Comparative Effectiveness Review
Number 123

Effective Health Care Program

Stroke Prevention in Atrial Fibrillation

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]

Effective Health Care Program

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

The full report and this summary are available at **www.effectivehealthcare.ahrq.gov/reports/final.cfm**.

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]

Agency for Healthcare Research and Quality
Advancing Excellence in Health Care • www.ahrq.gov

Effective Health Care

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.)

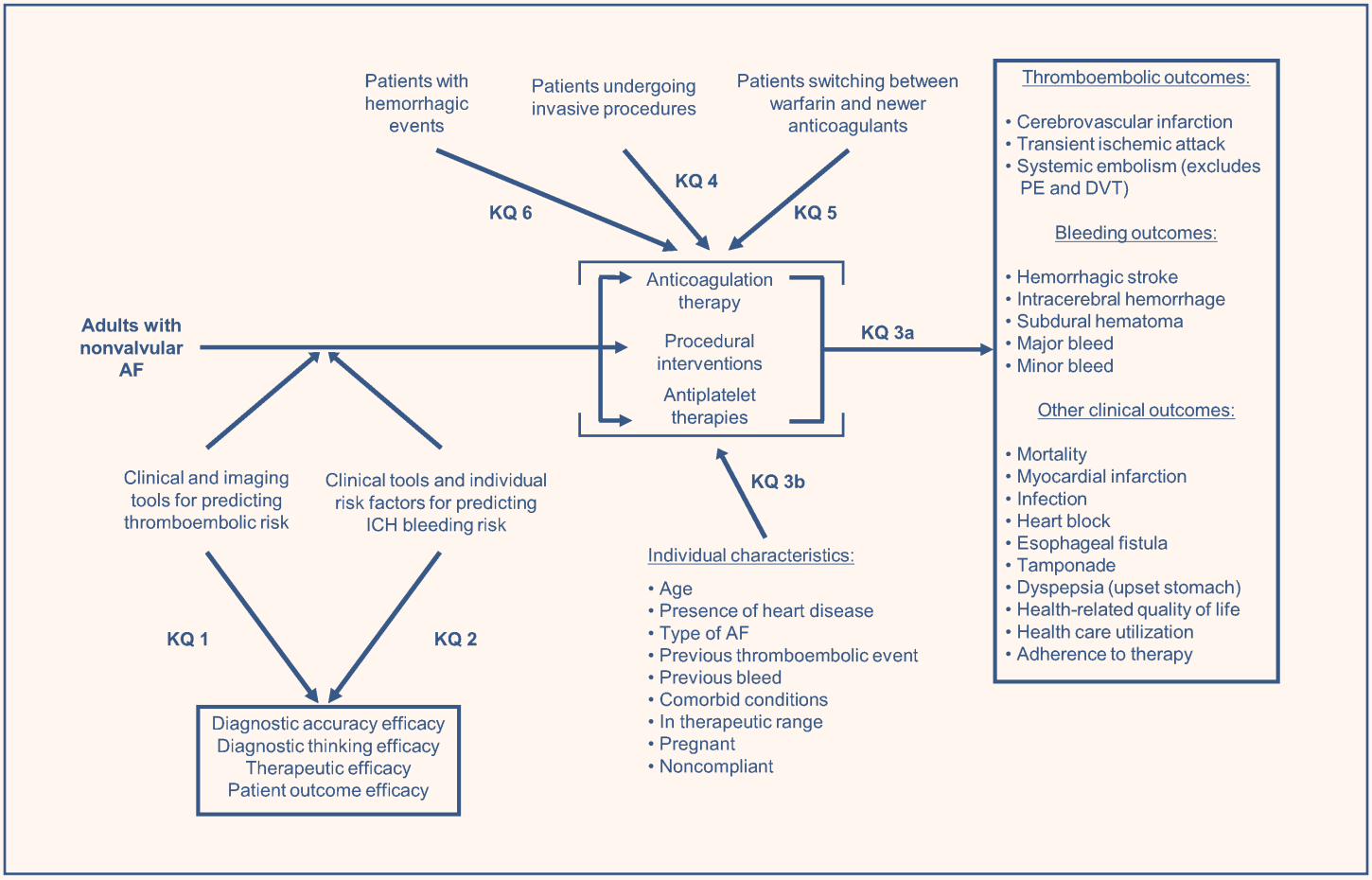
The KQs considered in this CER are as follows:

- **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.

