

Draft Comparative Effectiveness Review

Number XX

Stroke Prevention in Atrial Fibrillation

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Preface

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Stroke Prevention in Atrial Fibrillation

Structured Abstract

Objectives: Oral anticoagulation with vitamin K antagonists (VKAs) has long been the gold standard therapy for stroke prevention in nonvalvular atrial fibrillation (AF). Limitations with monitoring and compliance of VKAs have fueled the development of new antithrombotic strategies, devices, and oral anticoagulants, including oral direct thrombin inhibitors and factor Xa inhibitors. The best treatment options for individual patients, and the optimal risk stratification tools for stroke and bleeding prediction, are uncertain.

Data Sources: We searched PubMed[®], Embase[®], and the Cochrane Database of Systematic Reviews for relevant English-language comparative studies.

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

Results: Our review included 96 articles (74 unique studies). This included 30 studies relevant to predicting thromboembolic risk, 14 relevant to predicting bleeding risk, 35 relevant to interventions for preventing thromboembolic events, 8 relevant to anticoagulation strategies in patients undergoing invasive procedures, and no studies relevant to strategies for switching between warfarin and novel oral anticoagulants or to stroke prevention after a hemorrhagic event. Across the Key Questions addressing prediction of stroke and bleeding risk, evidence was limited by variability in reporting and underlying treatment of AF. Data suggests that the continuous CHADS₂ and CHA₂DS₂-VAsC scores have the greatest predictive power for stroke risk (c-statistics 0.71 [95% confidence interval (CI), 0.65 to 0.77] and 0.71 [95% CI, 0.64 to 0.79], respectively) and that the HAS-BLED score has the greatest predictive power for bleeding risk. Evidence evaluating interventions for stroke prevention was limited by the number of studies for specific comparisons and lack of direct comparisons of novel anticoagulants, although many included studies were good-quality randomized controlled trials involving >5,000 patients. Our review found that a Factor II inhibitor (dabigatran 150 mg) is superior to warfarin in reducing the incidence of stroke (including hemorrhagic) or systemic embolism (hazard ratio [HR] 0.66; 95% CI, 0.53 to 0.82), with no significant difference in the occurrence of major bleeding (HR 0.93; 95% CI, 0.81 to 1.07) (high strength of evidence). The direct Xa inhibitor apixaban compared with aspirin was superior in reducing the incidence of stroke and systemic embolism (HR 0.45; 95% CI, 0.32 to 0.62), with similar hemorrhagic events, including major bleeding (HR 1.13; 95% CI, 0.74 to 1.75) in patients who are not suitable for oral anticoagulation (high strength of evidence). Apixaban was also superior in reducing the incidence of stroke or systemic embolism (HR 0.79; 95% CI, 0.66 to 0.95), major bleeding (HR 0.69; 95% CI, 0.60 to 0.80), and all-cause mortality (HR 0.89; 95% CI, 0.80 to 0.998) when compared with warfarin (high strength of evidence). The Xa inhibitor rivaroxaban is superior to warfarin for the prevention of stroke (HR 0.79; 95% CI, 0.65 to 0.95) (high strength of evidence). Evidence for patients undergoing invasive procedures, switching among anticoagulant therapies, and starting or restarting anticoagulant therapy after previous major bleeding events was insufficient.

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

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Effective Health Care

Stroke Prevention in Atrial Fibrillation

Executive Summary

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

Background

Atrial Fibrillation and Stroke

Atrial fibrillation (AF) is a supraventricular tachyarrhythmia (any tachycardic rhythm originating above the ventricular tissue) and 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 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; by the year 2050 there will be an estimated 12.1 million (95% confidence interval [CI], 11.4 to 12.9) Americans with AF, representing a 2.4-fold increase since 2000. However, this estimate assumes no further increase in the age-adjusted incidence of AF beyond 2000. If the incidence of AF increases at the same pace, then the projected number of adults with AF would be 15.9 million, a 3-fold increase from 2000.⁵

Although generally not as immediately life-threatening as ventricular arrhythmias, AF is associated with significant morbidity and mortality. Patients with AF have increased risk of embolic stroke, heart failure, and cognitive impairment; reduced quality of life; and higher overall mortality.⁶⁻⁸ Patients with AF have a five-fold increased risk of stroke, and it is estimated that up to 25 percent of all strokes in the elderly are a consequence of AF.⁴ Furthermore, AF-related strokes are more severe, with patients twice as likely to be bedridden than 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, 2 to 7 times that of the general population.⁹ The risk of stroke increases from 1.5 percent for patients with AF who are 50–59 years old to 23 percent for those who are 80–89 years old.¹⁰

Congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, and prior stroke or transient ischemic attack (TIA) are considered independent risk factors for stroke as well as risk factors for AF. These risk factors are the elements that form the classic CHADS₂ risk score for stroke prevention (Congestive heart failure, Hypertension, Age ≥ 75 , Diabetes mellitus, prior Stroke/transient ischemic attack [2 points]).^{13,14} This score ranges from 0–6, with increasing scores corresponding to increasing stroke risk, and is easy to calculate and apply in clinical practice.¹ The adjusted annual rates of stroke vary from 1.9 percent in patients with a CHADS₂ score of 0, to 18.2 percent in patients with a CHADS₂ score of 6. Aggressive primary prevention and intervention once these risk factors are present are essential to optimally manage the increased risk of developing AF and stroke independently or as a result of AF.

Stroke Prevention Strategies in AF

Management of AF involves three distinct areas, namely, rate control, rhythm control, and prevention of thromboembolic events. This Comparative Effectiveness Review (CER) focuses on the last area. A separate CER focusing on the treatment of AF through rate or rhythm control is being conducted in parallel.

Strategies for preventing thromboembolic events can be categorized into (a) optimal risk stratification of patients, and (b) 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 TIA. As stated previously, these risk factors are the elements that form the CHADS₂ score.¹³ However, because of the overlap with factors also associated with increased risk of bleeding, the CHADS₂ score currently appears to be underused to guide decisions about antithrombotic therapy.

Lip and colleagues built upon the CHADS₂ score and other risk stratification schema to develop the CHA₂DS₂-VASc score (Congestive heart failure/left ventricular ejection fraction $\leq 40\%$, Hypertension, Age ≥ 75 [2 points], Diabetes mellitus, prior Stroke/transient ischemic attack/thromboembolism [2 points], Vascular disease, Age 65–74, Sex category female), which ranges from 0–9 and aims to be more sensitive than the CHADS₂ score, specifically seeking to identify patients at low risk for stroke based on earlier risk scores but for whom antithrombotic therapy may be beneficial, for example, women and younger patients.¹⁵

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 INR (international normalized ratio) value, which provides the result of the actual prothrombin time over a normalized value. It has

been demonstrated that an INR value of 2–3 provides the best trade-off between preventing ischemic events and causing bleeding. Clinicians use the prothrombin time and INR as useful 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 0–9. A score ≥ 3 indicates a high risk of bleeding with oral anticoagulation and/or aspirin.¹⁶ The HAS-BLED score may aid decisionmaking in clinical practice and is recommended by the current European Society of Cardiology (ESC) AF guidelines.¹⁷ However, uncertainty remains both about whether other clinical or imaging tools might improve prediction of stroke or bleeding risk prediction, 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 to predict events. A comparative and thorough assessment of current tools could assist providers in understanding the clinical value of appropriately judging risk and treating accordingly. Also, an assessment of how application of these tools may improve outcomes could help improve the utility of their use in clinical practice.

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

Therapeutic Options for Stroke Prevention in AF

Vitamin K antagonists (VKAs) are highly effective for the prevention of stroke in patients with nonvalvular AF. VKAs such as warfarin have been in use for over 50 years. These compounds create an anticoagulant effect by inhibiting the γ -carboxylation of vitamin K-dependent factors (II, VII, IX, and X).¹⁸ In a meta-analysis of 29 randomized controlled trials (RCTs) including 28,000 patients with nonvalvular AF, warfarin therapy led to a 64 percent reduction in stroke (95% CI, 49 to 74%) compared with placebo. Even more importantly, warfarin therapy was associated with a 26 percent reduction in all-cause mortality (95% CI, 3 to 34%).¹⁹

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 increases the risk of thromboembolic events and bleeding, respectively. Warfarin-naïve patients experience a three-fold increased risk of bleeding in the first 90 days of treatment compared with patients already on warfarin.^{20,21} This increased risk of hemorrhage in warfarin-naïve patients also contributes to the underuse of warfarin in the elderly population with AF. Failure to prescribe warfarin in eligible patients is a pervasive problem, despite the adoption of performance measures and guidelines advocating its use in patients with nonvalvular AF who have moderate to severe risk of stroke.^{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. Thus, a large number of patients with AF who might benefit from warfarin are either not being offered treatment, are refusing to take it, or are stopping it.

