** Trend toward a benefit of LAA (RR 0.62; 95% CI 0.34 to 1.24)
Adverse events	1 (707)	**SOE=Moderate** Higher rate with LAA (RR 1.69; 95% CI 1.01 to 3.19)

[a]All strength of evidence ratings of "Insufficient" are shaded.
Abbreviations: ASA=aspirin; CI=confidence interval; HR hazard ratio; LAA=left atrial appendage; RCT=randomized controlled trial; RR=relative risk; SOE=strength of evidence

KQ 4. Anticoagulation Strategies in Patients Undergoing Invasive Procedures

We identified 13 studies that assessed the comparative safety and effectiveness of available strategies for anticoagulation in patients with nonvalvular AF who are undergoing invasive procedures. These studies differed in design and invasive procedure, and they encompassed a wide variety of anticoagulation strategies, making synthesis of the findings difficult. Across the outcomes, the studies were often inconsistent, but given the variability described immediately above, the reasons for these inconsistencies are uncertain. As Table 37 demonstrates, we had insufficient evidence to draw conclusions about any of the outcomes of interest in this KQ. Details about the specific components of these ratings (risk of bias, consistency, directness, and precision) are available in the Results section.

Table 37. Summary of strength of evidence and effect estimates for KQ 4 (anticoagulation therapies for patients undergoing invasive procedures)

Outcome	Number of Studies (Subjects)	Strength of Evidence and Effect Estimate[a]
OAC After PCI With Stenting		
Major bleeding	3 (689)	**SOE=Insufficient**
Mortality	2 (585)	**SOE=Insufficient**
Myocardial infarction	2 (585)	**SOE=Insufficient**
Bridging Therapies		
Major and minor bleeding	6 (2,167)	**SOE=Insufficient**
Mortality	5 (1,932)	**SOE=Insufficient**
Other thomboembolic outcomes	5 (1,932)	**SOE=Insufficient**
Use of Dabigatran in Periprocedural Setting		
Major and minor bleeding	3 (5,037)	**SOE=Insufficient**

[a]All strength of evidence ratings of "Insufficient" are shaded.
Abbreviations: CI=confidence interval; OAC=oral anticoagulation; PCI=percutaneous coronary intervention; SOE=strength of evidence

KQ 5. Strategies for Switching Between Warfarin and Novel Oral Anticoagulants

We did not identify any relevant studies to assess the comparative safety and effectiveness of available strategies for switching between warfarin and other novel oral anticoagulants, in patients with nonvalvular AF. Although an important clinical question needing future research, the current evidence was insufficient to support any findings concerning this KQ.

KQ 6. Stroke Prevention After a Hemorrhagic Event

We did not identify any relevant studies to assess 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 AF. Although an important clinical question needing future research, the current evidence was insufficient to support any findings concerning this KQ.

Findings in Relationship to What Is Already Known

The need to ensure adequate benefit given the known bleeding risks of warfarin has led to the development of risk scores for thromboembolism and bleeding in patients with AF 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. A bleeding score, HAS-BLED, has recently been developed and was also reviewed. Although the $CHADS_2$, CHA_2DS_2VASc, and HAS-BLED scores aid in estimating the risk of stroke and bleeding in patients with AF and help guide decisions regarding the use of warfarin, the value of these scores in guiding decisionmaking in patients with AF receiving other novel agents is still emerging, with evidence so far based solely on patients in RCTs rather than on actual clinical practice. Further improvement in the tools and methods for risk stratification of both stroke and bleeding will be important to better individualize treatment using novel oral anticoagulants in patients with AF.

With more available treatments, our review suggests that not only do risk algorithms need to be updated, but physician decisionmaking about when to use which agent does as well. When anticoagulating a patient with an acute coronary syndrome, for example, physicians have an extensive array of effective parenteral and oral agents from which to choose. However, until very recently, there was only one established oral anticoagulant available for stroke prophylaxis 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. Historically, this fundamental lack of choices in oral anticoagulation in AF was particularly challenging, given the significant heterogeneity present in the increasingly elderly AF population. In the setting of multiple limitations of current treatment with warfarin or other vitamin K antagonists (VKAs), several new oral anticoagulants have been developed for stroke prevention in nonvalvular AF. Trials of dabigatran, rivaroxaban, and apixaban have demonstrated favorable efficacy and safety results compared with warfarin, but conclusions about the comparative efficacy and safety of the newer oral anticoagulants cannot be drawn because these medications have not been directly compared with one another, and indirect (cross-trial) comparisons may not be reliable. In addition, the trials of these newer agents used different dosing strategies, were performed in different health systems, used varying event

definitions, and recruited populations at varying risk for stroke and bleeding. The newer oral anticoagulants do, however, have different attributes and important advantages over warfarin. After many years without options, they offer new alternatives for the treatment of patients with nonvalvular AF who are at risk for stroke. Specifically, our review adds the following to what is already known within the field of stroke prevention for patients with AF:

- New oral anticoagulants preserve the benefits of warfarin for stroke prevention, and two of them (apixaban and higher dose dabigatran) have been demonstrated in large RCTs to be more effective than warfarin.
- In addition to these stroke prevention benefits, the new oral anticoagulants appear to be safer than warfarin in that:
    - All of them caused less intracranial bleeding than warfarin.
    - Two of them (apixaban or lower dose dabigatran) caused less major bleeding, including gastrointestinal bleeding, than warfarin.
- For patients not suitable for oral anticoagulation, apixaban was more effective than aspirin in stroke prevention. In addition, apixaban was better tolerated than and as safe as aspirin.
- All the new oral anticoagulants tested in a blinded fashion were better tolerated than warfarin, and rates of study drug discontinuation were lower with the new agents than with warfarin.
- Apixaban reduced all-cause mortality in patients with AF. Dabigatran and rivaroxaban appear to have similar all-cause mortality as warfarin.

Despite all the potential advantages of the new drugs demonstrated in the clinical trials when compared with warfarin, the new drugs still do not have a well-validated and studied immediate antidote. Similarly, although there are data showing that fresh frozen plasma or vitamin K can help in normalizing INRs for warfarin-treated patients, there are not good data on actually stopping or reversing bleeding events for them. 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 novel drugs 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. This half-life is similar to the time needed to reverse INR (not bleeding) of patients on warfarin with vitamin K. The shorter half-life of these novel agents may, however, be a disadvantage in poorly compliant patients, emphasizing the need for additional evidence outside of RCTs and within actual clinical practice.

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.

Nearly all the studies were conducted in Europe, the United States or Canada, suggesting that the level of care and co-medications were roughly similar to those available to the U.S. population. Table 38 illustrates the specific issues with the applicability of our included evidence base by KQ.

Table 38. Potential issues with applicability of included studies

Issues	Key Question						
	KQ 1 N=37	KQ 2 N=17	KQ 3 N=43	KQ 4 N=13	KQ 5 N=0	KQ 6 N=0	Total[a] N=92
Population (P)							
Narrow eligibility criteria and exclusion of those with comorbidities	0	0	2	0	0	0	2
Large differences between demographics of study population and community patients	2	0	2	0	0	0	4
Narrow or unrepresentative severity, stage of illness, or comorbidities	0	0	0	0	0	0	0
Run-in period with high exclusion rate for nonadherence or side effects	0	0	1	0	0	0	1
Event rates much higher or lower than observed in population-based studies	0	0	1	0	0	0	1
Intervention (I)							
Doses or schedules not reflected in current practice	0	0	1	0	0	0	1
Monitoring practices or visit frequency not used in typical practice	1	1	0	0	0	0	1
Older versions of an intervention no longer in common use	2	1	1	0	0	0	3
Cointerventions that are likely to modify effectiveness of therapy	0	0	1	0	0	0	1
Highly selected intervention team or level of training/proficiency not widely available	0	0	0	0	0	0	0
Comparator (C)							
Inadequate comparison therapy	1	2	1	1	0	0	5
Use of substandard alternative therapy	0	0	0	0	0	0	0
Outcomes (O)							
Composite outcomes that mix outcomes of different significance	2	1	2	0	0	0	4
Short-term or surrogate outcomes	1	0	7	0	0	0	8
Setting (S)							
Standards of care differ markedly from setting of interest	0	0	0	0	0	0	0
Specialty population or level of care differs from that seen in community	0	0	0	0	0	0	0

[a]Some studies were relevant to more than one KQ. Abbreviation: KQ=Key Question

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 (9% of studies overall, representing 3%, 0%, 16%, and 0% of KQ 1, KQ 2, KQ 3, and KQ 4 studies, respectively); concerns about large differences between demographics of study populations and community patients in terms of age, renal function, and comorbidities (4% of studies overall, representing 5%, 0%, 5%, and 0% of KQ 1, KQ 2, KQ 3, and KQ 4 studies, respectively); and concerns about use of older versions of an intervention no longer in common

use (3% of studies overall, representing 5%, 6%, 2%, and 0% of KQ 1, KQ 2, KQ 3, and KQ 4 studies, respectively).

Implications for Clinical and Policy Decisionmaking

Stroke prevention in patients with nonvalvular AF in contemporary clinical practice is complex and challenging, but critically important given the morbidity and mortality associated with stroke events. The use of common antiplatelet agents such as aspirin and traditional anticoagulants can significantly reduce the risk of stroke in patients with AF, however, bleeding risks increase with these agents, potentially attenuating their effects. Newer anticoagulants promise improved efficacy with reduction in bleeding events and more predictable pharmacokinetics. However, the long-term effects of these newer 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.

Despite the availability and validation of numerous risk tools for both stroke and bleeding risk in patients with nonvalvular AF, evidence has shown that the routine use of these tools is low, and patients are sometimes paradoxically treated (e.g., low-risk patients with anticoagulants and high-risk patients with antiplatelet or no therapy). At the time the current U.S. guidelines for management of AF were developed (2006,[1] with a focused update in 2011[62]), the primary focus was on risk stratification and treatment with antiplatelets or VKAs. Since that time, newer anticoagulants have entered the marketplace, but the guidelines have not yet been updated to reflect this new evidence. Furthermore, there have not been any comparative effectiveness studies examining these new agents head-to-head. The task of stroke prevention for busy clinicians is no longer simply risk stratification and deciding between aspirin versus warfarin, but much more complex. Clinicians will have to understand the risk and benefits, indications, side effects, and monitoring of new anticoagulants, further complicating treatment decisions in patients with AF.

In its most recent update in 2012, the ESC has published guidelines that acknowledge the limitation of current risk tools to identify patients at high risk for thromboembolic risk. In fact, the current ESC guidelines recommend a strategy of identifying those individuals with AF who are “truly low risk” for thromboembolic events, i.e., no risk factors for stroke, and thus do not need oral anticoagulant therapy. The current guidelines recommend all other patients should be considered for oral anticoagulant therapy. To provide further guidance, the AFib Optimal Treatment Task Force convened a roundtable of experts to develop a statement on the best practices for assessing stroke and bleeding risk for anticoagulation decision-making using available risk assessment tools. The group proposed a three-step approach to assessing stroke and bleeding risk in AF patients:

1. Assess and record an individual’s stroke risk annually using an established scoring tool. Intermediate or high risk individuals should be place on an anticoagulant. Aspirin was not recommended by the task force for stroke prophylaxis in AF.
2. If the individual requires anticoagulation therapy, then the bleeding risk should be evaluated to estimate the net clinical benefit of anticoagulation. Risk factors for intracranial hemorrhage should be considered although routine screening for these risk factors was not recommended.
3. The decision to start anticoagulation therapy must reflect patient preferences and values. The patient must also understand the relative benefits and risks involved in the discussion and decision surrounding the clinical net benefit of anticoagulation therapy.