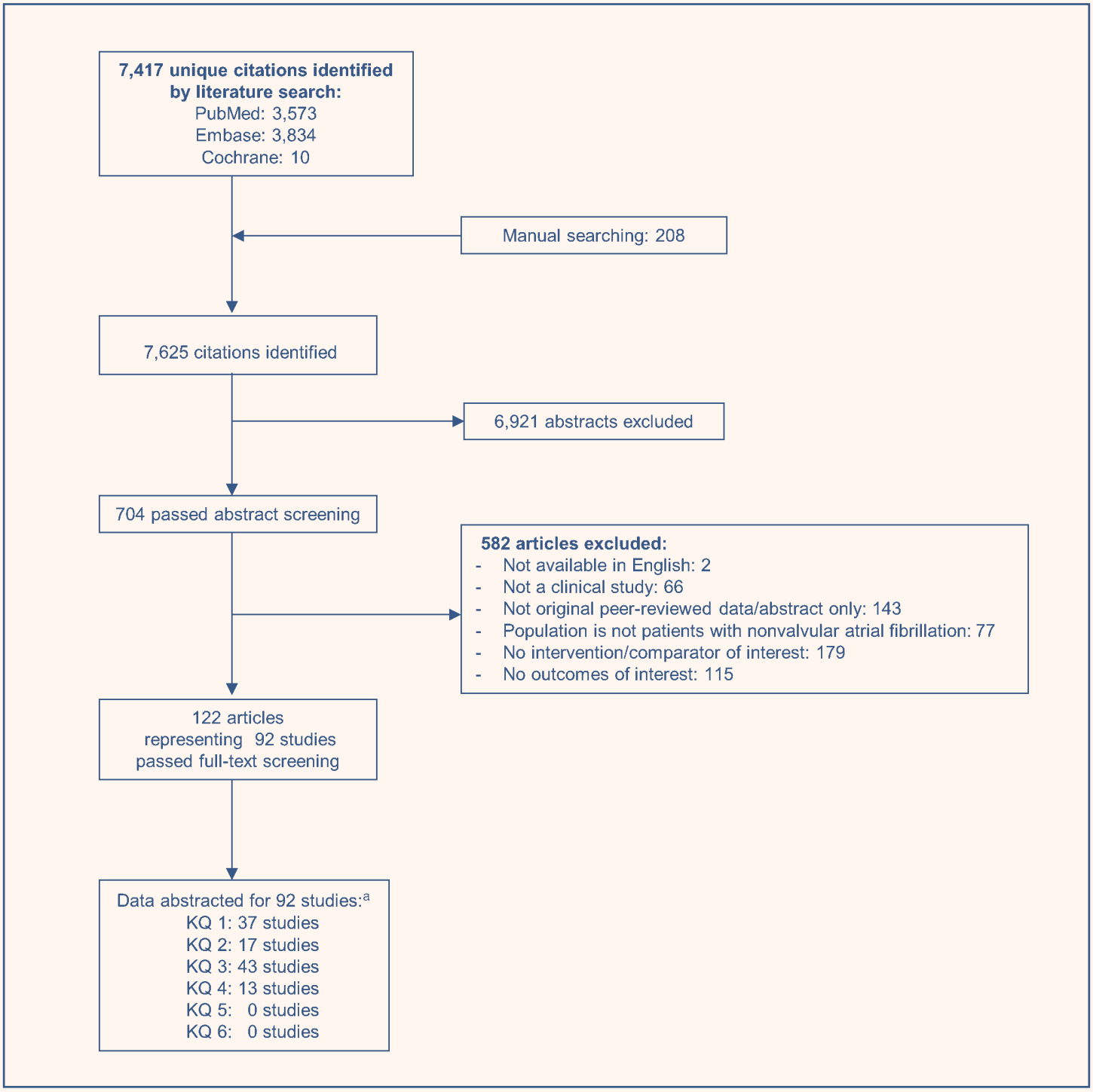
Results

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 CHADS2 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: CHADS2 = Congestive heart failure, Hypertension, Age ≥75, Diabetes mellitus, prior Stroke/transient ischemic attack (2 points); CHA2DS2-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 HEMORR2HAGES (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^{2}HAGES 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^{2}HAGES, 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^{2}HAGES, 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 [SDTINR]).