New devices and systemic therapies have been developed for stroke prophylaxis and are in testing or have been approved for use. Mechanical interventions for stroke prophylaxis have emerged and are growing in use. For example, left atrial appendage (LAA) occlusive devices are an alternative treatment strategy used to prevent blood clot formation in patients with AF. 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, with approximately 18,000 subjects and evaluating the new direct Factor II (thrombin) dabigatran²⁶
- ROCKET AF, with approximately 14,000 subjects and evaluating the new direct factor Xa inhibitor rivaroxaban²⁷
- ARISTOTLE, with approximately 18,000 subjects and evaluating the new direct factor Xa inhibitor apixaban²⁸

The evolution of newer anticoagulation agents, per the large trials above, as well as the risks and benefits when compared to LAA occlusion devices and older antiplatelet and anticoagulation strategies, makes stroke prevention in AF an area of further clinical uncertainty that supports both the importance and appropriateness of further evidence development and a new systematic review of existing evidence. Furthermore, these new therapies highlight the need to reconsider their comparative effectiveness and safety when compared with standard antithrombotic and antiplatelet therapies and with each other.

Even with treatment for stroke prophylaxis in patients with nonvalvular AF, numerous unanswered questions persist around managing patients undergoing invasive or surgical procedures. Patients receiving long-term anticoagulation therapy may need to stop this therapy temporarily before undergoing certain procedures where the risk of bleeding is high. Because VKAs have a long half-life, patients need to stop these medications approximately 5 days before

an invasive procedure. However, 5 days without an oral anticoagulant can increase the risk of ischemic events. Thus, one option often used in clinical practice is “bridging,” where 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. In summary, the real risk-benefit of bridging from VKAs to a parenteral anticoagulant in patients with AF undergoing an invasive procedure is unknown, and is currently under study in an NIH sponsored trial called BRIDGE (Bridging Anticoagulation in Patients who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure or Surgery).

In addition, there is uncertainty regarding strategies for switching patients from warfarin to the new generation of direct thrombin inhibitors, and 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 current 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 KQs using the general approach of specifying the Populations, Interventions, Comparators, Outcomes, Timings, and Settings of interest (PICOTS; see the section on “Inclusion and Exclusion Criteria” in the Methods chapter for details).

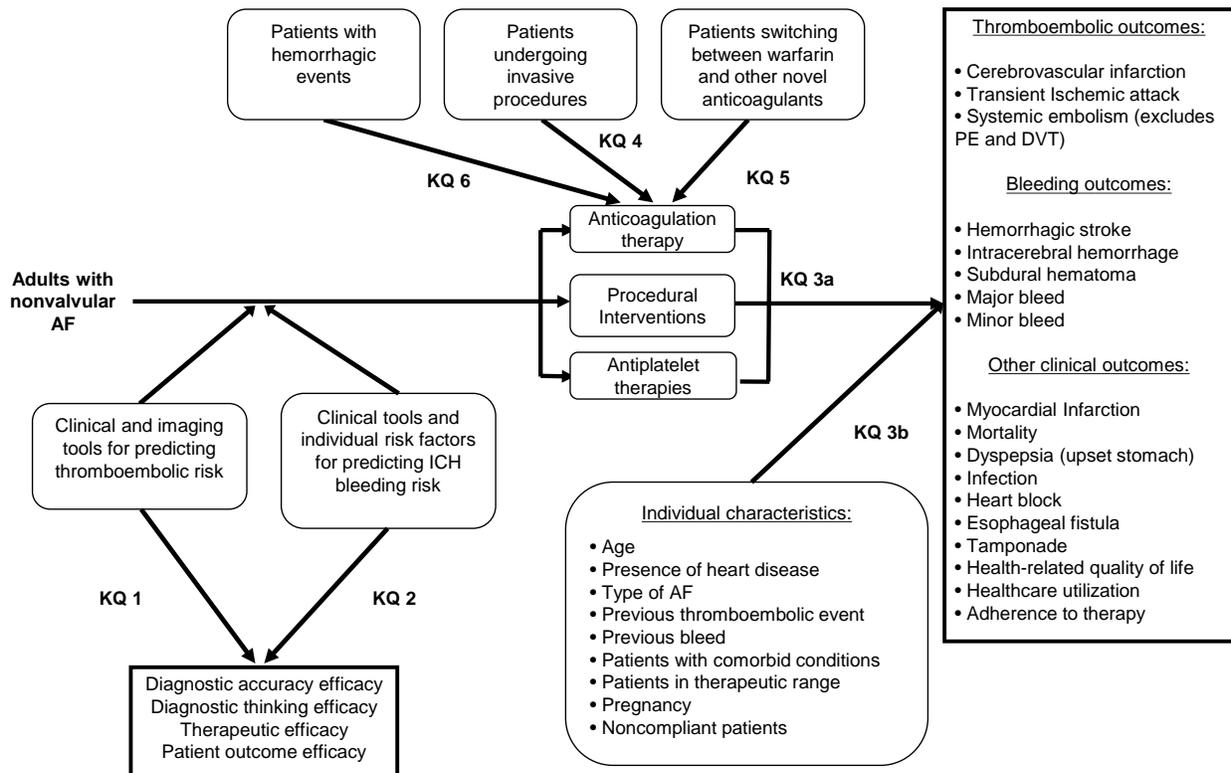
The KQs considered in this CER are:

- **KQ 1:** In patients with nonvalvular atrial fibrillation, what are the comparative diagnostic accuracy and impact on clinical decisionmaking (diagnostic thinking, therapeutic, and patient outcome efficacy) of available clinical and imaging tools for predicting thromboembolic risk?
- **KQ 2:** In patients with nonvalvular atrial fibrillation, what are the comparative diagnostic accuracy and impact on clinical decisionmaking (diagnostic thinking, therapeutic, and patient outcome efficacy) of clinical tools and associated risk factors for predicting bleeding events?

- **KQ 3:** What are the comparative safety and effectiveness of specific anticoagulation therapies, antiplatelet therapies, and procedural interventions for preventing thromboembolic events:
 - (a) In patients with nonvalvular atrial fibrillation?
 - (b) In specific subpopulations of patients with nonvalvular atrial fibrillation?
- **KQ 4:** What are the comparative safety and effectiveness of available strategies for anticoagulation in patients with nonvalvular atrial fibrillation who are undergoing invasive procedures?
- **KQ 5:** What are the comparative safety and effectiveness of available strategies for switching between warfarin and other novel oral anticoagulants, in patients with nonvalvular atrial fibrillation?
- **KQ 6:** What are the comparative safety and effectiveness of available strategies for resuming anticoagulation therapy or performing a procedural intervention as a stroke prevention strategy following a hemorrhagic event (stroke, major bleed, or minor bleed) in patients with nonvalvular atrial fibrillation?

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

Figure A. Analytic framework



Abbreviations: AF=atrial fibrillation; DVT=deep vein thrombosis; ICH=intracerebral 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* (hereafter referred to as the *Methods Guide*)²⁹ and *Methods Guide for Medical Test Reviews* (hereafter referred to as the *Medical Test Guide*).³⁰

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 at the AHRQ Effective Health Care Website.³¹

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 the present. 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. All citations were imported into an electronic database (EndNote[®] X4; Thomson Reuters, Philadelphia, PA).

As a mechanism to ascertain publication bias, we searched ClinicalTrials.gov to identify completed but unpublished studies. While the draft report is under peer review, we will update the literature search and include any eligible studies identified either during that search or through peer or public reviews in the final report.

We used several approaches to identify relevant grey 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. Grey literature databases included ClinicalTrials.gov; the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) 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 main report. For all KQs, the search focused on English-language studies (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, Intracerebral hemorrhage, subdural hematoma, major and minor bleed); other clinical outcomes (MI, mortality), and 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. When the two reviewers arrived at different decisions about whether to include or exclude an article, they reconciled the difference through review and discussion, or through a third-party arbitrator if needed. Full-text articles meeting our eligibility criteria were included for data abstraction. 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, ON, 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. One investigator abstracted the data, and the second reviewed the completed abstraction form alongside the original article to check for accuracy and completeness. Disagreements were resolved by consensus, or by obtaining a third reviewer’s opinion if consensus could not be reached.

We designed the data abstraction forms to collect the data required to evaluate the specified eligibility criteria for inclusion in this review, as well as demographic and other data needed for determining outcomes (intermediate, final, and adverse events outcomes). We paid particular attention to describing the details of treatment, patient characteristics, and study design that may be related to outcomes. In addition, we described comparators carefully, as treatment standards may have changed during the period covered by this review. The safety outcomes were framed to help identify adverse events, including those from drug therapies and those resulting from procedural complications. Data necessary for assessing quality and applicability were also abstracted. Before the data abstraction form templates were used, they were pilot-tested with a sample of included articles and revised as necessary.

Quality Assessment of Individual Studies

We evaluated the quality of individual studies using the approach described in the Methods Guide.²⁹ To assess quality, we used the strategy to (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)-2³² 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 began our data synthesis by summarizing key features of the included studies for each KQ. To the degree that data were available, we abstracted information on study design; patient characteristics; clinical settings; interventions; and intermediate, final, and adverse event outcomes.