In light of these recent recommendations, the current review underscores that further efforts are needed to continue to refine risk prediction tools, particularly in the context of newly available anticoagulants. With the growing prevalence of digitized medical records, there is an opportunity to monitor the real world uptake of the newer anticoagulants. Additionally, with these electronic records, there will be the opportunity to continue to evaluate and modify risk prediction tools to improve their discrimination for stroke and bleeding risk, particularly with these newer anticoagulants diffusing into clinical practice. Also, newer clinical markers, comorbidities (i.e., renal failure, etc.) and biomarkers should be tested and validated with or alongside current risk tools to improve their discrimination 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. Finally, gaps have been identified in the current evidence for increasingly common clinical scenarios for patients on therapies for stroke prevention. Evidence is needed on the best strategies for patients undergoing invasive procedures, switching among anticoagulant therapies, and starting or restarting anticoagulant therapy in patients with previous major bleeding events.

As new drugs 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. Even though the ESC 2012 guidelines for AF recommend that the critical assessment necessary in the era of newer oral anticoagulants is the differentiation of "truly low-risk" patients—i.e., those who do not need oral anticoagulation—from those who have one or more risk factors for stroke and should be recommended for oral anticoagulation, appropriate and accurate risk assessment is required, as these newer anticoagulants are still not without bleeding risk. 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 newer agents are rapidly entering into broader clinical practice.

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: (1) few or no studies focusing on stroke prevention for patients undergoing invasive procedures (KQ 4), switching between warfarin and other novel anticoagulants (KQ 5), and determining optimal stroke prevention following a hemorrhagic event (KQ 6); (2) inconsistency across studies that assess prediction tools for thromboembolic or bleeding risk in terms of the methods used and findings reported; (3) few studies which compare specific stroke prevention therapies allowing quantitative synthesis especially involving the newer anticoagulant agents (KQ 3); and (4) inadequate comparison therapies in terms of representing either standard of care of novel alternative therapy.

Our review methods also had limitations. Our study was limited to English-language publications. It was the opinion of the investigators and the Technical Expert Panel (TEP) that the resources required to translate non-English articles would not be justified by the low potential likelihood of identifying relevant data unavailable from English-language sources. We also limited our analysis to studies published since 2000. Given the rapidly changing treatment alternatives for stroke prevention for patients with AF it was the opinion of the investigators and

the TEP that this recent literature was the most relevant to today's clinical and policy uncertainties. Finally, as a comparative effectiveness study, for KQ3 we restricted our analysis to studies that compared two active therapies for AF stroke prevention and did not include placebo (only)-controlled trials. Inclusion of such placebo-controlled trials may have allowed additional quantitative analyses to be performed used mixed treatment meta-analyses. We did not perform meta-analysis using indirect comparisons of treatment given the heterogeneity of study designs, therapies, populations, and concomitant therapies in the included studies. Of note, a recent meta-analysis[221] combined 12 studies (3 administering dabigatran, 4 administering rivaroxaban, 2 administering apixaban, and 3 administering edoxaban) involving 54 875 patients and found that these novel oral anticoagulants as a group significantly reduced total mortality (RR, 0.89; 95% CI 0.83 to 0.96), cardiovascular mortality (RR, 0.89; 95% CI 0.82 to 0.98), and stroke/systemic embolism (RR, 0.77; 95% CI 0.70 to 0.86). There was a trend toward reduced major bleeding (RR, 0.86; 95% CI 0.72 to 1.02) and a significant reduction of intracranial hemorrhage (RR, 0.46; 95% CI 0.39 to 0.56). No difference in myocardial infarction was observed. The authors acknowledge the limitation of their analyses given differences in trial design and populations, and given that direct thrombin inhibitors and factor Xa inhibitors have different pharmacodynamic and pharmacokinetic properties.

Research Gaps

In our analyses, we have identified research gaps for all the Key Questions (KQs) examined. We used the framework recommended by Robinson et al. to identify gaps in evidence and describe why these gaps exist.[222] This approach considers PICOTS (Populations, Interventions, Comparators, Outcomes, Timings, and Settings of interest) to identify gaps and classifies gaps as due to (a) insufficient or imprecise information; (b) biased information; (c) inconsistency or unknown consistency; and (d) not the right information. Results are described for each KQ below.

KQs 1–2: Predicting Thromboembolic and Bleeding Risk

While there are several scores available in clinical practice to predict stroke and bleeding in patients with AF, the major limitation of these scores is the overlap of clinical factors that go into both types of scores. We therefore think that the evidence gaps for these two questions are best addressed together.

Many of the available studies for KQ1 and KQ2 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 discrimination, 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.

Additional research is also needed to: (1) refine risk scores to better identify truly "low risk" patients with respect to stroke for whom anticoagulation may not be necessary; (2) gather real-

world data on new anticoagulants; and (3) better define biological age, frailty, and specific brain imaging findings as RFs for ICH.

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. Another challenge is that both stroke events and bleeding events are on a spectrum of severity. 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.

Another issue was not addressed in this review: in an era of personalized medicine, it may be important to have the "omics" profile (genomics, proteomics, metabolomics) incorporated into the risk scores, which could help to more accurately stratify AF patients according to their thromboembolic and bleeding risks.

Additionally, even assuming that an optimal risk prediction score can be identified, further work is needed to clarify how scores should be used prospectively in clinical practice.

Finally, for future studies of available tools, reporting the raw data rather than c-statistics would allow more informative assessment of the predictive model performance. If we had had such raw data, we could have considered the net reclassification index (NRI) or integrated discrimination index, which summarize the incremental benefit of a score when added to a model with other covariates.

Therefore four specific evidence gaps identified from KQ 1 and KQ 2 are:

1. In patients with nonvalvular AF, what are the comparative diagnostic accuracy and impact on clinical decisionmaking of *clinical tools* with modest or better predictive value for predicting the overall clinical risk of patients combining both their risk of stroke and their risk of bleeding?
2. In patients with nonvalvular AF, what are the comparative diagnostic accuracy and impact on clinical decisionmaking of *imaging tools* with modest or better predictive value for predicting the overall clinical risk of patients combining both their risk of stroke and their risk of bleeding?
3. What are the benefits, harms, and costs of incorporating genomics, proteomics, and metabolomics into risk scores for the prediction of thromboembolic and/or bleeding risk?
4. What is the most effective way to prospectively use thromboembolic and/or bleeding risk scores with evidence of modest or better predictive value in clinical practice? Specifically, how can we increase dissemination of point-of-care tools to improve risk assessment and treatment choices for clinicians?

KQ 3: Interventions for Preventing Thromboembolic Events

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. Given the risks associated with AF, the growing number of patients with AF, and

the costs and risks associated with stroke prevention for AF, a better understanding of comparative safety and effectiveness of newer anticoagulant therapies is of paramount importance. There is a need for further study of these newer agents, particularly focusing on methods of monitoring adequacy of anticoagulation, as well as the development of antidotes for severe bleeding events. There is also a need for future studies in special populations and clinical scenarios. In addition, 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 should be avoided. Patients with AF usually have comorbidities that require the use of antithrombotic agents other than those used to treat AF. Many antithrombotic agents are available at different doses for different clinical indications. 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. For example, nothing is known about the use of triple therapy in patients with coronary artery disease/acute coronary syndrome and AF in the new era with new antiplatelet (prasugrel and ticagrelor) and new anticoagulant agents (dabigatran, rivaroxaban, apixaban).

There are also many novel invasive treatments for AF. Studies are needed to determine if and how anticoagulation strategies should be modified for patients receiving these procedures. For example, studies are needed to determine the comparative effectiveness and safety of new oral anticoagulants and percutaneous left atrial appendage (LAA) closure for stroke prevention in nonvalvular AF patients. Studies are needed to determine if and when it is safe to discontinue all oral anticoagulants after successful AF ablation. Studies also are needed to determine the thromboembolic and bleeding risk associated with the procedures themselves over the long term.

Therefore, we have identified the following specific evidence gaps related to KQ 3:

1. What are the comparative safety and effectiveness of specific anticoagulation therapies, antiplatelet therapies, and procedural interventions for preventing thromboembolic events?
    a. For the above evidence gap, we suggest focusing specifically on the comparative effectiveness of Factor IIa inhibitors, Xa inhibitors, and other novel anticoagulants and procedural interventions.
    b. Safety issues include reversal of anticoagulant effects for severe bleeding events and monitoring of therapeutic status.
2. What are the comparative safety and effectiveness of specific anticoagulation therapies, antiplatelet therapies, and procedural interventions for preventing thromboembolic events specific to patients who have recently undergone rate or rhythm control procedures for treating their AF?
    a. For the above evidence gap, we suggest focusing on methods of determining the comparative effectiveness and safety of available stroke prevention therapies, and strategies for determining longer term therapy given successful AF treatment.
3. What are the comparative safety and effectiveness of specific anticoagulation therapies, antiplatelet therapies, and procedural interventions for preventing thromboembolic events specific to special subpopulations such as patients with advanced renal failure or on dialysis, elderly patients, and others?
    a. For the above evidence gap, we suggest focusing specifically on the comparative effectiveness of Factor IIa inhibitors, Xa inhibitors, and other novel anticoagulants and procedural interventions

KQ 4: Anticoagulation Strategies in Patients Undergoing Invasive Procedures

Our review identified limited studies assessing the optimal strategy for anticoagulation either peri-radiofrequency ablation (RFA) or in the setting of other operative procedures. In addition, the few studies available suggest that ischemic event rates are likely to be extremely low; thus, trials powered adequately to assess the impact of different strategies, especially on ischemic events, would have to be large. Given the number of these procedures performed per year, as well as the apparent uncertainty about optimal treatment of the patients undergoing such procedures, RCTs to answer these questions are sorely needed. Trials should be done with traditional anticoagulants as well as the newer antiplatelet and antithrombotic agents. Given the number of treatment strategies available, initial research might be focused on comparing continued anticoagulant therapy versus bridging therapies versus interruption of therapy (i.e., stopping anticoagulant therapy before the procedure). Given the current insufficient evidence pertinent to this KQ, we think that the original KQ represents the remaining evidence gap and need for future research. Perhaps an additional evidence gap, given the need for a large sample size in an RCT addressing this question, would be explore whether study designs other than RCTs would possibly help decrease the evidence gap in this area.

KQs 5–6: Switching Between Warfarin and Novel Oral Anticoagulants and Stroke Prevention After a Hemorrhagic Event

We found no peer-reviewed published studies for either of these KQs, and so these are both clearly remaining evidence gaps, needing future evidence generation before evidence synthesis is possible.

Due to the increasing popularity of the new Xa agents, RCTs are needed to establish evidence to guide providers in managing patients with AF who are currently on warfarin and being switched to the newer Xa agents. Trials should seek to provide directions for managing patients who may be at different risk levels (as defined by $CHADS_2$, CHA_2DS_2VASc, or Framingham risk scores), including type of AF, sex, age, and other co-existing risk factors. Additionally, evidence needs to be published in peer-reviewed journals on how to manage patients being switched off of the newer Xa agents and onto warfarin.

Similarly, trials are needed to determine the comparative safety and effectiveness of available strategies for resuming anticoagulation therapy following a hemorrhagic event. These trials should be evaluated in patients based on type of hemorrhagic event, as well as based on traits that may affect risk of bleeding, such as age, comorbidities, and other medical therapies.

Conclusions

Overall, we found that $CHADS_2$ and CHA_2DS_2-VASc scores have the best prediction for stroke events in patients with AF among the risk scores we reviewed, whereas HAS-BLED provides the best prediction for 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 outweigh the stroke prevention benefit. 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.