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:

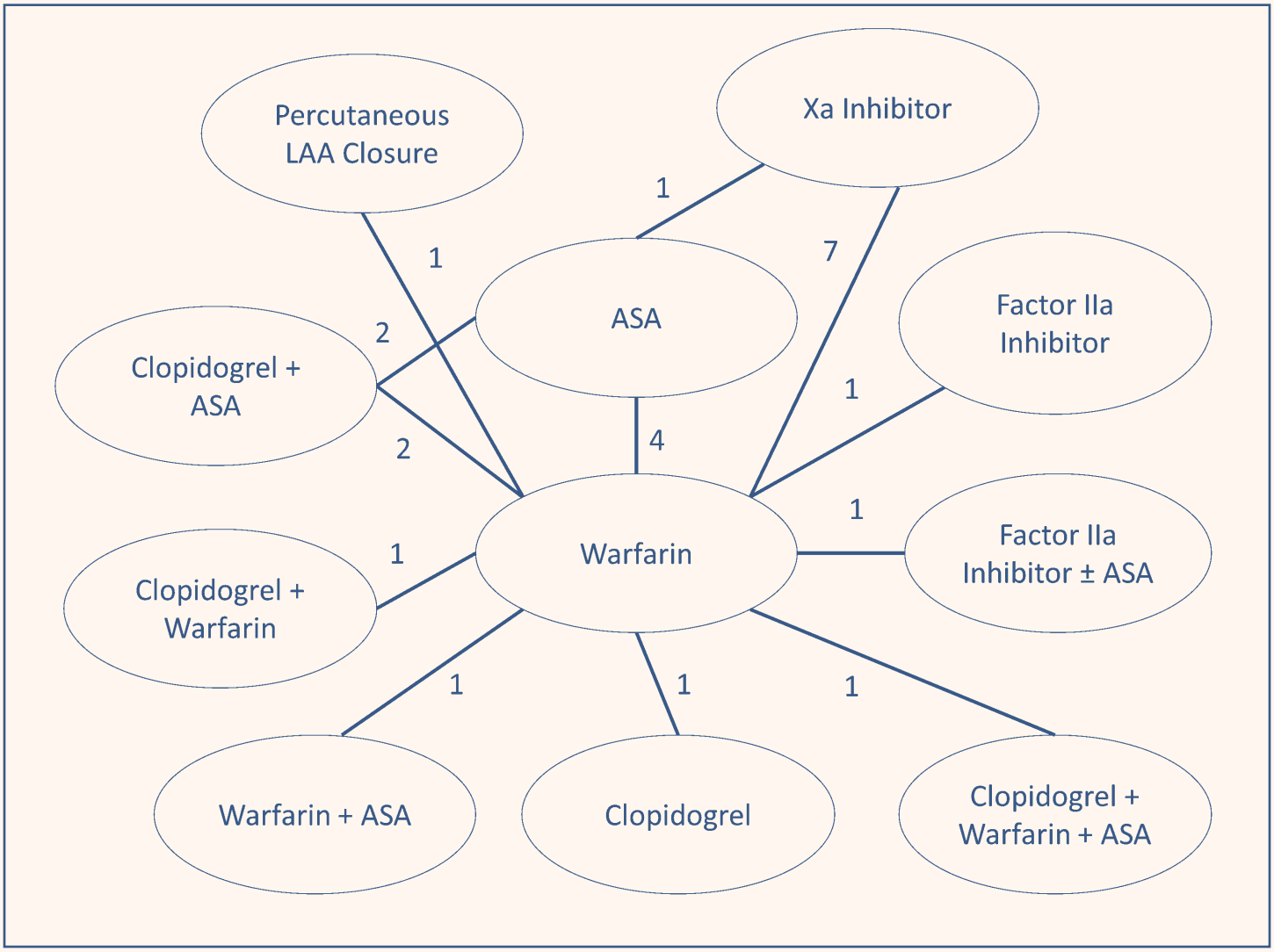
- Based on four retrospective studies (one good quality, two fair quality, and one poor quality) involving 170,642 patients, warfarin reduces the risk of nonfatal and fatal ischemic stroke compared with aspirin (moderate strength of evidence); on the other hand, based on three studies (one good quality, 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)

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% CI)**
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)

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% CI)**
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)

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% CI)**
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)
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)

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% CI)**
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)

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% CI)**
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)
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)

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% CI)**
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

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% CI)**
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 SDTINR 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.