We determined the feasibility of completing a quantitative synthesis (i.e., meta-analysis). 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 considered meta-analysis for comparisons where at least three studies reported the same outcome. We grouped interventions by prediction tool (KQs 1–2) 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). 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. For comparison, we also performed fixed-effect meta-analyses. We present summary estimates, standard errors, and confidence intervals in our data synthesis. When we were able to calculate hazard ratios (HRs), we assumed that a HR between 0.9 and 1.2 with a narrow confidence interval which 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 KQ 1 and KQ 2 we synthesized available c-statistics for the predictive 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.³³ Of note, a risk score may have a statistically significant association with a clinical outcome, but the relationship may not discriminate 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 predictive accuracy in the patient data set used to develop the model than in independent sets of patients; we therefore indicate when studies being discussed were actually used to develop the models they describe.

We anticipated that intervention effects might be heterogeneous. We hypothesized that the methodological quality of individual studies, study type, the characteristics of the comparator, and patients' underlying clinical presentation would be associated with the intervention effects. 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.^{29,34} In brief, the approach requires assessment of four domains: risk of bias, consistency, directness, and precision. Additional domains were used when appropriate: strength of association (magnitude of effect), and 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. For outcomes where confounding was not believed to be an issue (e.g. predictive value of stroke and bleeding risk tools in KQ1/2), evidence based on observational studies started with a “moderate” strength of evidence rating. We assumed outcomes based on only one study to be consistent.

Applicability

We assessed applicability across our KQs using the method described in the Methods Guide.^{29,35} 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 used checklists to guide the assessment of applicability. We used these data to evaluate the applicability to clinical practice, paying special attention to study eligibility criteria, demographic features of the enrolled population in comparison to the target population, characteristics of the intervention used in comparison with care models currently in use, and clinical relevance and timing of the outcome measures. We summarized issues of applicability qualitatively.

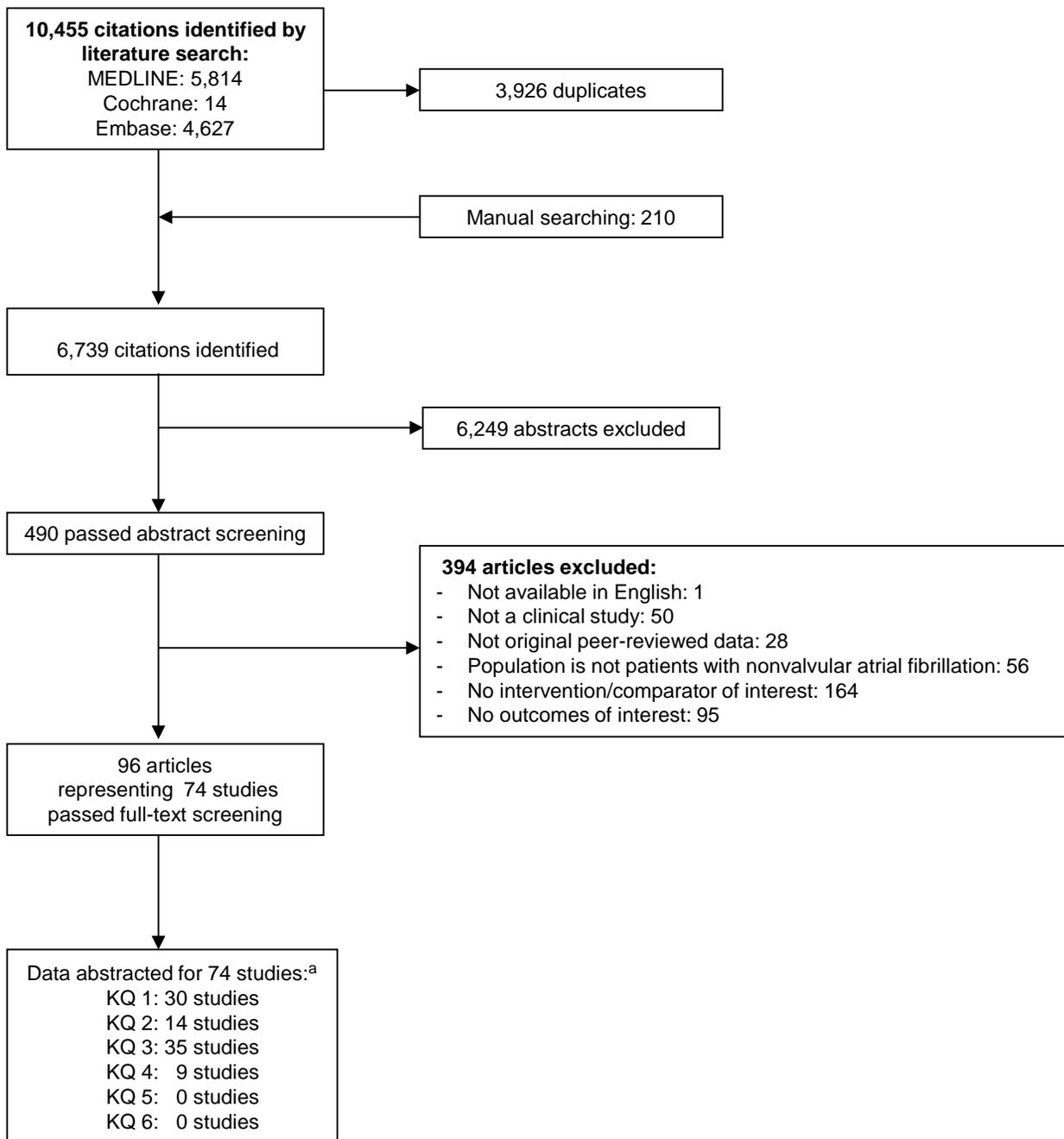
Results

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 10,455 citations, 3,926 of which were duplicate citations. Manual searching identified 210 additional citations, for a total of 6,739 citations. After applying inclusion/exclusion criteria at the title-and-abstract level, 490 full-text articles were retrieved and screened. Of these, 394 were excluded at the full-text screening stage, leaving 96 articles for data abstraction. These 96 articles described 74 unique studies. The relationship of studies to the review questions is as follows: 30 studies relevant to KQ 1, 14 studies relevant to KQ 2, 35 studies relevant to KQ 3, 9 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). Studies were conducted wholly or partly in continental Europe (47%), the United States or Canada (31%), Asia (19%), the UK (15%), South or Central America (7%), Australia or New Zealand (7%), Africa (4%), and unspecified or other locations (7%).

As described in the Methods chapter, we searched ClinicalTrials.gov to identify completed but unpublished studies as a mechanism for ascertaining publication bias. Our search yielded 170 trial records. A single reviewer identified 52 of these records as potentially relevant; 29 had been completed at least 1 year prior to our search of the database and review of the published literature. Of those 29, we identified and screened publications for 15. All of the 14 trial records for which we did not identify publications were relevant to KQ 3. These 14 trials could potentially provide additional evidence on the comparative safety and effectiveness of specific anticoagulation therapies, antiplatelet therapies, and procedural interventions for preventing thromboembolic events involving 9,230 patients. Note that our included 35 studies for KQ 3 involved approximately 114,000 patients and therefore we did not believe that these trials would significantly impact our findings.

Figure B. Literature flow diagram



^aSome studies were relevant to more than one KQ.

Abbreviation: KQ=Key Question

KQ 1. Predicting Thromboembolic Risk

Key Points from the Results chapter are:

- Based on a meta-analysis of seven studies, there is low strength of evidence that the continuous CHADS₂ score provides modest stroke risk prediction (c-statistic of 0.71; 95% CI, 0.65 to 0.77).
- Based on a meta-analysis of four studies, there is low strength of evidence that the continuous CHA₂DS₂-VASc score provides modest stroke risk prediction (c-statistic of 0.71; 95% CI, 0.64 to 0.79).
- Based on a meta-analysis of four studies, the categorical Framingham score provides limited risk prediction with an estimated c-statistic of 0.62 (95% CI, 0.61 to 0.64) (moderate strength of evidence).
- There is insufficient evidence for the relationship between LA thrombus on echocardiograph and subsequent stroke based on five studies which reported discrepant results.
- Of the tools reviewed, the CHADS₂ and CHA₂DS₂-VASc continuous risk scores appear to be similar and the most predictive of stroke events when compared with the CHADS₂ categorical score, the CHA₂DS₂-VASc categorical score, and the Framingham categorical score. This finding was, however, statistically significant only when compared with the Framingham categorical score. Other comparisons were not possible given limited data.

Overall, 31 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, 15 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 and multisite design, with about a third of all studies taking place in the United States and the rest in other countries, primarily in Europe.

The number of patients included in studies ranged from fewer than 200 to 132,372, with overlap in patient populations between some studies; altogether, the included studies analyzed data from over 400,000 unique patients. The mean age of study participants ranged from 53–81 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 1–12 years.

Thirteen studies used prospective cohorts to identify patients, while 16 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 CHADS₂ score (22 studies). Six studies examined the CHA₂DS₂-VASc, and five the Framingham risk tool. Five studies examined the use of transesophageal echocardiography (TEE) for evaluation of left atrial characteristics and stroke risk, and one study used magnetic resonance imaging (MRI) to examine this relationship. Finally, three studies described the prediction role of international normalized ratio (INR) values for stroke risk.