Newer anticoagulants show early promise of reducing stroke and bleeding events when compared with warfarin, and apixaban shows safety and efficacy in patients who are not candidates for warfarin. However, further studies are required for key clinical scenarios involving anticoagulation use and procedures, switching or bridging therapies, and when to start anticoagulation after a hemorrhagic event.

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Abbreviations

AF	atrial fibrillation
AHRQ	Agency for Healthcare Research and Quality
ARISTOTLE	Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation
ASA	aspirin
ATRIA	Anticoagulation and Risk Factors in Atrial Fibrillation
AVERROES	Apixaban Versus Acetylsalicylic acid (ASA) to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment
BRI	Bleeding Risk Index
BRIDGE	Bridging Anticoagulation in Patients who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure or Surgery
CDSR	Cochrane Database of Systematic Reviews
CER	Comparative Effectiveness Review
$CHADS_2$	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
CT	computed tomography
eGFR	estimated glomerular filtration rate
ESC	European Society of Cardiology
FDA	U.S. Food and Drug Administration
GUSTO	Global Use of Strategies to Open Occluded Coronary Arteries
GWTG	Get With The Guidelines
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, Re-bleeding risk (2 points), Hypertension (uncontrolled), Anemia, Genetic factors, Excessive fall risk, Stroke
HR	hazard ratio
ICH	intracranial hemorrhage
INR	international normalized ratio
ISTH	International Society on Thrombosis and Haemostasis
ITT	intention-to-treat
IV	intravenous
KQ	Key Question
LAA	left atrial appendage
LMWH	low molecular weight heparin

MI	myocardial infarction
MRA	magnetic resonance angiography
MRI	magnetic resonance imaging
NIH	National Institutes of Health
NRI	net reclassification improvement
OR	odds ratio
PCI	percutaneous coronary intervention
PICOTS	Populations, Interventions, Comparators, Outcomes, Timings, and Settings of interest
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QUADAS-2	QUality Assessment tool for Diagnostic Accuracy Studies-2
RCT	randomized controlled trial
RE-LY	Randomized Evaluation of Long-Term Anticoagulation Therapy
RFA	radiofrequency ablation
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
SDT_{INR}	standard deviation of transformed international normalized ratio
SE	standard error
TEE	transesophageal echocardiography
TEP	Technical Expert Panel
TIA	transient ischemic attack
TIMI	Thrombolysis in Myocardial Infarction
TTE	transthoracic echo
TTR	time in therapeutic range
VKA	vitamin K antagonist

Appendix A. Exact Search Strings

PubMed® Search Strategy (August 14, 2012)

KQ1: 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

KQ2: 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

KQ3: 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

KQ4: 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

KQ5: 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

KQ6: 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 (August 14, 2012)

Platform: Embase.com

KQ1: 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

KQ2: 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

KQ3: 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

KQ4: 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

KQ5: 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

KQ6: 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 (August 14, 2012)

Platform: Wiley
Database searched: Cochrane Database of Systematic Reviews

KQ1: 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

KQ2: 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

KQ3: 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

KQ4: 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

KQ5: 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

KQ6: 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

Grey Literature Searches

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
    - Women
    - Pregnant women
    - 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, Dabigatran (Pradaxa), Rivaroxaban (Xarelto), Apixaban (Eliquis), Edoxaban (DU-176b)
                    - If 'Vitamin K antagonists' selected:
                        - Warfarin (Coumadin), Other
        - If 'Procedural interventions' selected:
            - Procedural interventions
                - Surgical LAA resection, Surgical LAA ligation, Surgical – other (specify), Minimally invasive – Atriclip, 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
    - Intercerebral hemorrhage
    - Subdural hematoma
    - Major bleed
    - Minor bleed
    - Myocardial infarction
    - All-cause mortality
    - CV mortality
    - Health-related QOL/Functional capacity
    - Healthcare utilization – Hospital admissions
    - Healthcare utilization – Other measures
    - Long-term adherence to therapy
    - 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 of individual risk factor being tested
    - $CHADS_2$ score
    - CHA_2DS_2-VASc 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
- 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. 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

Quality

- 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

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.

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.

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.

Azoulay L, Dell'aniello S, Simon TA, et al. A net clinical benefit analysis of warfarin and aspirin on stroke in patients with atrial fibrillation: a nested case-control study. BMC Cardiovasc Disord. 2012;12(1):49. PMID: 22734842.

Baruch L, Gage BF, Horrow J, et al. Can patients at elevated risk of stroke treated with anticoagulants be further risk stratified?. Stroke. 2007;38(9):2459-63. PMID: 17673721.

Beinart R, Heist EK, Newell JB, et al. Left atrial appendage dimensions predict the risk of stroke/TIA in patients with atrial fibrillation. J Cardiovasc Electrophysiol. 2011;22(1):10-5. PMID: 20662984.

Berge E, Abdelnoor M, Nakstad PH, et al. Low molecular-weight heparin versus aspirin in patients with acute ischaemic stroke and atrial fibrillation: a double-blind randomised study. HAEST Study Group. Heparin in Acute Embolic Stroke Trial. Lancet. 2000;355(9211):1205-10. PMID: 10770301.

Bousser MG, Bouthier J, Buller HR, et al. Comparison of idraparinux with vitamin K antagonists for prevention of thromboembolism in patients with atrial fibrillation: a randomised, open-label, non-inferiority trial. Lancet. 2008;371(9609):315-21. PMID: 18294998.

Bunch TJ, Crandall BG, Weiss JP, et al. Warfarin is not needed in low-risk patients following atrial fibrillation ablation procedures. J Cardiovasc Electrophysiol. 2009;20(9):988-93. PMID: 19473299.

Burton C, Isles C, Norrie J, et al. The safety and adequacy of antithrombotic therapy for atrial fibrillation: a regional cohort study. Br J Gen Pract. 2006;56(530):697-702. PMID: 16954003.

Cafolla A, Campanelli M, Baldacci E, et al. Oral anticoagulant therapy in Italian patients 80 yr of age or older with atrial fibrillation: A pilot study of low vs. standard PT/INR targets. Eur J Haematol. 2012;89(1):81-86. PMID: 22519759.

Connolly S, Pogue J, Hart R, et al. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. Lancet. 2006;367(9526):1903-12. PMID: 16765759.

Connolly SJ, Eikelboom J, Joyner C, et al. Apixaban in patients with atrial fibrillation. N Engl J Med. 2011;364(9):806-17. PMID: 21309657.

Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361(12):1139-51. PMID: 19717844.

Connolly SJ, Pogue J, Hart RG, et al. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. N Engl J Med. 2009;360(20):2066-78. PMID: 19336502.

Crandall MA, Horne BD, Day JD, et al. Atrial fibrillation significantly increases total mortality and stroke risk beyond that conveyed by the CHADS2 risk factors. Pacing Clin Electrophysiol. 2009;32(8):981-6. PMID: 19659615.

Diener HC, Connolly SJ, Ezekowitz MD, et al. Dabigatran compared with warfarin in patients with atrial fibrillation and previous transient ischaemic attack or stroke: a subgroup analysis of the RE-LY trial. Lancet Neurol. 2010;9(12):1157-63. PMID: 21059484.

Diener HC, Eikelboom J, Connolly SJ, et al. Apixaban versus aspirin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a predefined subgroup analysis from AVERROES, a randomised trial. Lancet Neurol. 2012;11(3):225-31. PMID: 22305462.

Doucet J, Greboval-Furstenfeld E, Tavildari A, et al. Which parameters differ in very old patients with chronic atrial fibrillation treated by anticoagulant or aspirin? Antithrombotic treatment of atrial fibrillation in the elderly. Fundam Clin Pharmacol. 2008;22(5):569-74. PMID: 18844728.

Easton JD, Lopes RD, Bahit MC, et al. Apixaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a subgroup analysis of the ARISTOTLE trial. Lancet Neurol. 2012;11(6):503-11. PMID: 22572202.

Eikelboom JW, Connolly SJ, Gao P, et al. Stroke risk and efficacy of apixaban in atrial fibrillation patients with moderate chronic kidney disease. J Stroke Cerebrovasc Dis. 2012;21(6):429-35. PMID: 22818021.

Eikelboom JW, Wallentin L, Connolly SJ, et al. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) trial. Circulation. 2011;123(21):2363-72. PMID: 21576658.

Ezekowitz MD, Reilly PA, Nehmiz G, et al. Dabigatran with or without concomitant aspirin compared with warfarin alone in patients with nonvalvular atrial fibrillation (PETRO Study). Am J Cardiol. 2007;100(9):1419-26. PMID: 17950801.

Fang MC, Go AS, Chang Y, et al. A new risk scheme to predict warfarin-associated hemorrhage: The ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) Study. J Am Coll Cardiol. 2011;58(4):395-401. PMID: 21757117.

Fang MC, Go AS, Chang Y, et al. Comparison of risk stratification schemes to predict thromboembolism in people with nonvalvular atrial fibrillation. J Am Coll Cardiol. 2008;51(8):810-5. PMID: 18294564.

Fosbol EL, Wang TY, Li S, et al. Safety and effectiveness of antithrombotic strategies in older adult patients with atrial fibrillation and non-ST elevation myocardial infarction. Am Heart J. 2012;163(4):720-8. PMID: 22520540.

Fox KA, Piccini JP, Wojdyla D, et al. Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-valvular atrial fibrillation and moderate renal impairment. Eur Heart J. 2011;32(19):2387-94. PMID: 21873708.

Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. Eur Heart J. 2012;33(12):1500-10. PMID: 22246443.

Frost L, Johnsen SP, Pedersen L, et al. Atrial fibrillation or flutter and stroke: a Danish population-based study of the effectiveness of oral anticoagulation in clinical practice. J Intern Med. 2002;252(1):64-9. PMID: 12074740.

Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA. 2001;285(22):2864-70. PMID: 11401607.

Gage BF, Yan Y, Milligan PE, et al. Clinical classification schemes for predicting hemorrhage: results from the National Registry of Atrial Fibrillation (NRAF). Am Heart J. 2006;151(3):713-9. PMID: 16504638.

Gallego P, Roldan V, Torregrosa JM, et al. Relation of the HAS-BLED bleeding risk score to major bleeding, cardiovascular events, and mortality in anticoagulated patients with atrial fibrillation. Circ Arrhythm Electrophysiol. 2012;5(2):312-8. PMID: 22319005.

Gao F, Zhou YJ, Wang ZJ, et al. Comparison of different antithrombotic regimens for patients with atrial fibrillation undergoing drug-eluting stent implantation. Circ J. 2010;74(4):701-8. PMID: 20208381.

Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365(11):981-92. PMID: 21870978.

Hammerstingl C, Schmitz A, Fimmers R, et al. Bridging of chronic oral anticoagulation with enoxaparin in patients with atrial fibrillation: results from the prospective BRAVE registry. Cardiovasc Ther. 2009;27(4):230-8. PMID: 19903186.