References

1. Fuster V, Ryden LE, Cannom DS, et al. ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Circulation. 2006;114(7):e257-354. PMID: 16908781.
2. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA. 2001;285(18):2370-5. PMID: 11343485.
3. Furberg CD, Psaty BM, Manolio TA, et al. Prevalence of atrial fibrillation in elderly subjects (the Cardiovascular Health Study). Am J Cardiol. 1994;74(3):236-41. PMID: 8037127.
4. Lloyd-Jones D, Adams RJ, Brown TM, et al. Heart disease and stroke statistics—2010 update: a report from the American Heart Association. Circulation. 2010;121(7):e46-e215. PMID: 20019324.
5. Miyasaka Y, Barnes ME, Gersh BJ, et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. Circulation. 2006;114(2):119-25. PMID: 16818816.
6. Lee WC, Lamas GA, Balu S, et al. Direct treatment cost of atrial fibrillation in the elderly American population: a Medicare perspective. J Med Econ. 2008;11(2):281-98. PMID: 19450086.
7. Thrall G, Lane D, Carroll D, et al. Quality of life in patients with atrial fibrillation: a systematic review. Am J Med. 2006;119(5):448.e1-19. PMID: 16651058.
8. Stewart S, Hart CL, Hole DJ, et al. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. Am J Med. 2002;113(5):359-64. PMID: 12401529.
9. Dulli DA, Stanko H, Levine RL. Atrial fibrillation is associated with severe acute ischemic stroke. Neuroepidemiology. 2003;22(2):118-23. PMID: 12629277.
10. Lin HJ, Wolf PA, Kelly-Hayes M, et al. Stroke severity in atrial fibrillation. The Framingham Study. Stroke. 1996;27(10):1760-4. PMID: 8841325.
11. Paciaroni M, Agnelli G, Caso V, et al. Atrial fibrillation in patients with first-ever stroke: frequency, antithrombotic treatment before the event and effect on clinical outcome. J Thromb Haemost. 2005;3(6):1218-23. PMID: 15892862.
12. Caro JJ. An economic model of stroke in atrial fibrillation: the cost of suboptimal oral anticoagulation. Am J Manag Care. 2004;10 (14 Suppl):S451-58; discussion S8-61. PMID: 15696909.
13. Stroke Risk in Atrial Fibrillation Working Group. Independent predictors of stroke in patients with atrial fibrillation: a systematic review. Neurology. 2007;69(6):546-54. PMID: 17679673.
14. 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.
15. Lip GY, Nieuwlaat R, Pisters R, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on Atrial Fibrillation. Chest. 2010;137(2):263-72. PMID: 19762550.
16. Pisters R, Lane DA, Nieuwlaat R, et al. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest. 2010;138(5):1093-100. PMID: 20299623.
17. Camm AJ, Kirchhof P, Lip GY, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J. 2010;31(19):2369-429. PMID: 20802247.
18. Ansell J, Hirsh J, Hylek E, et al. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008;133(6 Suppl):160S-98S. PMID: 18574265.

19. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med. 2007;146(12):857-67. PMID: 17577005.

20. Gitter MJ, Jaeger TM, Petterson TM, et al. Bleeding and thromboembolism during anticoagulant therapy: a population-based study in Rochester, Minnesota. Mayo Clin Proc. 1995;70(8):725-33. PMID: 7630209.

21. Hylek EM, Evans-Molina C, Shea C, et al. Major hemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial fibrillation. Circulation. 2007;115(21):2689-96. PMID: 17515465.

22. Singer DE, Albers GW, Dalen JE, et al. Antithrombotic therapy in atrial fibrillation: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008;133(6 Suppl):546S-92S. PMID: 18574273.

23. Estes NA, 3rd, Halperin JL, Calkins H, et al. ACC/AHA/Physician Consortium 2008 clinical performance measures for adults with nonvalvular atrial fibrillation or atrial flutter: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures and the Physician Consortium for Performance Improvement (Writing Committee to Develop Clinical Performance Measures for Atrial Fibrillation): developed in collaboration with the Heart Rhythm Society. Circulation. 2008;117(8):1101-20. PMID: 18283199.

24. Birman-Deych E, Radford MJ, Nilasena DS, et al. Use and effectiveness of warfarin in Medicare beneficiaries with atrial fibrillation. Stroke. 2006;37(4):1070-4. PMID: 16528001.