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

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

Tool	Number of Studies (Patients)	Strength of Evidence and Effect Estimate ^a
CHADS ₂ (Categorical)	6 (210,033)	SOE=Insufficient
CHADS ₂ (Continuous)	7 (209,464)	SOE=Low Modest risk prediction (c-statistic=0.71; 95% CI, 0.65 to 0.77)
CHA ₂ DS ₂ -VASc (Categorical)	4 (161,373)	SOE=Insufficient
CHA ₂ DS ₂ -VASc (Continuous)	4 (201,620)	SOE=Low Modest risk prediction (c-statistic=0.71; 95% CI, 0.64 to 0.79)
Framingham (Categorical)	4 (88,962)	SOE=Moderate Limited risk prediction (c-statistic=0.62; 95% CI, 0.61 to 0.74)
Framingham (Continuous)	2 (80,928)	SOE=Insufficient
Imaging	0	SOE=Insufficient
INR	0	SOE=Insufficient

^aAll strength of evidence ratings of “Insufficient” are shaded in grey.

Abbreviations: CI=confidence interval; 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; INR=international normalized ratio; SOE=strength of evidence

KQ 2. Predicting Bleeding Risk

Key Points from the Results chapter are:

- Based on five studies comparing the Bleeding Risk Index (BRI), HEMORR₂HAGES, HAS-BLED, and ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation), in predicting major bleeding rates among patients with AF on warfarin, the HAS-BLED tool appears to have the highest predictive accuracy for bleeding events in this population, although no study directly compared HAS-BLED with ATRIA (low strength of evidence).
- Based on three studies comparing BRI, HEMORR₂HAGES, and HAS-BLED, in predicting major bleeding rates among patients with AF off of antithrombotic therapy, the HAS-BLED tool appears to have the highest predictive accuracy for bleeding events in this population (low strength of evidence).
- Based on two studies comparing BRI, HEMORR₂HAGES, and HAS-BLED, in predicting major bleeding rates among patients with AF on aspirin alone, the HAS-BLED tool appeared to have the highest predictive accuracy for bleeding events in this population (low strength of evidence).
- Although six studies generally suggested increasing rates of major bleeding with increasing CHADS₂ among patients on warfarin, aspirin, and off antithrombotic therapy, data were not provided to fully evaluate the predictive accuracy of CHADS₂ for major bleeding events (insufficient strength of evidence).
- Although one study suggested increasing rates of major bleeding with increasing CHA₂DS₂-VASc among patients on warfarin, aspirin, and off antithrombotic therapy, data were not provided to fully evaluate the predictive accuracy of CHA₂DS₂-VASc for major bleeding events (insufficient strength of evidence).

Fifteen studies met our inclusion criteria. Apart from a shared focus on outpatient settings, the included studies represented variation in geographical location, study design, quality, and patient characteristics. Seven studies analyzed prospective data (including data from RCTs), while eight analyzed retrospective data (including registries). All studies were conducted primarily in the outpatient setting, although one study did not report setting. Two-thirds of the studies were multicenter, and all but two were conducted in Europe and the United States. Nine studies were of good methodological quality, four were of fair quality, and two were of poor quality.

The number of patients included in studies ranged from fewer than 300 to 132,372, with overlap in patient populations between some studies; altogether, the included studies analyzed data from approximately 219,363 unique patients. The mean age of study participants ranged from 65–80 years. The proportion of male patients ranged from approximately 40–60 percent. Study followup duration ranged from 1–12 years.

Regarding the outcomes assessed, 14 studies reported the diagnostic accuracy and impact on clinical decisionmaking of bleeding risk scores with respect to major bleeding, two reported these outcomes with respect to intracranial hemorrhage, and a single study reported these outcomes with respect to minor bleeding. Clinical tools of interest included risk scores and INR indices (INR, time in therapeutic range [TTR], and standard deviation of transformed INR [SDT_{INR}]).

Table B summarizes the strength of evidence for tools predicting bleeding risk. Details about the specific components of these ratings (risk of bias, consistency, directness, and precision) are available in the main report.

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

Tool	Number of Studies (Patients)	Strength of Evidence and Effect Estimate ^a
Summary c-statistic		
ATRIA	1 (3,063)	SOE=Insufficient
Bleeding Risk Score	3 (14,183)	SOE=Moderate Limited risk prediction (c-statistic ranging from 0.56 to 0.65)
HAS-BLED	3 (129,369)	SOE=Moderate Modest risk prediction (c-statistic ranging from 0.66 to 0.80)
HEMORR ₂ HAGES	5 (135,233)	SOE=Moderate Limited risk prediction (c-statistic=0.68; 95% CI, 0.61 to 0.74)
CHADS ₂	6 (155,220)	SOE=Insufficient
CHA ₂ DS ₂ -VASc	1 (132,372)	SOE=Insufficient
Comparative Predictive Abilities		
Major bleeding rates among patients with AF on warfarin	5 (142,346)	SOE=Low HAS-BLED tool appears to have the highest predictive accuracy
Major bleeding rates among patients with AF off of antithrombotic therapy	3 (14,576)	SOE=Low HAS-BLED tool appears to have the highest predictive accuracy
Major bleeding rates among patients with AF on aspirin alone	2 (7,247)	SOE=Low HAS-BLED tool appears to have the highest predictive accuracy

^aAll strength of evidence ratings of “Insufficient” are shaded in light grey.

Abbreviations: AF=atrial fibrillation; ATRIA=Anticoagulation and Risk Factors in Atrial Fibrillation; CHADS₂=Congestive heart failure, Hypertension, Age \geq 75, Diabetes mellitus, prior Stroke/transient ischemic attack (2 points); CHA₂DS₂-VASc=Congestive heart failure/left ventricular ejection fraction \leq 40%, Hypertension, Age \geq 75 (2 points), Diabetes mellitus, prior Stroke/transient ischemic attack/thromboembolism (2 points), Vascular disease, Age 65–74, Sex category female; 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; HEMORR₂HAGES=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 from the Results chapter are:

- Warfarin reduces the risk of non-fatal and fatal ischemic stroke when compared with aspirin (moderate strength of evidence); on the other hand, warfarin is associated with increased annual rates of severe bleeding complications (moderate strength of evidence). These findings are based on two retrospective studies (one good quality and one poor quality) involving 99,061 patients.
- The combination of aspirin + clopidogrel demonstrated similar rates of stroke when compared with aspirin alone in one trial involving 7,554 patients, but showed a significant reduction in stroke in the aspirin + clopidogrel arm in a smaller study of 593 patients (low strength of evidence for similar rates of stroke between treatments); in both RCTs, the combination was associated with higher rates of major bleeding (high strength of evidence).
- Clopidogrel monotherapy is associated with increased risk of non-fatal and fatal ischemic stroke when compared with warfarin monotherapy, with no differences in major bleeding (moderate strength of evidence). This is based on one large retrospective good-quality study involving 54,636 patients.
- Warfarin is superior to aspirin plus clopidogrel for the prevention of stroke, systemic embolism, MI, or vascular death, with similar rates of major bleeding (moderate strength of evidence). This finding is based on one large good-quality RCT of 6,706 patients which was stopped early and a retrospective good-quality study of 53,778 patients.
- Adding clopidogrel to warfarin has no benefits on stroke prevention (low strength of evidence) and is associated with increased risk of non-fatal and fatal bleeding when compared with warfarin alone (moderate strength of evidence). This finding is based on one good-quality retrospective study involving 52,349 patients
- Triple therapy with warfarin + ASA + clopidogrel substantially increases the risk of non-fatal and fatal bleeding (moderate strength of evidence) with no benefits on preventing ischemic stroke when compared with warfarin alone (low strength of evidence). This finding is based on one good-quality retrospective study involving 52,180 patients
- A Factor II inhibitor (dabigatran) at a 150 mg is superior to warfarin in reducing the incidence of composite of stroke (including hemorrhagic) or systemic embolism, with no significant difference in the occurrence of major bleeding (high strength of evidence). Dabigatran increased MI risk (moderate strength of evidence). This finding is based on one large good-quality RCT involving 12,098 patients from the larger RE-LY trial of 18,113 patients.
- A Factor II inhibitor (dabigatran) at a 110 mg dose is non-inferior to warfarin for the outcome of the composite of stroke or systemic embolism and is associated with a reduction in major bleeding when compared with warfarin. Dabigatran increased MI risk