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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 Available in English

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Appendix E. Key to Included Primary and Companion Articles

Appendix Table E-1. Key to included primary and companion articles*

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]*
ACTIVE-W (The Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events - W)	Connolly, 2006[5]	Healey, 2008[6] Hohnloser, 2007[7] Connolly, 2006[4]*
AFCAS (Atrial Fibrillation undergoing Coronary Artery Stenting)	Lahtela, 2012[8]	None
AMADEUS (Evaluating the Use of SR34006 Compared to Warfarin or Acenocoumarol in Patients With Atrial Fibrillation)	Bousser, 2008[9]	Apostolakis, 2012[10] Lane, 2011[11]
ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation)	Granger, 2011[12]	Easton, 2012[13] Hohnloser, 2012[14] Lopes, 2012[15] Lopes, 2010[16]*
ARISTOTLE-J (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation—Japanese)	Ogawa, 2011[17]	
ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation)	Fang, 2011[18]	None
	Fang, 2008[19]	None
	Hylek, 2003[20]	Go, 1999[21]*
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[22]	Diener, 2012[23] Eikelboom, 2012[24] Eikelboom, 2010[25]*
BAFTA (Birmingham Atrial Fibrillation Treatment of the Aged Study)	Mant, 2007[26]	Hobbs, 2011[27] Mant, 2003[28]*
BRAVE (Bonn Registry of Alternative Anticoagulation to Prevent Vascular Events)	Hammerstingl, 2009[29]	None
Belgrade Atrial Fibrillation Study	Potpara, 2012[30]	None
CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance)	Hart, 2008[31]	None
CLAAF (Clopidogrel-Aspirin Atrial Fibrillation)	Lorenzoni, 2004[32]	None
CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress ADverse Outcomes with Early Implementation of the ACC/AHA Guidelines)	Fosbol, 2012[33]	None
Danish National Patient Registry	Olesen, 2012[34]	None
ELAT (Embolism in Left Atrial Thrombi)	Stollberger, 2004[35]	None
Euro Heart Survey for AF	Pisters, 2010[36]	Nieuwlaat, 2008[37]* Nieuwlaat, 2005[38]*
	Lip, 2010[39]	None
HAEST (Heparin in Acute Embolic Stroke Trial)	Berge, 2000[40]	None
J-ROCKET AF (Japanese Rivaroxaban Once-daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation)	Hori, 2012[41]	None
Loire Valley Atrial Fibrillation Project	Lip, 2012[42]	Olesen, 2012[43]
Medicare National Stroke Project	Shireman, 2004[44]	None
NRAF (National Registry of Atrial Fibrillation)	Gage, 2006[45]	None
	Gage, 2001[46]	None
PETRO (Prevention of Embolic and Thrombotic Events in Patients with Persistent AF)	Ezekowitz, 2007[47]	None
PROTECT-AF (Percutaneous Closure of the Left Atrial Appendage Versus Warfarin Therapy for Prevention of Stroke in Patients With Atrial Fibrillation)	Holmes, 2009[48]	Viles-Gonzalez, 2012[49] Fountain, 2006[50]*

Study Designation	Primary Abstracted Article	Companion Articles*
RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy)	Connolly, 2009[51]	Oldgren, 2011[52] Eikelboom, 2011[53] Diener, 2010[54] Hohnloser, 2012[55] Nagarakanti, 2011[56] Hart, 2012[57] Healey, 2012[58] Ezekowitz, 2009[59]*
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[60]	Hankey, 2012[61] Fox, 2011[62] Anonymous, 2010[63]*
SPORTIF (Stroke Prevention using an ORal Thrombin Inhibitor in atrial Fibrillation)	Baruch, 2007[64]	Lip, 2011[65] Lip, 2010[66] Halperin, 2003[67]* Olsson, 2003[68]*
Swedish Atrial Fibrillation cohort study	Friberg, 2012[69]	None
Framingham Heart Study	Sam, 2004[70]	None
	Wang, 2003[71]	None
WASPO (Warfarin Versus Aspirin for Stroke Prevention in Octogenarians with Atrial Fbrillation)	Rash, 2007[72]	None
None	Ad, 2010[73]	None
None	Aspinall, 2005[74]	None
None	Azoulay, 2012[75]	None
None	Beinart, 2011[76]	None
None	Bunch, 2009[77]	None
None	Burton, 2006[78]	None
None	Cafolla, 2012[79]	None
None	Crandall, 2009[80]	None
None	Doucet, 2008[81]	None
None	Frost, 2002[82]	None
None	Gallego, 2012[83]	None
None	Gao, 2010[84]	None
None	Hansen, 2010[85]	Hansen, 2008[86]*
None	Inoue, 2006[87]	Nozawa, 2004[88]*
None	Jacobs, 2009[89]	None
None	Kiviniemi, 2012[90]	None
None	Komatsu, 2010[91]	None
None	Kwak, 2010[92]	None
None	Lakkireddy, 2012[93]	None
None	Lee, 2010[94]	None
None	Lind, 2012[95]	None
None	Maegdefessel, 2008[96]	None
None	Manzano-Fernandez, 2008[97]	None
None	Masaki, 2009[98]	None
None	Miyazaki, 2001[99]	None
None	Morgan, 2009[100]	None
None	Naganuma, 2012[101]	None
None	Nair, 2009[102]	None
None	Okuyama, 2008[103]	None
None	Olesen, 2011[104]	None
None	Olesen, 2011[105]	None
None	Olesen, 2011[106]	None
None	Olesen, 2012[107]	None
None	Poli, 2009[108]	Poli, 2009[109]
None	Poli, 2011[110]	None
None	Poli, 2011[111]	None
None	Rietbrock, 2008[112]	Rietbrock, 2009[113]

Study Designation	Primary Abstracted Article	Companion Articles*
None	Roldan, 2012[114]	None
None	Ruiz Ortiz, 2008[115]	None
None	Ruiz Ortiz, 2010[116]	None
None	Ruiz-Nodar, 2008[117]	None
None	Ruiz-Nodar, 2011[118]	None
None	Ruiz-Nodar, 2012[119]	None
None	Saad, 2011[120]	None
None	Sadanaga, 2010[121]	Sadanaga, 2010[122]*
None	Shireman, 2006[123]	None
None	Snipelisky, 2012[124]	None
None	Stoddard, 2003[125]	None
None	Taillandier, 2012[126]	None
None	Tamura, 2012[127]	None
None	Tentschert, 2004[128]	None
None	Tsivgoulis, 2005[129]	None
None	Van Staa, 2011[130]	None
None	Vemmos, 2004[131]	None
None	Vemmos, 2006[132]	None
None	Wazni, 2007[133]	None
None	Weitz, 2010[134]	None
None	Yamaguchi, 2000[135]	None
None	Yamashita, 2012[136]	None
None	Yang, 2011[137]	None
None	Yigit, 2003[138]	None

*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).

References to Appendix E

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Appendix F. Study Characteristics Tables

Appendix Table F-1. Study characteristics—KQ 1

Study: Author Year Acronym	Study Design; Setting; Location; Funding Source; Quality	Tools Assessed	Total N	Mean Follow up period	Mean Age	Special Population
Friberg, 2012[1] Swedish Atrial Fibrillation cohort study	Prospective cohort; Inpatient, Outpatient; Europe; Government, Nongovernment, Nonindustry; Low risk of bias	$CHADS_2$ score CHA_2DS_2-VASc score Framingham score HAS-BLED $HEMORR_2HAGES$	170,291	Total: Median 1.4 yr (IQR 1.8)	Total: 76.2	None
Lind, 2012[2]	Retrospective cohort; Outpatient; Europe; NR; High risk of bias	INR	19,180	NR	NR	None
Naganuma, 2012[3]	Retrospective cohort; Outpatient; Asia Nongovernment, Nonindustry; Low risk of bias	$CHADS_2$ score HAS-BLED	845	Total: Median 27 mo	Total: Median 74	None
Olesen, 2012[4] Danish National Patient Registry	Retrospective cohort; Inpatient, NR; Europe; None; Unclear	$CHADS_2$ score	87,202	NR	Arm 1: 74.2 (SD 14.2) Arm 2: 76.9 (SD 10.3)	None
Olesen, 2012[5]	Retrospective cohort; Outpatient; Europe; NR; Low risk of bias	$CHADS_2$ score CHA_2DS_2-VASc score	47,576	Total: 12 yr Arm 1: 12 yr Arm 2: 12 yr	Total: 69.4 (SD 14.7)	None

Study: Author Year Acronym	Study Design; Setting; Location; Funding Source; Quality	Tools Assessed	Total N	Mean Follow up period	Mean Age	Special Population
Olesen, 2012[6]	Retrospective cohort; Inpatient; Europe; NR; Unclear	$CHADS_2$ score CHA_2DS_2-VASc score	6,438	NR	Arm 1: 54.9 (46.5-60.5) Arm 2: 70.7 (68.2-72.9) Arm 3: 81.7 (78.3-85.9)	None
Potpara, 2012[7] Belgrade Atrial Fibrillation Study	Prospective cohort; NR; Europe; Government; Unclear	$CHADS_2$ score CHA_2DS_2-VASc score	345	Total: 12.1 yr (SD 7.3)	Total: 43.2 (SD 9.9)	None
Ruiz-Nodar, 2012[8]	Retrospective cohort; NR; Europe; NR; High risk of bias	HAS-BLED CHA_2DS_2-VASc score	590	Total: ~12 mo	Total: 72.2 (SD 8.1)	None
Tamura, 2012[9]	Prospective cohort; Inpatient; Asia; Government, Nongovernment, Nonindustry; Low risk of bias	TTE	179	Total: Median 397 days	Total: 72 (SD 11)	Patients with prior stroke
Beinart, 2011[10]	Retrospective cohort; Inpatient, Outpatient; US; Other (specify) : The study was supported by a grant from the Deane Institute for Integrative Research in Stroke and Atrial Fibrillation at the Massachusetts General Hospital.; High risk of bias	Cardiac MRI	144	NR	Total: 54.5 (SD 9.9)	None

Study: Author Year Acronym	Study Design; Setting; Location; Funding Source; Quality	Tools Assessed	Total N	Mean Follow up period	Mean Age	Special Population
Olesen, 2011[11]	Retrospective cohort; Inpatient; Europe; NR; High risk of bias	$CHADS_2$ score CHA_2DS_2-VASc score	132,372	Total: Max 12 yr	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[12]	Retrospective cohort; Outpatient; Europe; None; Low risk of bias	$CHADS_2$ score CHA_2DS_2-VASc score	73,538	NR	NR	None
Poli, 2011[13]	Prospective cohort; NR; Europe; None; Low risk of bias	$CHADS_2$ score Bleeding Risk Index	3,302	Total: Median 2.3 yr (IQR 0.8 to 4.4)	Total: Median 74 (IQR 68 to 80)	None
Poli, 2011[14]	Prospective cohort; Outpatient; Europe; NR; Low risk of bias	$CHADS_2$ score CHA_2DS_2-VASc score	662	Total: 3.6 yr (SD 2.7) Arm 1: 3.6 yr (SD 2.7) Arm 2: 3.6 yr (SD 2.7)	Total: 74 (SD 7.7)	None
Ruiz-Nodar, 2011[15]	Retrospective cohort; Outpatient; Europe; NR; Low risk of bias	$CHADS_2$ score	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
Van Staa, 2011[16]	Retrospective cohort; Outpatient; UK; NR; High risk of bias	$CHADS_2$ score CHA_2DS_2-VASc score Framingham score	79,844	Total: 4.0 yr	Total: 73.3 (SD 12.5)	None