25. Piccini JP, Hernandez AF, Zhao X, et al. Quality of care for atrial fibrillation among patients hospitalized for heart failure. J Am Coll Cardiol. 2009;54(14):1280-9. PMID: 19778670.

26. 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.

27. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365(10):883-91. PMID: 21830957.

28. Lopes RD, Alexander JH, Al-Khatib SM, et al. Apixaban for reduction in stroke and other ThromboembolLic events in atrial fibrillation (ARISTOTLE) trial: design and rationale. Am Heart J. 2010;159(3):331-9. PMID: 20211292.

29. Lip GY, Andreotti F, Fauchier L, et al. Bleeding risk assessment and management in atrial fibrillation patients: a position document from the European Heart Rhythm Association, endorsed by the European Society of Cardiology Working Group on Thrombosis. Europace. 2011;13(5):723-46. PMID: 21515596.

30. Douketis JD, Berger PB, Dunn AS, et al. The perioperative management of antithrombotic therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008;133(6 Suppl):299S-339S. PMID: 18574269.

31. Kearon C, Hirsh J. Management of anticoagulation before and after elective surgery. N Engl J Med. 1997;336(21):1506-11. PMID: 9154771.

32. Siegal D, Yudin J, Kaatz S, et al. Periprocedural heparin bridging in patients receiving vitamin K antagonists: systematic review and meta-analysis of bleeding and thromboembolic rates. Circulation. 2012;126(13):1630-9. PMID: 22912386.

33. Spyropoulos AC. Bridging therapy and oral anticoagulation: current and future prospects. Curr Opin Hematol. 2010;17(5): 444-9. PMID: 20613508.

34. Agency for Healthcare Research and Quality. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(11)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality; March 2011. Chapters available at: www.effectivehealthcare.ahrq.gov. Accessed May 7, 2012.

35. Agency for Healthcare Research and Quality. Methods Guide for Medical Test Reviews. AHRQ Publication No. 12-EC017. Rockville, MD: Agency for Healthcare Research and Quality; June 2012. www.effectivehealthcare.ahrq.gov. Accessed May 30, 2012.

36. Evidence-based Practice Center Systematic Review Protocol. Project Title: Stroke Prevention in Atrial Fibrillation. January 30, 2012. www.effectivehealthcare.ahrq.gov. Accessed June 21, 2012.

37. Whiting PF, Rutjes AWS, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011;155(8):529-36. PMID: 22007046.

38. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7(3):177-88. PMID: 3802833.

39. Ohman EM, Granger CB, Harrington RA, et al. Risk stratification and therapeutic decision making in acute coronary syndromes. JAMA. 2000;284(7):876-8. PMID: 10938178.

40. Owens DK, Lohr KN, Atkins D, et al. AHRQ series paper 5: grading the strength of a body of evidence when comparing medical interventions-Agency for Healthcare Research and Quality and the Effective Health Care Program. J Clin Epidemiol. 2010;63(5):513-23. PMID: 19595577.

41. Schunemann HJ, Oxman AD, Brozek J, et al. Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. BMJ. 2008;336(7653):1106-10. PMID: 18483053.

42. Atkins D, Chang SM, Gartlehner G, et al. Assessing applicability when comparing medical interventions: AHRQ and the Effective Health Care Program. J Clin Epidemiol. 2011;64(11):1198-207. PMID: 21463926.

43. Fuster V, Ryden LE, Cannom DS, et al. 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 Guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines developed in partnership with the European Society of Cardiology and in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. J Am Coll Cardiol. 2011;57(11):e101-98. PMID: 21392637.

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
CHADS2	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

Full Report

This executive summary is part of the following document: Lopes RD, Crowley MJ, Shah BR, Melloni C, Wood KA, Chatterjee R, Povsic TJ, Dupre ME, Kong DF, Barros e Silva PGM, Santos MHH, Armaganijan LV, Katz M, Kosinski A, McBroom AJ, Chobot MM, Gray R, Sanders GD. Stroke Prevention in Atrial Fibrillation. Comparative Effectiveness Review No. 123. (Prepared by the Duke Evidence-based Practice Center under Contract No. 290-2007-10066-I.) AHRQ Publication No. 13-EHC113-EF. Rockville, MD: Agency for Healthcare Research and Quality; August 2013. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

AHRQ Pub. No. 13-EHC113-1-EF
August 2013