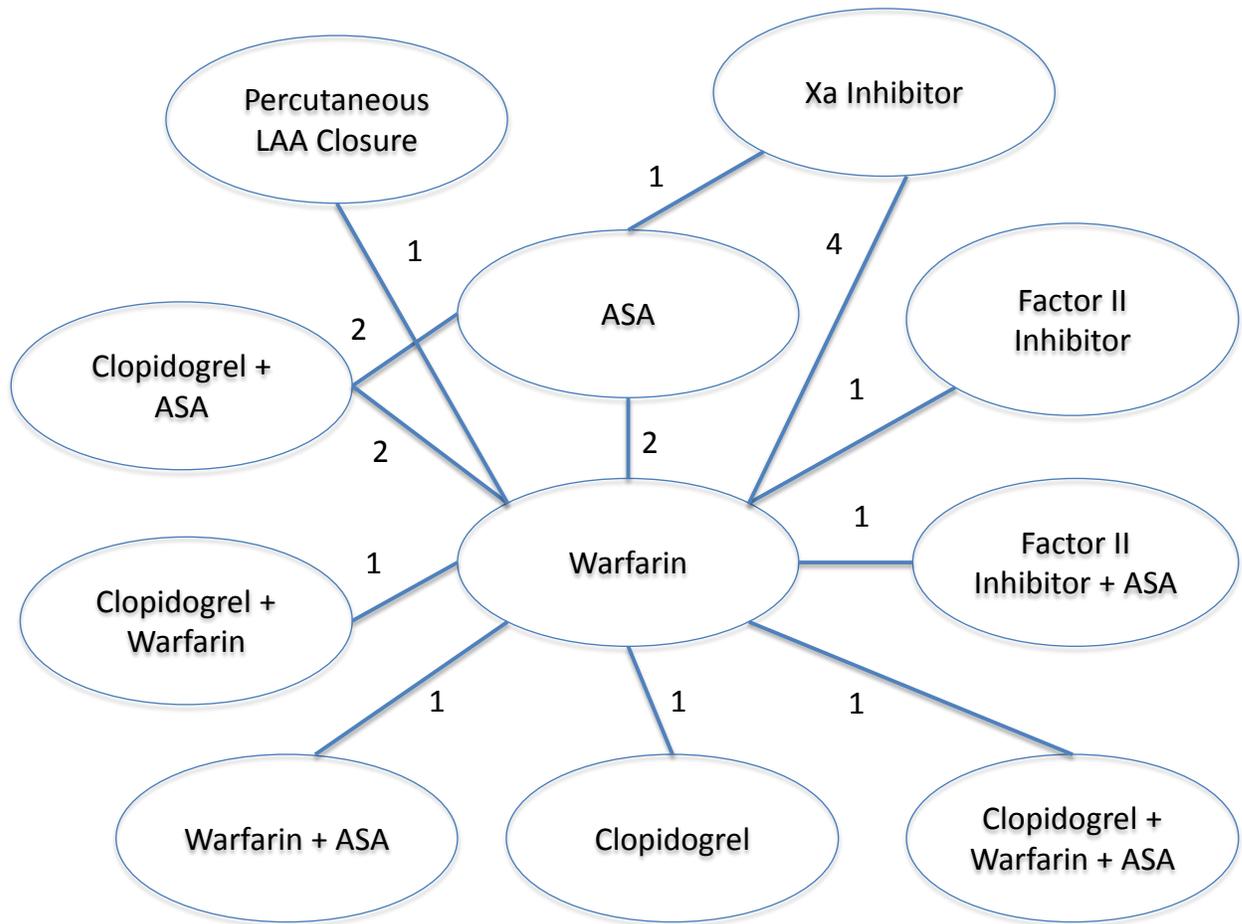
(moderate strength of evidence). The rates of intracerebral hemorrhage are significantly lower with both dabigatran doses compared with warfarin (high strength of evidence). This finding is based on one large good-quality RCT involving 12,037 patients from the larger RE-LY trial of 18,113 patients.

- The direct Xa inhibitor apixaban compared with aspirin was superior in reducing the incidence of stroke and systemic embolism, with similar hemorrhagic events, including major bleeding in patients who are not suitable for oral anticoagulation (high strength of evidence). This finding is based on one good-quality RCT involving 5,599 patients.
- The Xa inhibitor apixaban is superior in reducing the incidence of stroke, systemic embolism, major bleeding, and all-cause mortality when compared with warfarin (high strength of evidence). This finding is based on one good-quality RCT involving 18,201 patients.
- The Xa inhibitor rivaroxaban is non-inferior to warfarin in preventing stroke and systemic embolism, with similar rates of major bleeding and death. Among patients receiving the drug, rivaroxaban is superior to warfarin for the prevention of stroke (high strength of evidence). This finding is based on one good quality RCT involving 14,264 patients.
- Percutaneous left atrial appendage (LAA) closure is non-inferior to warfarin on the primary composite outcome of stroke, cardiovascular death, and systemic embolism, with less risk of hemorrhagic stroke (low strength of evidence). Adverse safety events occur at a higher rate with the procedure. This is based on one good-quality RCT involving 707 patients.
- Patients with renal impairment, with different INR control, and with prior stroke seem to benefit equally from the new anticoagulant agents when compared with warfarin (low strength of evidence). This finding is based on one study of patients with renal impairment, two studies of patients with different INR control, and seven studies of patients with prior stroke.

Thirty-six studies published between 2000 and 2011 were identified. The majority of studies (n=24) were multicenter and included outpatients (n=20). A total of 20 RCTs, 9 retrospective studies, and 7 prospective cohorts were included in our analyses. The number of patients included in studies ranged from 30 to 132,372, with a total of 245,828 patients. Sixteen studies were sponsored by industry, 3 by government, and 17 had either no sponsorship or this information was unclear. Nineteen studies were considered of good quality, 10 of fair quality, and 7 were of poor quality.

Figure C represents the treatment comparisons evaluated for this KQ.

Figure C. Overview of treatment comparisons evaluated for KQ 3



Abbreviations: ASA=aspirin; KQ=Key Question; LAA=left atrial appendage

As Figure C shows, most comparisons were only explored in a limited number of studies, although many of these were good-quality RCTs involving over 5,000 patients. The Xa inhibitor versus warfarin comparison was the only comparison 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 when 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 main report.

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

Outcome	Number of Studies (Subjects)	SOE and Magnitude of Effect^a (95% CI)
ASA versus Warfarin		
Ischemic stroke	2 (99,061)	SOE=Moderate Two retrospective studies showing consistent reduction in stroke for patients on warfarin compared to ASA
Bleeding	2 (99,061)	SOE=Moderate Warfarin is associated with increased rates of severe bleeding
All-cause mortality	1 (601)	SOE=Insufficient
Warfarin + ASA versus Warfarin		
Ischemic stroke	1 (69,264)	SOE=Moderate HR 1.27 (95% CI, 1.14 to 1.40) increase in warfarin + ASA arm
Bleeding	1 (69,264)	SOE=Moderate HR 1.83 (95% CI, 1.72 to 1.96) increase in warfarin + ASA arm
Clopidogrel + ASA versus ASA		
Any stroke	2 (8,147)	SOE=Low One large RCT showing similar rates (HR 1.03 [95% CI, 0.49 to 2.13]), but another smaller study showed significant reduction in clopidogrel + ASA arm (HR 0.72 [95% CI, 0.62 to 0.83]); low strength of evidence of similar rates of stroke between treatment arms
Ischemic stroke	2 (8,147)	SOE=Low One large RCT showing similar rates (HR 0.96 [95% CI, 0.46 to 2.01]), but another smaller study showed significant reduction in clopidogrel + ASA arm (HR 0.68 [95% CI, 0.57 to 0.80]); low strength of evidence of similar rates of stroke between treatment arms
Hemorrhagic stroke	2 (8,147)	SOE=Moderate Similar between treatment groups in both studies
Major bleeding	1 (7,554)	SOE=High Clopidogrel + ASA associated with higher rates (HR 1.57 [95% CI, 1.29 to 1.92])
Intracranial bleeding	2 (8,147)	SOE=Low One large RCT showing higher rate with clopidogrel + ASA (HR 1.87 [95% CI, 1.19 to 2.94]), but other study showed other showed no difference (0.62)
Extracranial bleeding	2 (8,147)	SOE=Low One large RCT showing higher rate with clopidogrel + ASA (HR 1.51 [95% CI, 1.21 to 1.88]), but other study showed other showed no difference (0.51)
All-cause mortality	2 (8,147)	SOE=Moderate Did not differ between arms in either study (in the 2 studies, HR 0.98 [95% CI, 0.89 to 1.08] and HR 1.12 [95% CI, 0.65 to 1.90])
Death from vascular causes	2 (8,147)	SOE=Moderate Did not differ between arms in either study (in the 2 studies, HR 1.00 [95% CI, 0.89 to 1.12] and HR 1.68 [95% CI, 0.83 to 3.42])
Myocardial infarction	2 (8,147)	SOE=Moderate Did not differ between arms in either study (in the 2 studies, HR 0.78 [95% CI, 0.59 to 1.03] and HR 1.43 [95% CI, 0.51 to 4.01])
Clopidogrel versus 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 groups (HR 1.06 [95% CI, 0.87 to 1.29])
Clopidogrel + ASA versus Warfarin		
Stroke or systemic embolism	2 (60,484)	SOE=High Clopidogrel + ASA increased risk (in the 2 studies, HR 1.56 [95% CI, 1.17 to 2.10] and HR 1.72 [95% CI, 1.24 to 2.37])