Study: Author Year Acronym	**Study Design; Setting; Location; Funding Source; Quality**	**Tools Assessed**	**Total N**	**Mean Follow up period**	**Mean Age**	**Special Population**
Ad, 2010[17]	Prospective cohort; Outpatient; US; NR; Low risk of bias	$CHADS_2$ score	347	Total: 32.77 mo (SD 16.33)	Total: 64.5 (SD 11.6)	None
Komatsu, 2010[18]	Retrospective cohort; Outpatient; Asia; NR; Low risk of bias	$CHADS_2$ score	344	Total: 60 mo (SD 35)	Total: 68 (SD 12)	Paroxysmal AF
Lip, 2010[19] Euro Heart Survey for AF	Retrospective cohort; Outpatient; UK, Europe; Industry, Nongovernment, Nonindustry; Low risk of bias	$CHADS_2$ score Framingham score CHA_2DS_2-VASc score	1,084	Total: 1 yr	Total: 66 (SD 14)	None
Ruiz Ortiz, 2010[20]	Prospective cohort; Outpatient; Europe; Other (specify) : This work was supported by a grant from the Spanish Society of Cardiology.; Low risk of bias	$CHADS_2$ score	796	Total: 2.4 yr (SD 1.9)	Total: 73 (SD 8)	Permanent AF
Sadanaga, 2010[21]	Prospective cohort; Outpatient; Asia; NR; Low risk of bias	$CHADS_2$ score	245	Total: 753 days (SD 223) Arm 1: 753 days (SD 223) Arm 2: 753 days (SD 223)	Total: 74 (SD 9)	None

Study: Author Year Acronym	Study Design; Setting; Location; Funding Source; Quality	Tools Assessed	Total N	Mean Follow up period	Mean Age	Special Population
Connolly, 2009[22] 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	$CHADS_2$ score	18,113	Total: Median 2.0 yr	Total: 71	None
Crandall, 2009[23]	Retrospective cohort; NR; US; Other (specify) : Deseret Foundation; High risk of bias	$CHADS_2$ score	343	Arm 1: 9.1 yr (SD 1.8)	Total: 69 (SD 10)	None
Masaki, 2009[24]	Prospective cohort; Outpatient; Asia; NR; Low risk of bias	$CHADS_2$ score	265	Total: 703 days (SD 88)	Total: 72 (SD 11)	None
Morgan, 2009[25]	Retrospective cohort; Inpatient; UK; Industry; High risk of bias	$CHADS_2$ score	5,513	Total: 1025.1 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[26]	Prospective cohort; NR; US; NR; Low risk of bias	TEE	226	Arm 1: 13 mo (SD 17) Arm 2: 93 mo (SD 173)	Arm 1: 72 (SD 11) Arm 2: 70 (SD 12)	None
Poli, 2009[27]	Prospective cohort; Inpatient, Outpatient; Europe; NR; Low risk of bias	$CHADS_2$ score	662	Total: Median 3.1 yr	Total: 75	None

Study: Author Year Acronym	Study Design; Setting; Location; Funding Source; Quality	Tools Assessed	Total N	Mean Follow up period	Mean Age	Special Population
Fang, 2008[28] ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation)	Retrospective cohort; Outpatient; US; Government, Nongovernment, Nonindustry; Low risk of bias	$CHADS_2$ score Framingham score	10,932	Total: Median 6.0 yr (IQR 3.1 to 6.7)	Total: 72	None
Okuyama, 2008[29]	Retrospective cohort; Inpatient; Asia; Government, Other (specify) : partial funding from government; Low risk of bias	TEE	192	Total: 450 days (SD 120) Arm 1: 450 days (SD 120)	Total: 70 (SD 11)	Patients with prior stroke
Rietbrock, 2008[30]	Retrospective cohort; Outpatient; UK; Industry; Low risk of bias	$CHADS_2$ score	51,807	Total: Median 2.5 yr Arm 1: Median 2.5 yr Arm 2: Median 2.5 yr	Total: 76.01 (SD 10.13)	None
Ruiz Ortiz, 2008[31]	Prospective cohort; Outpatient; Europe; Nongovernment, Nonindustry; Low risk of bias	$CHADS_2$ score	296	Total: 21 mo (SD 17) Arm 1: 21 mo (SD 17)	Total: 75 (SD 9)	Permanent AF
Baruch, 2007[32] SPORTIF	RCT; Outpatient; NR; Industry; Low risk of bias	HAS-BLED $CHADS_2$ score CHA_2DS_2-VASc score	7,329	Total: 1.5 years	Arm 1: 73.9 (SD 8.6) Arm 2: 70.9 (SD 8.9)	None
Stollberger, 2004[33] ELAT (Embolism in Left Atrial Thrombi)	Prospective cohort; Outpatient; Europe; NR; Low risk of bias	TTE TEE	409	Total: 101 mo (SD 2)	Total: 62 (IQR 61 to 64)	None

Study: Author Year Acronym	Study Design; Setting; Location; Funding Source; Quality	Tools Assessed	Total N	Mean Follow up period	Mean Age	Special Population
Hylek, 2003[34] ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation)	Retrospective cohort; Outpatient; US; Government; Low risk of bias	INR	596	NR	Arm 1: 79 Arm 2: 80 Arm 3: 76	Patients with ischemic stroke
Stoddard, 2003[35]	Prospective cohort; Outpatient; US; NR; Low risk of bias	TEE	272	Total: 30.3 mo (SD 20.6) Arm 1: 28.3 mo (SD 23.3) Arm 2: 30.9 mo (SD 20)	Total: 66 (SD 11)	None
Wang, 2003[36] Framingham Heart Study	Prospective cohort; Outpatient; US; Government, Nongovernment, Nonindustry; Low risk of bias	Framingham score	705	Total: 4.0 yr	Total: 75 (SD 9)	None
Gage, 2001[37] NRAF (National Registry of Atrial Fibrillation)	Retrospective cohort; Outpatient; US; Government; Low risk of bias	$CHADS_2$ score	1,733	Total: 1.2 yr	Total: 81	None
Miyazaki, 2001[38]	Prospective cohort; Outpatient; Asia; NR; Low risk of bias	TEE	89	Total: 29 mo Arm 1: 29 mo	Total: 66 (SD 9)	Persistent AF

Abbreviations: AF = atrial fibrillation; IQR = interquartile range; N = number of patients; NR = not reported; 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	Mean Follow up period	Mean Age (years)	Special Population
Apostolakis, 2012[39] AMADEUS	RCT; NR; US, Canada, UK, Europe, Australia/NZ; Industry; Low risk of bias	HEMORR$_2$HAGES HAS-BLED ATRIA	2,293	Total: 429 days (+/- 118)	Total: 70.2 (SD 9.1)	None
Friberg, 2012[1] Swedish Atrial Fibrillation cohort study	Prospective cohort; Inpatient, Outpatient; Europe; Government, Nongovernment, Nonindustry; Low risk of bias	CHADS$_2$ score CHA$_2$DS$_2$-VASc score Framingham score HAS-BLED HEMORR$_2$HAGES	170,291	Total: Median 1.4 yr (IQR 1.8)	Total: 76.2	None
Gallego, 2012[40]	Retrospective cohort; Outpatient; Europe, NR; Government; Unclear	HAS-BLED	965	Total: Median 861 days	Total: Median 76 (IQR 70-81)	Patients in the therapeutic range
Lip, 2012[41] Loire Valley Atrial Fibrillation Project	Retrospective cohort; Inpatient; Europe; NR; Unclear	HAS-BLED HEMORR$_2$HAGES ATRIA Bleeding Risk Index	7,156	NR	Arm 1: 77.7 (SD 8.2) Arm 2: 73.8 (SD 11.6) Arm 3: 49.0 (SD 13.1)	None
Naganuma, 2012[3]	Retrospective cohort; Outpatient; Asia Nongovernment, Nonindustry; Low risk of bias	CHADS$_2$ score - Low HAS-BLED - Unclear	845	Total: Median 27 mo	Total: Median 74	None
Roldan, 2012[42]	Retrospective cohort; Outpatient; Europe; NR; Unclear	ATRIA HAS-BLED	937	Total: Median 952 days (IQR 785-1074)	Total: Median 76 (IQR 70-81)	Patients in the therapeutic range

Study: Author Year Acronym	Study Design; Setting; Location; Funding Source; Quality	Tools Assessed	Total N	Mean Follow up period	Mean Age (years)	Special Population
Ruiz-Nodar, 2012[8]	Retrospective cohort; NR; Europe; NR; High risk of bias	HAS-BLED CHA_2DS_2-VASc score	590	Total: ~12 mo	Total: 72.2 (SD 8.1)	None
Fang, 2011[43] ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation)	Retrospective cohort; Outpatient; US; Government, Industry, Nongovernment, Nonindustry; Low risk of bias	ATRIA $HEMORR_2HAGES$ Bleeding Risk Index	9,186	Total: Median 3.5 yr (IQR 1.2-6.0)	NR	None
Lind, 2011[2]	Retrospective cohort; Outpatient; Europe; NR; High risk of bias	INR	19,180	NR	NR	None
Lip, 2011[44] SPORTIF (Stroke Prevention using an ORal Thrombin Inhibitor in atrial Fibrillation)	RCT; Outpatient; NR; Industry; Low risk of bias	HAS-BLED $CHADS_2$ score	7,329	NR	Arm 1: 73.9 (SD 8.6) Arm 2: 70.9 (SD 8.9)	None
Olesen, 2011[11]	Retrospective cohort; Inpatient; Europe; NR; High risk of bias	$CHADS_2$ score CHA_2DS_2-VASc score	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

Study: Author Year Acronym	**Study Design; Setting; Location; Funding Source; Quality**	**Tools Assessed**	**Total N**	**Mean Follow up period**	**Mean Age (years)**	**Special Population**
Olesen, 2011[45]	Retrospective cohort; Inpatient; Europe; NR; Low risk of bias	HAS-BLED HEMORR$_2$HAGES	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
Poli, 2011[13]	Prospective cohort; NR; Europe; None; Low risk of bias	CHADS$_2$ score Bleeding Risk Index	3,302	Total: Median 2.3 (IQR 0.8 to 4.4)	Total: Median 74 (IQR 68 to 80)	None
Pisters, 2010[46] Euro Heart Survey for AF	Prospective cohort; Inpatient, Outpatient; Europe; Industry; Low risk of bias	HAS-BLED HEMORR$_2$HAGES	3,456	Total: ~1 yr	66.8 (SD12.8)	None
Gage, 2006[47] NRAF (National Registry of Atrial Fibrillation)	Retrospective cohort; Outpatient; US; Government, Nongovernment, Nonindustry; Low risk of bias	HEMORR$_2$HAGES Bleeding Risk Index	3,791	Total: 0.82 yr (3138 pt-yrs/3791 yrs)	Total: 80.2	None
Shireman, 2006[48]	Retrospective cohort; Outpatient; US; Government; Low risk of bias	Bleeding Risk Index	26,345	NR	NR	None
Aspinall, 2005[49]	Retrospective cohort; Outpatient; US; None; Low risk of bias	Bleeding Risk Index	1,269	NR	Total: 67.9 (SD 11.4)	None

Study: Author Year Acronym	Study Design; Setting; Location; Funding Source; Quality	Tools Assessed	Total N	Mean Follow up period	Mean Age (years)	Special Population
Hylek, 2003[34] ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation)	Retrospective cohort; Outpatient; US; Government; Low risk of bias	INR	596	NR	Arm 1: 79 Arm 2: 80 Arm 3: 76	Patients with prior stroke