Outcome	Number of Studies (Subjects)	SOE and Magnitude of Effect^a (95% CI)
Hemorrhagic stroke	1 (6,706)	SOE=Moderate Increased risk in warfarin group (HR 0.34 [95% CI, 0.12 to 0.93])
Major bleeding	2 (60,484)	SOE=Low Large RCT showed no difference (HR 1.10 [95% CI, 0.83 to 1.45]), retrospective study showed greater risk in clopidogrel + ASA arm (HR 1.66 [95% CI, 1.34 to 2.04]); low strength of evidence of similar rates of major bleeding between treatment arms
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 MI occurred at rates of less than 1% per year in both groups and was not significantly different between treatments
Clopidogrel + Warfarin versus Warfarin		
Ischemic stroke	1 (52,349)	SOE=Low No difference between treatments (HR 0.70 [95% CI, 0.35 to 1.40])
Bleeding	1 (52,349)	SOE=Moderate Higher for patients on clopidogrel + warfarin (HR 3.08 [95% CI, 2.32 to 3.91])
Warfarin + ASA + Clopidogrel versus Warfarin		
Ischemic stroke	1 (52,180)	SOE=Low No difference between treatments (HR 1.45 [95% CI, 0.84 to 2.52])
Bleeding	1 (52,180)	SOE=Moderate Higher for patients on clopidogrel + warfarin (HR 3.70 [95% CI, 2.89 to 4.76])
Factor II Inhibitor (Dabigatran 150 mg) versus Warfarin		
Stroke or systemic embolism	1 (12,098)	SOE=High Dabigatran reduced risk (HR 0.66 [95% CI, 0.53 to 0.82])
Ischemic or uncertain stroke	1 (12,098)	SOE=Moderate Dabigatran reduced risk (HR 0.76 [95% CI, 0.60 to 0.98])
Hemorrhagic stroke	1 (12,098)	SOE=High Dabigatran reduced risk (HR 0.26 [95% CI, 0.14 to 0.49])
Major bleeding	1 (12,098)	SOE=High No difference (HR 0.93 [95% CI, 0.81 to 1.07])
Intracranial bleeding	1 (12,098)	SOE=High Dabigatran reduced risk (HR 0.40 [95% CI, 0.27 to 0.60])
All-cause mortality	1 (12,098)	SOE=Moderate No difference (HR 0.88 [95% CI, 0.77 to 1.00])
Death from vascular causes	1 (12,098)	SOE=Moderate Dabigatran reduced risk (HR 0.85 [95% CI, 0.72 to 0.99])
Myocardial infarction	1 (12,098)	SOE=Moderate Dabigatran increased risk (HR 1.38 [95% CI, 1.00 to 1.91])
Adverse events	1 (12,098)	SOE=Moderate Dyspepsia was more common with dabigatran (11.3% of patients with 150 mg compared with 5.8% with warfarin, p<0.001). No differences in liver function or other adverse events were seen between groups.
Factor II Inhibitor (Dabigatran 110 mg) versus Warfarin		
Stroke or systemic embolism	1 (12,037)	SOE=High No difference (HR 0.91 [95% CI, 0.74 to 1.11])

Outcome	Number of Studies (Subjects)	SOE and Magnitude of Effect^a (95% CI)
Ischemic or uncertain stroke	1 (12,037)	SOE=Moderate No difference (HR 1.11 [95% CI, 0.89 to 1.40])
Hemorrhagic stroke	1 (12,037)	SOE=High Dabigatran reduced risk (HR 0.31 [95% CI, 0.17 to 0.56])
Major bleeding	1 (12,037)	SOE=High Dabigatran reduced risk (HR 0.80 [95% CI, 0.69 to 0.93])
Intracranial bleeding	1 (12,037)	SOE=High Dabigatran reduced risk (HR 0.31; 95% CI, 0.20 to 0.47))
All-cause mortality	1 (12,037)	SOE=Moderate No difference (HR 0.91 [95% CI, 0.80 to 1.03])
Death from vascular causes	1 (12,037)	SOE=Moderate No difference (HR 0.90 [95% CI, 0.77 to 1.06])
Myocardial infarction	1 (12,037)	SOE=Moderate Dabigatran increased risk (HR 1.35 [95% CI, 0.98 to 1.87])
Adverse events	1 (12,037)	SOE=Moderate Dyspepsia was more common with dabigatran (11.8% of patients with 110 mg compared with 5.8% with warfarin, p<0.001). No differences in liver function or other adverse events were seen between groups.
Xa Inhibitor (apixaban) versus 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 No difference (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])
Intracranial bleeding	1 (5,599)	SOE=Moderate No difference (HR 0.85 [95% CI, 0.38 to 1.90])
All-cause mortality	1 (5,599)	SOE=Moderate No difference (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])
Adverse events	1 (5,599)	SOE=Moderate No differences in liver function or other adverse events were seen between groups
Xa Inhibitor (apixaban) versus Warfarin		
Stroke or systemic embolism	1 (18,201)	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])
Major bleeding	1 (18,201)	SOE=High Apixaban reduced risk (HR 0.69 [95% CI, 0.60 to 0.80])
All-cause mortality	1 (18,201)	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])

Outcome	Number of Studies (Subjects)	SOE and Magnitude of Effect^a (95% CI)
Myocardial infarction	1 (18,201)	SOE=Moderate No difference (HR 0.88 [95% CI, 0.66 to 1.17])
Intracranial bleeding	1 (18,201)	SOE=High Apixaban reduced risk (HR 0.42 [95% CI, 0.30 to 0.58])
Adverse events	1 (18,201)	SOE=Moderate Adverse events occurred in almost equal proportions of patients in the apixaban group and the warfarin group (81.5% and 83.1%, respectively). Rates of abnormalities on liver function testing and liver-related serious adverse events were also similar in the two groups.
Xa Inhibitor (rivaroxaban) versus Warfarin		
Stroke or systemic embolism	1 (14,264)	SOE=High Rivaroxaban reduced risk (HR 0.79 [95% CI, 0.65 to 0.95])
Major bleeding	1 (14,264)	SOE=High No difference (HR 1.04 [95% CI, 0.90 to 1.20])
All-cause mortality	1 (14,264)	SOE=High No difference (HR 0.85 [95% CI, 0.70 to 1.02])
Myocardial infarction	1 (14,264)	SOE=High No difference (HR 0.81 [95% CI, 0.63 to 1.06])
Intracranial bleeding	1 (14,264)	SOE=High Rivaroxaban reduced risk (HR 0.67 [95% CI, 0.47 to 0.93])
Percutaneous LAA Closure versus Warfarin		
Ischemic stroke	1 (707)	SOE=Low 9 patients in the LAA group (1.3 events per 100 patient-years) and 6 patients in the warfarin group (1.6 events per 100 patient-years) had ischemic stroke.
All strokes	1 (707)	SOE=Moderate No difference (RR 0.71 [95% CI, 0.35 to 1.64])
Major bleeding	1 (707)	SOE=Low Less frequent in the LAA group than in the warfarin group (3.5% vs. 4.1%)
All-cause mortality	1 (707)	SOE=Moderate No difference (RR 0.0.62 [95% CI, 0.34 to 1.24])
Adverse events	1 (707)	SOE=Moderate Higher rate in LAA group (RR 1.69 [95% CI, 1.01 to 3.19])

^aAll strength of evidence ratings of “Insufficient” are shaded in light grey.

Abbreviations: ASA=aspirin; CI=confidence interval; HR hazard ratio; LAA=left atrial appendage; RCT=randomized controlled trial; RR=relative risk; SOE=strength of evidence

KQ 4. Anticoagulation Strategies for Patients Undergoing Invasive Procedures

Key Points from the Results chapter are:

- The included post-PCI studies were too small to be conclusive and reached different conclusions regarding the effectiveness of triple therapy compared with other combinations of therapies for both bleeding and ischemic outcomes.
- Studies of bridging strategies were hampered by the variety of procedures (RFA, other surgeries) and strategies assessed and provided inconclusive findings.
- Current evidence is insufficient to make any statements about the comparative safety and effectiveness of available strategies for anticoagulation in patients with nonvalvular AF who are undergoing invasive procedures (insufficient strength of evidence).

A total of eight studies were included in our analysis, of which five were prospective cohort studies and three were retrospective cohort studies. These studies assessed anticoagulation during or after ablation procedures, other operative procedures, or after a percutaneous coronary intervention (PCI). Studies were conducted in the United States, South America, Asia, and Europe between the years 1999 and 2009. Five of the studies were considered of good quality, two of fair quality, and one was rated as poor quality. The funding source was reported by only two studies, one of which was government funded, and one sponsored by industry.

Subjects ranged in age from a mean of 55–78.6 years; a total of 2,621 subjects were enrolled. Five studies evaluated anticoagulation therapies around non-PCI procedures, while three studies evaluated oral anticoagulation after a PCI with stenting.

Among studies looking at bridging therapies, two compared heparin with low molecular weight heparin (LMWH; enoxaparin specified in one study), while two compared different doses of enoxaparin with concomitant warfarin therapy or as standalone bridging therapy. Four of the studies assess anticoagulation strategies during or after RFA procedures, while one assessed bridging anticoagulation during other operative procedures.

Of the three post-PCI studies, all compared warfarin plus antiplatelet therapy with antiplatelet therapy alone; however, the specific individual comparator arms were different in each study. In addition, a single study also compared a strategy of LMWH with dual antiplatelet therapy.

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 main report.

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

Outcome	Number of Studies (Patients)	Strength of Evidence and Effect Estimate ^a
PCI/Stenting		
Major bleeding	2 (263)	SOE=Insufficient
Myocardial infarction	2 (585)	SOE=Insufficient
Mortality	2 (585)	SOE=Insufficient
Bridging Therapies		
Major and minor bleeding	4 (1,828)	SOE=Insufficient
Mortality	3 (874)	SOE=Insufficient
Other thromboembolic outcomes	5 (1,932)	SOE=Insufficient

^aAll strength of evidence ratings of “Insufficient” are shaded in light grey.

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

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

Key Points from the Results chapter are:

- 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

Key Points from the Results chapter are:

- 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 74 unique studies represented by 96 publications and involving over 700,000 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; however, the evidence was very limited or nonexistent regarding AF patients undergoing invasive procedures, switching among anticoagulant therapies, and starting or restarting anticoagulant therapy in patients with previous major bleeding events.

The current review underscores that further efforts are needed to continue to refine risk prediction tools, particularly in the context of newly available anticoagulants. 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, 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 (developed in 2006 and then the topic of a focused update in 2011) 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 (namely dabigatran, rivaroxaban, and apixaban), but the guidelines have not yet been updated to reflect this new evidence. Our systematic review provides a timely review of the evidence both in stroke prediction and prevention in the new era of oral anticoagulants and potential stroke prevention therapies.

Trials of dabigatran, rivaroxaban, and apixaban have demonstrated favorable efficacy and safety results compared with warfarin, but direct comparisons of their efficacy and safety are not possible because these medications have not been compared with one another. In addition, the trials used different dosing strategies, were performed in different health systems, used varying event definitions, and recruited populations at varying risk for stroke and bleeding. Thus, it is not possible to affirm here which medication is better, and cross-trial comparisons may not be reliable. The newer oral anticoagulants do, however, have different attributes and important advantages over warfarin and offer, after many years without options, new alternatives for the treatment of patients with nonvalvular AF who are at risk for stroke. 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 some of them have been demonstrated in large RCTs to be more effective than warfarin (apixaban and higher dose dabigatran).

- In addition to these stroke prevention benefits, these new oral anticoagulants appear to be safer than warfarin in that:
 - All of them caused less intracranial bleeding than warfarin.
 - Some of them (apixaban or dabigatran [lower dose]) caused less major bleeding, including gastrointestinal bleeding, than warfarin.
- Apixaban was more effective than aspirin in stroke prevention for patients not suitable for oral anticoagulation. In addition, apixaban was better tolerated than and as safe as aspirin.
- All the new oral anticoagulants were better tolerated than warfarin, and rates of study drug discontinuation were lower with the new agents when compared with warfarin.
- Recent evidence showed that for the first time a new oral anticoagulant agent (apixaban) reduced all-cause mortality in patients with AF.

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. It is, however, important to note that the shorter half-life of these drugs is a key feature that helps in the management of bleeding episodes in patients receiving these drugs.

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

Applicability

Studies were conducted wholly or partly in continental Europe and the United States or Canada. In general, concerns about study applicability were not a major factor for this project's body of evidence. The main issues related to applicability of the evidence base included concerns about short-term outcomes (8% of studies); concerns about large differences between demographics of study populations and community patients in terms of age, renal function, and comorbidities (5% of studies); concerns about composite outcomes that mix outcomes of different significance (5% of studies); and concerns about use of older versions of an intervention no longer in common use (5% of studies).

Research Gaps

In our analyses, we have identified research gaps for all the KQs examined, including research gaps in the areas of risk stratification for thromboembolic and bleeding risk, comparative effectiveness and safety of different anticoagulation strategies, as well as the comparative effectiveness and safety of changing anticoagulation treatments for different reasons. Results are described for each KQ below.

KQs 1–2: Predicting Thromboembolic and Bleeding Risk

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

We can identify well patients at risk for stroke, who usually are the same patients at high risk for bleeding. Thus, there is a need for a score that could be used for decisionmaking about antithrombotic therapy in AF patients taking into account both thromboembolic and bleeding risks. Scores that identify only patients at risk for stroke or only those at risk for bleeding are not so helpful since the clinical factors in these scores are usually similar. Another challenge is that both stroke events and bleeding events are on a spectrum of severity. For example, some strokes may have symptoms lasting <24 hours with complete resolution, whereas others can cause death. Additional studies utilizing prospectively constructed databases with longer-term outcomes data that compare all available risk prediction scores would be of great use in better clarifying which risk score system is superior in predicting major bleeding or thromboembolic risk. Specific to bleeding risk, additional prospective comparisons of the SDT_{INR} and TTR are needed to establish which variable has better predictive accuracy for major bleeding.

Also of note, although not addressed in this review, in an era of personalized medicine, it will 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.

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

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

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

KQ 3: Interventions for Preventing Thromboembolic Events

Although recent years have been exciting in stroke prevention and development of new agents as alternatives to warfarin, there are several evidence gaps that remain and should inform future research needs. Given the risks associated with AF, the growing number of patients with AF, and the costs and risks associated with stroke prevention for AF, our review highlights that a better understanding of comparative safety and effectiveness of newer anticoagulant therapies is of paramount importance. There is 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. 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 other comorbidities that also require the use of other antithrombotic agents. There are many antithrombotic agents 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 area with new antiplatelet (prasugrel and ticagrelor) and new anticoagulant agents (dabigatran, rivaroxaban, apixaban).

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

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

1. What are the comparative safety and effectiveness of specific anticoagulation therapies, antiplatelet therapies, and procedural interventions for preventing thromboembolic events?
 - a. For the above evidence gap, we suggest focusing specifically on the comparative effectiveness of Factor II inhibitors, Xa inhibitors, and other novel anticoagulants, and procedural interventions.
2. What are the comparative safety and effectiveness of specific anticoagulation therapies, antiplatelet therapies, and procedural interventions for preventing thromboembolic events specific to patients who have recently undergone rate or rhythm control procedures for treating their AF?
 - a. For the above evidence gap, we suggest focusing on methods of determining the comparative effectiveness and safety of available stroke prevention therapies, and strategies for determining longer term therapy given successful AF treatment.

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. Nonetheless, given the number of these procedures performed per year as well as the apparent uncertainty about optimal treatment of these patients, 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 numbers of treatment strategies available, initial research might be focused on comparing on continued anticoagulant therapy versus bridging therapies versus interruption of therapy (i.e., stopping anticoagulant therapy pre-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 required of an RCT to address this question, would be explore whether study designs other than RCTs would possible help decrease the evidence gap in this area.

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

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

Due to the increasing popularity of the new Xa agents, RCTs are needed to establish evidence to guide providers in managing patients with AF who are currently on warfarin and being switched to the newer Xa agents. Trials that include directions for managing patients who may be at different risk levels (as defined by CHADS₂ or Framingham risk scores), including type of AF, sex, age, and other co-existing risk factors. Additionally, evidence needs to be published in peer-reviewed journals on how to manage patients being switched off of the newer Xa agents and onto warfarin.

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

Conclusions

Overall, we found that CHADS₂ and CHA₂DS₂-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 initial early promise of reducing stroke and bleeding events when compared with warfarin, and apixaban in particular shows safety and efficacy in patients who are not candidates for warfarin. However, further studies are required for key clinical scenarios involving anticoagulation use and procedures, switching or bridging therapies, and when to start anticoagulation after a hemorrhagic event.

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Introduction

Background

Atrial Fibrillation and Stroke

Atrial fibrillation (AF) is a supraventricular tachyarrhythmia (any tachycardic rhythm originating above the ventricular tissue) and 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 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; by the year 2050 there will be an estimated 12.1 million (95% confidence interval [CI], 11.4 to 12.9) Americans with AF, representing a 2.4-fold increase since 2000. However, this estimate assumes no further increase in the age-adjusted incidence of AF beyond 2000. If the incidence of AF increases at the same pace, then the projected number of adults with AF would be 15.9 million, a 3-fold increase from 2000.⁵

Although generally not as immediately life-threatening as ventricular arrhythmias, AF is associated with significant morbidity and mortality. Patients with AF have increased risk of embolic stroke, heart failure, and cognitive impairment; reduced quality of life; and higher overall mortality.⁶⁻⁸ Patients with AF have a five-fold increased risk of stroke, and it is estimated that up to 25 percent of all strokes in the elderly are a consequence of AF.⁴ Furthermore, AF-related strokes are more severe, with patients twice as likely to be bedridden than 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, 2 to 7 times that of the general population.⁹ The risk of stroke increases from 1.5 percent for patients with AF who are 50–59 years old to 23 percent for those who are 80–89 years old.¹⁰ Congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, and prior stroke or transient ischemic attack (TIA) are considered independent risk factors for stroke as well as risk factors for AF. These risk factors are the elements that form the classic CHADS₂ risk score for stroke prevention.^{13,14} This score ranges from 0–6, with increasing scores corresponding to increasing stroke risk, and is easy to calculate and apply in clinical practice.¹ The adjusted annual rates of stroke vary from 1.9 percent in patients with a CHADS₂ score of 0, to 18.2 percent in patients with a CHADS₂ score of 6. Aggressive primary prevention and intervention once these risk factors are present are essential to optimally manage the increased risk of developing AF and stroke independently or as a result of AF.