Abbreviations: AF = atrial fibrillation; IQR = interquartile range; N = number of patients; NR = not reported; 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)	Mean Follow up period	Mean Age	Special Population	Outcomes Assessed
Azoulay, 2012[50]	Case-control Outpatient; UK; Industry; Fair	Arm 1: No therapy Arm 2: VKA (Warfarin) Arm 3: Aspirin	70,766; NR	Total: 3.9 yr (SD 3.3)	Total: 74.1 (SD 11.8)	None	Ischemic stroke Intracerebral hemorrhage Composite outcome (CV infarction/stroke, Intracerebral hemorrhage)
Cafolla, 2012[51]	Prospective cohort; Outpatient; Europe; NR; Fair	Arm 1: VKA (Warfarin INR 1.5-2.5) Arm 2: VKA (Warfarin INR 2.0-3.0)	112; Arm 1 (55) Arm 2 (57)	Total: 18 mo	Arm 1: 86 Arm 2: 85	None	Long-term adherence to therapy
Fosbol, 2012[52]	Retrospective cohort; Inpatient, Outpatient; US; Industry, Nongovernment, 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)	7,619; Arm 1 (2,213) Arm 2 (2,841) Arm 3 (563) Arm 4 (1,271) Arm 5 (731)	NR	Total: Median 80 (IQR 74 to 85) Arm 1 Median 80 (IQR 74 to 86) Arm 2: Median 80 (IQR 74 to 86) Arm 3: Median 80 (IQR 74 to 85) Arm 4: Median 80 (IQR 74 to 85) Arm 5: Median 78 (IQR 73 to 82)	None	Major Bleed Composite outcome: CV infarction/stroke, Myocardial infarction, All-cause mortality

Study: Author Year Acronym	Study Design; Setting; Location; Funding Source; Quality	Intervention or Tool and Comparators	Total N; Interventions (N)	Mean Follow up period	Mean Age	Special Population	Outcomes Assessed
Hori, 2012[53] J-ROCKET AF Study	RCT; Outpatient; Asia; Industry; Good	Arm 1: Rivaroxaban Arm 2: VKA (Warfarin)	1,278; Arm 1 (639) Arm 2 (639)	NR	Total: 71.1 Arm 1: 71.0 Arm 2: 71.2	None	Composite outcome: Major bleed; minor bleed Composite outcome: Cerebrovascular infarction, Systemic embolism, CV infarction/stroke, Intracerebral hemorrhage Composite outcome: Cerebrovascular infarction, Systemic embolism, CV infarction/stroke, Intracerebral hemorrhage, All-cause mortality
Taillandier, 2012[54]	Retrospective cohort; NR; Europe; None; Fair	Arm 1: Oral Anticoagulant Arm 2: Antiplatelet Agent Arm 3: No Antithrombotic Treatment	616; Arm 1 (273) Arm 2 (145) Arm 3 (198)	Total: 876 days (SD 1135)	Total: 47 (SD 13) Arm 1: 52 (SD 9) Arm 2: 46 (SD 13) Arm 3: 41 (SD 15)	None	All-cause mortality Cerebrovascular infarction Major bleed
Yamashita, 2012[55]	RCT; NR; Asia; Industry; Good	Arm 1: Edoxaban (30mg qd) Arm 2: Edoxaban (45mg qd) Arm 3: Edoxaban (60mg qd) Arm 4: VKA (Warfarin)	525; Arm 1 (131) Arm 2 (134) Arm 3 (131) Arm 4 (129)	Total: 12 wk	Arm 1: 69.4 Arm 2: 69.5 Arm 3: 68.4 Arm 4: 68.8	None	Major bleed Composite outcome: Major bleed, minor bleed, clinically-relevant non major bleeds Composite outcome: Intracerebral hemorrhage, Major bleed, Minor bleed

Study: Author Year Acronym	Study Design; Setting; Location; Funding Source; Quality	Intervention or Tool and Comparators	Total N; Interventions (N)	Mean Follow up period	Mean Age	Special Population	Outcomes Assessed
Connolly, 2011[56] AVERROES	RCT; Outpatient; NR; Industry; Good	Arm 1: Apixaban Arm 2: Aspirin	5,599; Arm 1 (2,808) Arm 2 (2,791)	Total: 1.1 yr Arm 1: 1.1 yr Arm 2: 1.1 yr	Arm 1: 70 (SD 9) Arm 2: 70 (SD 10)	None	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 outcome: Systemic embolism, CV infarction/stroke, All-cause mortality Composite outcome: Systemic embolism, CV infarction/stroke, Myocardial infarction, CV mortality Composite outcome: Systemic embolism, CV infarction/stroke Composite outcome: Cerebrovascular infarction, Systemic embolism, CV infarction/stroke, Intracerebral hemorrhage Composite outcome: Cerebrovascular infarction, Systemic embolism, CV infarction/stroke

Study: Author Year Acronym	Study Design; Setting; Location; Funding Source; Quality	Intervention or Tool and Comparators	Total N; Interventions (N)	Mean Follow up period	Mean Age	Special Population	Outcomes Assessed
Granger, 2011[57] ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation)	RCT; NR; US, Canada, Europe, Asia, Australia/NZ; Industry; Good	Arm 1: Apixaban Arm 2: VKA (Warfarin)	18,201; Arm 1 (9,120) Arm 2 (9,081)	Total: ~2 yr Arm 1: ~2 yr Arm 2: ~2 yr	Arm 1: Median 70 (IQR 63 to 76) Arm 2: Median 70 (IQR 63 to 76)	None	Ischemic stroke CV infarction/stroke Intracerebral hemorrhage Systemic embolism All-cause mortality Myocardial infarction Major bleed Cerebrovascular infarction CV mortality Composite outcome: Systemic embolism, CV infarction/stroke Composite outcome: Systemic embolism, CV infarction/stroke, All-cause mortality Composite outcome: Systemic embolism, CV infarction/stroke, Myocardial infarction, All-cause mortality Composite outcome: Cerebrovascular infarction, Systemic embolism, Major bleed Composite outcome: Cerebrovascular infarction, Systemic embolism, Major bleed, All-cause mortality Composite outcome: Cerebrovascular infarction, Systemic embolism, CV infarction/stroke, Intracerebral hemorrhage Composite outcome: Cerebrovascular infarction, Systemic embolism, CV infarction/stroke, Intracerebral hemorrhage, Ischemic stroke

Study: Author Year Acronym	Study Design; Setting; Location; Funding Source; Quality	Intervention or Tool and Comparators	Total N; Interventions (N)	Mean Follow up period	Mean Age	Special Population	Outcomes Assessed
Ogawa, 2011[58] ARISTOTLE-J (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation—Japan)	RCT; NR; Asia; Industry; Fair	Arm 1: Apixaban (2.5mg bid) Arm 2: Apixaban (5mg bid) Arm 3: VKA (Warfarin)	222; Arm 1 (74) Arm 2 (74) Arm 3 (74)	Arm 1: 85 days Arm 2: 85 days Arm 3: 84 days	Arm 1: 69.3 Arm 2: 70.0 Arm 3: 71.7	None	All-cause mortality CV infarction/stroke Major bleed Minor bleed Myocardial infarction Systemic embolism Composite outcome: Major bleed, Minor bleed
Olesen, 2011[11]	Retrospective cohort; Inpatient; Europe; NR; Poor	Arm 1: Placebo Arm 2: VKA (unspecified) Arm 3: Aspirin Arm 4: VKA (unspecified); Aspirin	132,372; Arm 1 (58,883) Arm 2 (37,425) Arm 3 (24,984) Arm 4 (11,080)	Total: Max 12 yr	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)	Mean Follow up period	Mean Age	Special Population	Outcomes Assessed
Patel, 2011[59] ROCKET-AF	RCT; Outpatient; US, Canada, UK, Europe, S. America, Asia, Africa, Australia/NZ; Industry; Good	Arm 1: Rivaroxaban Arm 2: VKA (Warfarin)	14,264; Arm 1 (7,131) Arm 2 (7,133)	Total: Median 707 days	Total: Median 73 Arm 1: Median 73 (IQR 65 to 78) Arm 2: Median 73 (IQR 65 to 78)	None	Major bleed Ischemic stroke CV infarction/stroke Composite outcome: Cerebrovascular infarction, TIA, Systemic embolism, CV infarction/stoke, Intracerebral hemorrhage, CV mortality, Myocardial infarction, Composite outcome: Cerebrovascular infarction, TIA, Systemic embolism, CV infarction/stoke, Intracerebral hemorrhage, CV mortality Composite outcome: Cerebrovascular infarction, TIA, Systemic embolism, CV infarction/stoke, Intracerebral hemorrhage Composite outcome: Cerebrovascular infarction, Systemic embolism, CV infarction/stroke, Intracerebral hemorrhage, Ischemic stroke Composite outcome: Cerebrovascular infarction, Systemic embolism, CV infarction/stroke, Intracerebral hemorrhage, CV mortality, Ischemic stroke Composite outcome: Cerebrovascular infarction, Systemic embolism, CV infarction/stroke, Intracerebral hemorrhage, CV mortality, Ischemic stroke, Myocardial infarction

Study: Author Year Acronym	Study Design; Setting; Location; Funding Source; Quality	Intervention or Tool and Comparators	Total N; Interventions (N)	Mean Follow up period	Mean Age	Special Population	Outcomes Assessed
Yang, 2011[60]	Retrospective cohort; NR; Asia; NR; Fair	Arm 1: VKA (Warfarin) Arm 2: Antiplatelet therapy Arm 3: No treatment	815; Arm 1 (226) Arm 2 (512) Arm 3 (77)	Total: 2.5 yr	Arm 1: 71.5 (SD 11.7) Arm 2: 75.2 (SD 10.6) Arm 3: 76.6 (SD 11.5)	None	CV mortality Ischemic stroke Major bleed Minor bleed
Gao, 2010[61]	Prospective cohort; NR; Asia; NR; Fair	Arm 1: VKA (Warfarin); Clopidogrel; Aspirin Arm 2: Clopidogrel; Aspirin Arm 3: VKA (Warfarin); Aspirin or Clopidogrel	622; Arm 1 (142) Arm 2 (355) Arm 3 (125)	NR	Arm 1: 70.97 (SD 5.56) Arm 2: 71.70 (SD 5.40) Arm 3: 72.81 (SD 5.22)	None	All-cause mortality Myocardial infarction Ischemic stroke Major bleed Minor bleed Composite outcome: Myocardial infarction, All-cause mortality, Ischemic stroke Composite outcome: Major bleed, Myocardial infarction, All-cause mortality, Ischemic stroke

Study: Author Year Acronym	Study Design; Setting; Location; Funding Source; Quality	Intervention or Tool and Comparators	Total N; Interventions (N)	Mean Follow up period	Mean Age	Special Population	Outcomes Assessed
Hansen, 2010[62]	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	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 yr (SD 2.6)	Total: 73.7 (SD 12.3) Arm 1: 70.3 (SD 10.7) Arm 2: 74.7 (SD 11.4) Arm 3: 72.6 (SD 10.2) Arm 4: 72.1 (SD 10.3) Arm 5: 70.8 (SD 10.0) Arm 6: 70.2 (SD 8.9) Arm 7: 69.9 (SD 9.2)	None	Major bleed
Lee, 2010[63]	Retrospective cohort; NR; Asia; Government, Nongovernment, Nonindustry; Fair	Arm 1: No antiplatelet agent or anticoagulation Arm 2: Aspirin Arm 3: Clopidogrel; Ticlopidine Arm 4: VKA (Warfarin)	422; Arm 1 (110) Arm 2 (124) Arm 3 (45) Arm 4 (143)	Total: 22.3 mo (SD 17.8) Arm 1: 16.8 mo (SD 17.5) Arm 2: 24.9 mo (SD 17.1) Arm 3: 18.6 mo (SD 18.3) Arm 4: 25.6 (SD 17.4)	Total: 62.9 (SD 10.7) Arm 1: 64.1 (SD 12.6) Arm 2: 63.2 (SD 9.8) Arm 3: 62.8 (SD 11.0) Arm 4: 61.8 (SD 9.8)	None	Ischemic stroke All-cause mortality Intracerebral hemorrhage Minor bleed Cerebrovascular infarction

Study: Author Year Acronym	Study Design; Setting; Location; Funding Source; Quality	Intervention or Tool and Comparators	Total N; Interventions (N)	Mean Follow up period	Mean Age	Special Population	Outcomes Assessed
Ruiz Ortiz, 2010[20]	Prospective cohort; Outpatient; Europe; Other (specify) : This work was supported by a grant from the Spanish Society of Cardiology.; Fair	Arm 1: OAC Arm 2: Non-OAC	796; Arm 1 (564) Arm 2 (232)	Total: 2.4 yr (SD 1.9)	Total: 73 (SD 8)	Permanent AF	Major bleed All-cause mortality Composite outcome: TIA, Ischemic stroke Diagnostic Accuracy, Diagnostic Thinking/ Therapeutic Efficacy
Weitz, 2010[64]	RCT; Outpatient; 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)	1,143; Arm 1 (235) Arm 2 (244) Arm 3 (234) Arm 4 (180) Arm 5 (250)	Total: 12 wk	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)	Mean Follow up period	Mean Age	Special Population	Outcomes Assessed
Connolly, 2009[22] RE-LY	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)	18,113; Arm 1 (6,015) Arm 2 (6,076) Arm 3 (6,022)	Total: Median 2.0 yr	Arm 1: 71.4 (SD 8.6) Arm 2: 71.5 (SD 8.8) Arm 3: 71.6 (SD 8.6)	None	Intracerebral hemorrhage All-cause mortality Myocardial infarction Major bleed Minor bleed Healthcare utilization - Hospital admissions CV mortality Ischemic stroke Systemic embolism Composite outcome: Intracerebral hemorrhage, Subdural hematoma Composite outcome: Systemic embolism, Intracerebral hemorrhage, Subdural hematoma, Ischemic stroke Composite outcome: Systemic embolism, Intracerebral hemorrhage, Subdural hematoma, Major bleed, Myocardial infarction, All-cause mortality, Ischemic stroke Composite outcome: CV infarction/stroke, CV mortality, Ischemic stroke Diagnostic Thinking/ Therapeutic Efficacy

Study: Author Year Acronym	Study Design; Setting; Location; Funding Source; Quality	Intervention or Tool and Comparators	Total N; Interventions (N)	Mean Follow up period	Mean Age	Special Population	Outcomes Assessed
Connolly, 2009[65] ACTIVE-A	RCT; Outpatient; Other (specify) : 33 countries; Industry; Good	Arm 1: Clopidogrel; Aspirin Arm 2: Aspirin	7,554; Arm 1 (3,772) Arm 2 (3,782)	Total: 3.6 yr Arm 1: 3.6 yr Arm 2: 3.6 yr	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
Holmes, 2009[66] PROTECT-AF	RCT; Inpatient; US, Europe; Industry; Good	Arm 1: Transcatheter: WATCHMAN Arm 2: VKA (Warfarin)	707; Arm 1 (463) Arm 2 (244)	Arm 1: 18 mo (SD 10) Arm 2: 18 mo (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 mortaltiy Composite outcome: Major bleed, Minor bleed
Jacobs, 2009[67]	Retrospective cohort; Outpatient; US; Industry; Poor	Arm 1: VKA (Warfarin) Arm 2: Aspirin	106; Arm 1 (90) Arm 2 (16)	Total: 12 mo Arm 1: 12 mo Arm 2: 12 mo	all ≥65	None	All-cause mortality Major bleed CV infarction/stroke

Study: Author Year Acronym	Study Design; Setting; Location; Funding Source; Quality	Intervention or Tool and Comparators	Total N; Interventions (N)	Mean Follow up period	Mean Age	Special Population	Outcomes Assessed
Bousser, 2008[68] AMADEUS	RCT; NR; US, Canada, UK, Europe, Australia/NZ; Industry; Good	Arm 1: Factor Xa Inhibitors (Idraparinux) Arm 2: VKA (Warfarin or Acenocoumarol)	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
Doucet, 2008[69]	Prospective cohort; Inpatient; Europe; NR; Poor	Arm 1: VKA (Unspecified) Arm 2: Aspirin	209; Arm 1 (102) Arm 2 (107)	Total: 3 mo Arm 1: 3 mo Arm 2: 3 mo	Arm 1: 82.9 (SD 7.1) Arm 2: 86.5 (SD 6.5)	Permanent AF	Cerebrovascular infarction All-cause mortality Healthcare utilization - Hospital admissions 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)	Mean Follow up period	Mean Age	Special Population	Outcomes Assessed
Hart, 2008[70] CHARISMA	RCT; NR; US; Industry; Good	Arm 1: Clopidogrel; Aspirin Arm 2: Aspirin	583; Arm 1 (298) Arm 2 (285)	Total: 2.3 yr	Total: 70 Arm 1: 70 Arm 2: 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 storke Composite outcome: Cerebrovascular infarction, Intracerebral hemorrhage, Myocardial infarction, CV mortality, Healthcare utilization – Hospital admissions
Ezekowitz, 2007[71] 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	502; Arm 1 (105) Arm 2 (166) Arm 3 (161) Arm 4 (70)	Total: 3 mo	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

Study: Author Year Acronym	Study Design; Setting; Location; Funding Source; Quality	Intervention or Tool and Comparators	Total N; Interventions (N)	Mean Follow up period	Mean Age	Special Population	Outcomes Assessed
Mant, 2007[72] BAFTA	RCT; Inpatient; UK; Nongovernment, Nonindustry; Good	Arm 1: VKA (Warfarin) Arm 2: Aspirin	973; Arm 1 (488) Arm 2 (485)	Total: 2.7 yr (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 outcome: Systemic embolism, CV infarction/stroke, Intracerebral hemorrhage Composite outcome: CV infarction/stroke, Myocardial infarction, CV mortality Composite outcome: Systemic embolism, CV infarction/stroke, Intracerebral hemorrhage
Rash, 2007[73] WASPO	RCT; Outpatient; UK; NR; Good	Arm 1: VKA (Warfarin) Arm 2: Aspirin	75; Arm 1 (36) Arm 2 (39)	Total: 12 mo Arm 1: 12 mo Arm 2: 12 mo	Total: Median 83 (IQR 80 to 90) Arm 1: Median 83.5 (IQR 80 to 90) Arm 2: Median 82.6 (IQR 80 to 90)	Permanent AF	All-cause mortality TIA Composite outcome: TIA, Major bleed, Ischemic stroke

Study: Author Year Acronym	Study Design; Setting; Location; Funding Source; Quality	Intervention or Tool and Comparators	Total N; Interventions (N)	Mean Follow up period	Mean Age	Special Population	Outcomes Assessed
Burton, 2006[74]	Retrospective cohort; NR; UK; Government, Nongovernment, Nonindustry; Poor	Arm 1: Usual care/OMT Arm 2: Aspirin Arm 3: VKA (Warfarin)	601; NR	Total: up to 5 yr	Total: 77 Arm 1: 458 patient yrs (SD 21.48) Arm 2: 721 patient yrs (SD 33.82) Arm 3: 953 patient yrs (SD 44.7)	Persistent AF	CV infarction/stroke All-cause mortality Major bleed Composite outcome: Major bleed, Minor bleed
Connolly, 2006[75] ACTIVE-W	RCT; NR; US, Canada, UK, Europe, S. America, Asia, Africa, Australia/NZ; Industry; Good	Arm 1: Clopidogrel; Aspirin Arm 2: VKA (Unspecified)	6,706; Arm 1 (3,335) Arm 2 (3,371)	Total: Median 1.28 yr	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
Inoue, 2006[76]	Prospective cohort; NR; Asia; NR; Poor	Arm 1: Usual care/OMT Arm 2: Aspirin or ticlopidine Arm 3: VKA (Warfarin)	509; Arm 1 (83) Arm 2 (163) Arm 3 (263)	Total: 2.0 yr (SD 0.4)	Arm 1: 63.4 (SD 12) Arm 2: 67.5 (SD 11) Arm 3: 67.0 (SD 9)	None	Composite outcome: TIA, Systemic embolism, CV infarction/stroke

Study: Author Year Acronym	Study Design; Setting; Location; Funding Source; Quality	Intervention or Tool and Comparators	Total N; Interventions (N)	Mean Follow up period	Mean Age	Special Population	Outcomes Assessed
Vemmos, 2006[77]	RCT; Outpatient; Europe; NR; Fair	Arm 1: Aspirin Arm 2: VKA (Warfarin 1mg/day fixed dose) Arm 3: VKA (Warfarin adjusted dose)	45; Arm 1 (15) Arm 2 (14) Arm 3 (16)	Total: 3.7 (IQR 1 to 6 mo) Arm 1: 3.6 Arm 2: 3.9 Arm 3: 3.7	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
Tsivgoulis, 2005[78]	Prospective cohort; Inpatient, Outpatient; Europe; NR; Good	Arm 1: VKA (Warfarin) Arm 2: Aspirin	207; Arm 1 (72) Arm 2 (135)	Total 88.4 mo (IQR 3 to 120)	Arm 1: 79.9 (SD 2.8) Arm 2: 80.7 (SD 3.1)	Patients with prior stroke	All-cause mortality Composite outcome: Cerebrovascular infarction, Systemic embolism
Lorenzoni, 2004[79] CLAAF	RCT; Outpatient; Europe; Industry; Fair	Arm 1: VKA (Warfarin) Arm 2: Clopidogrel; Aspirin	30; Arm 1 (14) Arm 2 (16)	Arm 1: 3 mo Arm 2: 3 mo	Arm 1: Median 72 Arm 2: Median 68	None	Composite outcome: Major bleed, minor bleed
Sam, 2004[80] Framingham	Retrospective cohort; Outpatient; US; Government; Fair	Arm 1: no therapy Arm 2: Aspirin Arm 3: VKA (Warfarin)	393; Arm 1 (231) Arm 2 (82) Arm 3 (80)	Arm 1: ~ 5yr Arm 2: ~ 5yr Arm 3: ~ 5yr	Arm 1: 77.3 (SD 10.6) Arm 2: 76.4 (SD 10.6) Arm 3: 70.7 (SD 11.4)	None	Major bleed Minor bleed Intracerebral hemorrhage
Shireman, 2004[81] Medicaid National Stroke Project	Retrospective cohort; Inpatient; US; Nongovernment, Nonindustry; Fair	Arm 1: VKA (Warfarin) Arm 2: VKA (Warfarin); Clopidogrel or Aspirin or Ticlopidine	10,093; Arm 1 (8,131) Arm 2 (1,962)	Total: 90 days	Total: 77.2 Arm 1: 77.4 Arm 2: 76.2	None	Major bleed 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)	Mean Follow up period	Mean Age	Special Population	Outcomes Assessed
Stellbrink, 2004[82] ACE	RCT; Inpatient, Outpatient; Europe; Industry; Fair	Arm 1: LMWH (Enoxaparin) Arm 2: VKA (Phenprocoumon); UFH (IV Heparin)	496; Arm 1 (248) Arm 2 (248)	Total: 28 to 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
Tentschert, 2004[83]	Prospective cohort; Inpatient, Outpatient; Europe; Government, Industry; Good	Arm 1: Clopidogrel or Aspirin or ASA + dipyridamole Arm 2: VKA (Warfarin) Arm 3: LMWH (Unspecified)	401; Arm 1 (153) Arm 2 (188) Arm 3 (60)	Total: Median 25 mo (IQR 15 to 38) Arm 1: Median 24 mo (IQR 13 to 36) Arm 2: Median 27 mo (IQR 19 to 40) Arm 3: Median 19 mo (IQR 7 to 32)	Arm 1: 78 (IQR 73 to 86) Arm 2: 75 (IQR 69 to 78) Arm 3: 78 (IQR 74 to 81)	None	Cerebrovascular infarction Intracerebral hemorrhage All-cause mortality CV mortality Major bleed Composite outcome: Cerebrovascular infarction, Intracerebral hemorrhage, CV mortality
Vemmos, 2004[84]	Prospective cohort; Inpatient, Outpatient; Europe; NR; Fair	Arm 1: VKA (Warfarin) Arm 2: Aspirin	191; Arm 1 (67) Arm 2 (124)	Total: 50.4 mo (IQR 12 to 60)	Arm 1: 74.6 (SD 6.5) Arm 2: 76.2 (SD 6.9)	Patients with prior stroke	All-cause mortality Major bleed Composite outcome: Systemic embolism, Ischemic stroke
Hylek, 2003[34] ATRIA	Retrospective cohort; Outpatient; US; Government; Good	Arm 1: No antithrombotic therapy Arm 2: Aspirin Arm 3: VKA (Warfarin)	596; Arm 1 (248) Arm 2 (160) Arm 3 (188)	NR	Arm 1: 79 Arm 2: 80 Arm 3: 76	Patients with prior stroke	All-cause mortality Diagnostic Thinking/ Therapeutic Efficacy

Study: Author Year Acronym	Study Design; Setting; Location; Funding Source; Quality	Intervention or Tool and Comparators	Total N; Interventions (N)	Mean Follow up period	Mean Age	Special Population	Outcomes Assessed
Yigit, 2003[85]	RCT; Inpatient, Other (specify) : outpatients admitted for study procedures; Turkey; NR; Fair	Arm 1: TEE; VKA (Warfarin); LMWH (Dalteparin) Arm 2: TEE; VKA (Warfarin); UFH (IV Heparin)	170: Arm 1 (89) Arm 2 (81)	Total: 6 mo Arm 1: 4 wk Arm 2: 4 wk	Total: 62.6 (SD 10.2) Arm 1: 63.4 (SD 9.4) Arm 2: 61.9 (SD 10.2)	Persistent AF	Systemic embolism
Frost, 2002[86]	Retrospective cohort; Inpatient, Outpatient; Europe; Government, Nongovernment, Nonindustry; Poor	Arm 1: VKA (Warfarin) Arm 2: No oral anticaogulation	5,124; Arm 1 (1,390) Arm 2 (3,734)	Total: 2.31 yr	NR	None	CV infarction/stroke
Berge, 2000[87] HAEST	RCT; Inpatient; Europe; Nongovernment, Nonindustry; Good	Arm 1: LMWH (Dalteparin) Arm 2: Aspirin	449; Arm 1 (224) Arm 2 (225)	Total: 14 days	Arm 1: Median 80 (IQR 55 to 96) Arm 2: Median 80 (IQR 44 to 98)	Patients with prior stroke	Ischemic stroke Intracerebral hemorrhage All-cause mortality
Yamaguchi, 2000[88]	RCT; Outpatient; Asia; Government; Poor	Arm 1: VKA (Warfarin INR 2.2 to 3.5) Arm 2: VKA (Warfarin INR 1.5 to 2.1)	115; Arm 1 (55) Arm 2 (60)	Total: 658 days (SD 423) Arm 1: 605 days (SD 406) Arm 2: 706 days (SD 445)	Arm 1: 65.7 (SD 6.8) Arm 2: 67.6 (SD 6.1)	None	Ischemic stroke Major bleed Minor bleed

Abbreviations: AF = atrial fibrillation; IQR = interquartile range; N = number of patients; NR = not reported; RCT = randomized controlled trial; SD = standard deviation

Appendix Table F-4. Study characteristics—KQ 4

Study: Author Year Acronym	Study Design; Setting; Location; Funding Source; Quality	Intervention or Tool and Comparators	Total N; Interventions (N)	Mean Follow up period	Mean Age	Special Population	Outcomes Assessed
OAC After PCI With Stenting							
Maegdefessel, 2008[89]	Prospective cohort; Inpatient; Europe; NR; Good	Arm 1: Clopidogrel; Aspirin Arm 2: Clopidogrel; Aspirin; LMWH (Unspecified) Arm 3: Clopidogrel; Aspirin; VKA	159; Arm 1 (103) Arm 2 (42) Arm 3 (14)	Total: 1.4 mo (IQR 2 mo to 5.7 yr)	Arm 1: 69.8 (SD 9.2) Arm 2: 72.1 (SD 8.5) Arm 3: 68.5 (SD 10.6)	None	Major bleed Myocardial infarction Ischemic stroke CV mortality
Manzano-Fernandez, 2008[90]	Retrospective cohort; Inpatient; Europe; NR; Good	Arm 1: VKA (Warfarin); Clopidogrel; Aspirin Arm 2: Non-triple therapy	104; Arm 1 (51) Arm 2 (53)	Total: 12 mo (IQR 10 to 12)	Arm 1: 69 (SD 4) Arm 2: 74 (SD 8)	None	Major bleed Composite outcome: Myocardial infarction, CV mortality
Ruiz-Nodar, 2008[91]	Retrospective cohort; Inpatient; Europe; NR; Good	Arm 1: VKA (Warfarin); Clopidogrel; Aspirin Arm 2: Clopidogrel; Aspirin	426; Arm 1 (242) Arm 2 (184)	Total: Median 595 days (IQR 0 to 2190)	Arm 1: 71.6 (SD 8.7) Arm 2: 71.2 (SD 8.5)	None	Major bleed Minor bleed All-cause mortality Myocardial infarction Composite outcome: Myocardial infarction, All-cause mortality Composite outcome: CV infarction/stroke, Major bleed, Myocardial infarction, All-cause mortality

Study: Author Year Acronym	Study Design; Setting; Location; Funding Source; Quality	Intervention or Tool and Comparators	Total N; Interventions (N)	Mean Follow up period	Mean Age	Special Population	Outcomes Assessed
Bridging Therapies							
Kiviniemi, 2012[92]	Prospective cohort; Inpatient; Europe; Government; Fair	Arm 1: Oral anticoagulation Arm 2: Oral anticoagulation, heparin	414; Arm 1 (196) Arm 2 (218)	NR	Arm 1: 71.1 (SD 7.6) Arm 2: 72.4 (SD 8.7)	Patients in the therapeutic range	Cerebrovascular infarction Myocardial infarction All-cause mortality Major bleed Composite outcome: Cerebrovascular infarction, Myocardial infarction, All-cause mortality
Lahtela, 2012[93] AFCAS (Atrial Fibrillation undergoing Coronary Artery Stenting)	Prospective cohort; Outpatient; Europe; Government, Industry; Fair	Arm 1: VKA (Unspecified) Arm 2: LMWH (unspecified)	451; Arm 1 (290) Arm 2 (161)	Total: 30 days	Arm 1: 73.2 (SD 7.8) Arm 2: 73.1 (SD 8.0)	None	All-cause mortality Myocardial infarction CV infarction/stroke Major bleed Cerebrovascular infarction Composite outcome: Cerebrovascular infarction, Myocardial infarction, All-cause mortality Composite outcome: CV infarction/stroke, Myocardial infarction, All-cause mortality, Ischemic stroke
Saad, 2011[94]	Prospective cohort; Inpatient; S. America; None; Fair	Arm 1: LMWH (Enoxaparin) Arm 2: VKA (Warfarin)	140; Arm 1 (70) Arm 2 (70)	Arm 1: 16 mo (SD 8) Arm 2: 16 mo (SD 8)	Arm 1: 76 (SD 7.4) Arm 2: 73 (SD 5.6)	None	Minor bleed Major bleed CV mortality All-cause mortality Systemic embolism
Kwak, 2010[95]	Prospective cohort; Inpatient, Outpatient; Asia; Government; Good	Arm 1: LMWH (Enoxaparin) Arm 2: VKA (Warfarin)	104; Arm 1 (55) Arm 2 (49)	NR	Arm 1: 55 (SD 12) Arm 2: 56 (SD 12)	None	Major bleed Minor bleed Ischemic stroke

Study: Author Year Acronym	Study Design; Setting; Location; Funding Source; Quality	Intervention or Tool and Comparators	Total N; Interventions (N)	Mean Follow up period	Mean Age	Special Population	Outcomes Assessed
Bunch, 2009[96]	Prospective cohort; NR; US; NR; Poor	Arm 1: Aspirin Arm 2: VKA (Warfarin)	630; Arm 1 (123) Arm 2 (507)	Total: 12 mo Arm 1: 12 mo Arm 2: 12 mo	Arm 1: 59.8 (SD 10.7) Arm 2: 66.0 (SD 10.1)	None	All-cause mortality CV infarction/stroke TIA
Hammerstingl, 2009[97] BRAVE (Bonn Registry of Alternative Anticoagulation to Prevent Vascular Events)	Prospective cohort; Inpatient, Outpatient; Europe; Industry; Fair	Arm 1: LMWH (Enoxaparin 1mg/kg twice a day) Arm 2: LMWH (Enoxaparin 1mg/kg once a day)	703; Arm 1 (358) Arm 2 (345)	Arm 1: 30 days Arm 2: 30 days	Arm 1: 78.6 (SD 9.3) Arm 2: 73.9 (SD 10.8)	None	Major bleed Minor bleed Composite outcome: TIA, Systemic embolism, CV infarction/stroke
Wazni, 2007[98]	Prospective cohort; NR; US; NR; Good	Arm 1: LMWH (Enoxaparin 1mg/kg BID) Arm 2: LMWH (Enoxaparin 0.5 mg/kg) Arm 3: VKA (Warfarin)	355; Arm 1 (105) Arm 2 (100) Arm 3 (150)	Total: 3-4 mo Arm 1: 3-4 mo Arm 2: 3-4 mo Arm 3: 3-4 mo	Arm 1: 56 (SD 9.6) Arm 2: 55.5 (SD 12) Arm 3: 55.1 (SD 10.6)	Persistent AF	Ischemic stroke Minor bleed Major bleed
Dabigatran in the Periprocedural Setting							
Healey, 2012[99] RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy)	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)	4,591; Arm 1 (1,487) Arm 2 (1,546) Arm 3 (1,558)	Total: 2 yr	Arm 1: 72.3 (SD 7.7) Arm 2: 72.5 (SD 7.7) Arm 3: 72.6 (SD 7.4)	None	Minor bleed Major bleed Fatal bleed Transfusion CV mortality Stroke Systemic embolism Myocardial infarction Composite outcome: CV mortality, ischemic stroke, non-CNS embolism, and pulmonary embolism

Study: Author Year Acronym	Study Design; Setting; Location; Funding Source; Quality	Intervention or Tool and Comparators	Total N; Interventions (N)	Mean Follow up period	Mean Age	Special Population	Outcomes Assessed
Lakkireddy, 2012{Lakkireddy, 2012 #7209	Retrospective cohort; NR; US; NR; Good	Arm 1: Dabigatran Arm 2: VKA (Warfarin)	290; Arm 1 (145) Arm 2 (145)	Arm 1: 30 days Arm 2: 30 days	Arm 1: 60.4 (SD 9.6) Arm 2: 60.3 (SD 9.6)	Patients in the therapeutic range	Major bleed Minor bleed Cerebrovascular infarction Composite outcome: Cerebrovascular infarction, TIA, Major bleed, Minor bleed
Snipelisky, 2012[100]	Retrospective cohort; NR; US; NR; Poor	Arm1: VKA (Warfarin) Arm 2: Dabigatran	156; Arm 1 (125) Arm 2 (31)	Total: 1 wk	Arm 1: 64.6 Arm 2: 60.6	Patients in the therapeutic range	Minor bleed

Abbreviations: AF = atrial fibrillation; IQR = interquartile range; N = number of patients; NR = not reported; RCT = randomized controlled trial; SD = standard deviation

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