Stroke Prevention Strategies in AF

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

on the last area. A separate CER focusing on the treatment of AF through rate or rhythm control is being conducted in parallel.

Strategies for preventing thromboembolic events can be categorized into (a) optimal risk stratification of patients, and (b) 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 TIA. As stated previously, these risk factors are the elements that form the CHADS₂ score.¹³ However, because of the overlap with factors also associated with increased risk of bleeding, the CHADS₂ score currently appears to be underused to guide decisions about antithrombotic therapy.

Lip and colleagues built upon the CHADS₂ score and other risk stratification schema to develop the CHA₂DS₂-VASc score (Congestive heart failure/left ventricular ejection fraction $\leq 40\%$, Hypertension, Age ≥ 75 [2 points], Diabetes mellitus, prior Stroke/transient ischemic attack/thromboembolism [2 points], Vascular disease, Age 65–74, Sex category female), which ranges from 0–9 and aims to be more sensitive than the CHADS₂ score, specifically seeking to identify patients at low risk for stroke based on earlier risk scores but for whom antithrombotic therapy may be beneficial, for example, women and younger patients.¹⁵

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) can prolong the prothrombin time. In order to standardize the results, the prothrombin time test can be converted to an INR (international normalized ratio) value, which provides the result of the actual prothrombin time over a normalized value. It has been demonstrated that an INR value of 2–3 provides the best trade-off between preventing ischemic events and causing bleeding. Clinicians use the prothrombin time and INR as useful clinical tools to guide anticoagulation therapy.

Many factors are potentially related to bleeding risk in general (older age, known cerebrovascular disease, uncontrolled hypertension, history of myocardial infarction or ischemic heart disease, anemia, and concomitant use of antiplatelet therapy in anticoagulated patients). The HAS-BLED scale (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly [> 65 years], Drugs/alcohol concomitantly) was developed for estimating bleeding risk in patients with chronic AF treated with warfarin. Scores on this scale range from 0–9. A score ≥ 3 indicates a high risk of bleeding with oral anticoagulation and/or aspirin.¹⁶ The HAS-BLED score may aid decisionmaking in clinical practice and is recommended by the current European Society of Cardiology (ESC) AF guidelines.¹⁷ However, uncertainty remains both about whether other clinical or imaging tools might improve prediction of stroke or bleeding risk prediction, 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 to predict events. A comparative and thorough assessment of current tools could assist providers in understanding the clinical value of appropriately judging risk and treating accordingly. Also, an assessment of how application of these tools may improve outcomes could help improve the utility of their use in clinical practice.

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

Therapeutic Options for Stroke Prevention in AF

Vitamin K antagonists (VKAs) are highly effective for the prevention of stroke in patients with nonvalvular AF. VKAs such as warfarin have been in use for over 50 years. These compounds create an anticoagulant effect by inhibiting the γ -carboxylation of vitamin K-dependent factors (II, VII, IX, and X).¹⁸ In a meta-analysis of 29 randomized controlled trials (RCTs) including 28,000 patients with nonvalvular AF, warfarin therapy led to a 64 percent reduction in stroke (95% CI, 49 to 74%) compared with placebo. Even more importantly, warfarin therapy was associated with a 26 percent reduction in all-cause mortality (95% CI, 3 to 34%).¹⁹

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 increases the risk of thromboembolic events and bleeding, respectively. Warfarin-naïve patients experience a three-fold increased risk of bleeding in the first 90 days of treatment compared with patients already on warfarin.^{20,21} This increased risk of hemorrhage in warfarin-naïve patients also contributes to the underuse of warfarin in the elderly population with AF. Failure to prescribe warfarin in eligible patients is a pervasive problem, despite the adoption of performance measures and guidelines advocating its use in patients with nonvalvular AF who have moderate to severe risk of stroke.^{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. Thus, a large number of patients with AF who might benefit from warfarin are either not being offered treatment, are refusing to take it, or are stopping it.

New devices and systemic therapies have been developed for stroke prophylaxis and are in testing or have been approved for use. Mechanical interventions for stroke prophylaxis have emerged and are growing in use. For example, left atrial appendage (LAA) occlusive devices are an alternative treatment strategy used to prevent blood clot formation in patients with AF. 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, with approximately 18,000 subjects and evaluating the new direct Factor II (thrombin) dabigatran²⁶
- ROCKET AF, with approximately 14,000 subjects and evaluating the new direct factor Xa inhibitor rivaroxaban²⁷
- ARISTOTLE, with approximately 18,000 subjects and evaluating the new direct factor Xa inhibitor apixaban²⁸

The evolution of newer anticoagulation agents, per the large trials above, as well as the risks and benefits when compared to LAA occlusion devices and older antiplatelet and anticoagulation strategies, makes stroke prevention in AF an area of further clinical uncertainty that supports both the importance and appropriateness of further evidence development and a new systematic review of existing evidence. Furthermore, these new therapies highlight the need to reconsider their comparative effectiveness and safety when compared with standard antithrombotic and antiplatelet therapies and with each other.

Even with treatment for stroke prophylaxis in patients with nonvalvular AF, numerous unanswered questions persist around managing patients undergoing invasive or surgical procedures. Patients receiving long-term anticoagulation therapy may need to stop this therapy temporarily before undergoing certain procedures where the risk of bleeding is high. Because VKAs have a long half-life, patients need to stop these medications approximately 5 days before an invasive procedure. However, 5 days without an oral anticoagulant can increase the risk of ischemic events. Thus, one option often used in clinical practice is “bridging,” where 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. In summary, the real risk-benefit of bridging from VKAs to a parenteral anticoagulant in patients with AF undergoing an invasive procedure is unknown, and is currently under study in an National Institutes of Health (NIH) sponsored trial called BRIDGE (Bridging Anticoagulation in Patients who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure or Surgery).

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

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

Scope and Key Questions

Scope of the Review

This CER was funded by the Agency for Healthcare Research and Quality (AHRQ) and is designed to evaluate the comparative safety and effectiveness of stroke prevention strategies in patients with nonvalvular AF. Further details are provided under “Key Questions” and “Analytic Framework,” below, and in the section on “Inclusion and Exclusion Criteria” in the Methods chapter. To increase applicability to the U.S. setting, we restricted our review interventions available in the United States. For each Key Question (KQ), we further consider whether the comparative safety and effectiveness of the interventions evaluated differs among specific patient subgroups of interest, including patients with comorbid conditions, such as dementia, or renal or hepatic failure; patients with multiple coexisting conditions (e.g., combinations of hypertension, diabetes, congestive heart failure, coronary artery disease, and high cholesterol); patients with prior stroke (by type of event); patients with prior bleed (by type of bleed); patients in the therapeutic range (versus those not in range); type of AF (paroxysmal, persistent, and permanent); patients stratified by age; pregnant patients; patients stratified by race/ethnicity; and patients who are noncompliant with treatment.

Over the last decades, oral anticoagulation with VKAs has been the gold standard therapy for stroke prevention in nonvalvular AF. Limitations with monitoring and compliance of VKAs have fueled the development of new antithrombotic strategies, devices, and oral anticoagulants, including oral direct thrombin inhibitors and oral factor Xa inhibitors. After 60 years with essentially one class of drug for stroke prevention in nonvalvular AF, today there are several agents that are (or soon will be) available to treat these AF populations of varying CHADS₂ risk. So, there is a real challenge in how to best select the treatment option most suitable for a given patient as well as how to best utilize the available risk stratification tools to assist physicians in making important decisions. In the light of this new clinical scenario around patients with AF, comparative safety and effectiveness analyses of these novel agents and new strategies for patients with AF are needed. Existing systematic reviews of the evidence either do not include the most recent clinical evidence, or have not yet been performed exploring a broader spectrum of important clinical and policy questions of interest. Thus, a review of the available data will not only address these uncertainties, but it will define gaps in knowledge and identify important future research needs.

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

will be able to design and implement programs to make better use of scarce health care resources while improving the health status of adult patients with AF.

Key Questions

With input from our Key Informants, we constructed KQs using the general approach of specifying the Populations, Interventions, Comparators, Outcomes, Timings, and Settings of interest (PICOTS; see the section on “Inclusion and Exclusion Criteria” in the Methods chapter for details).

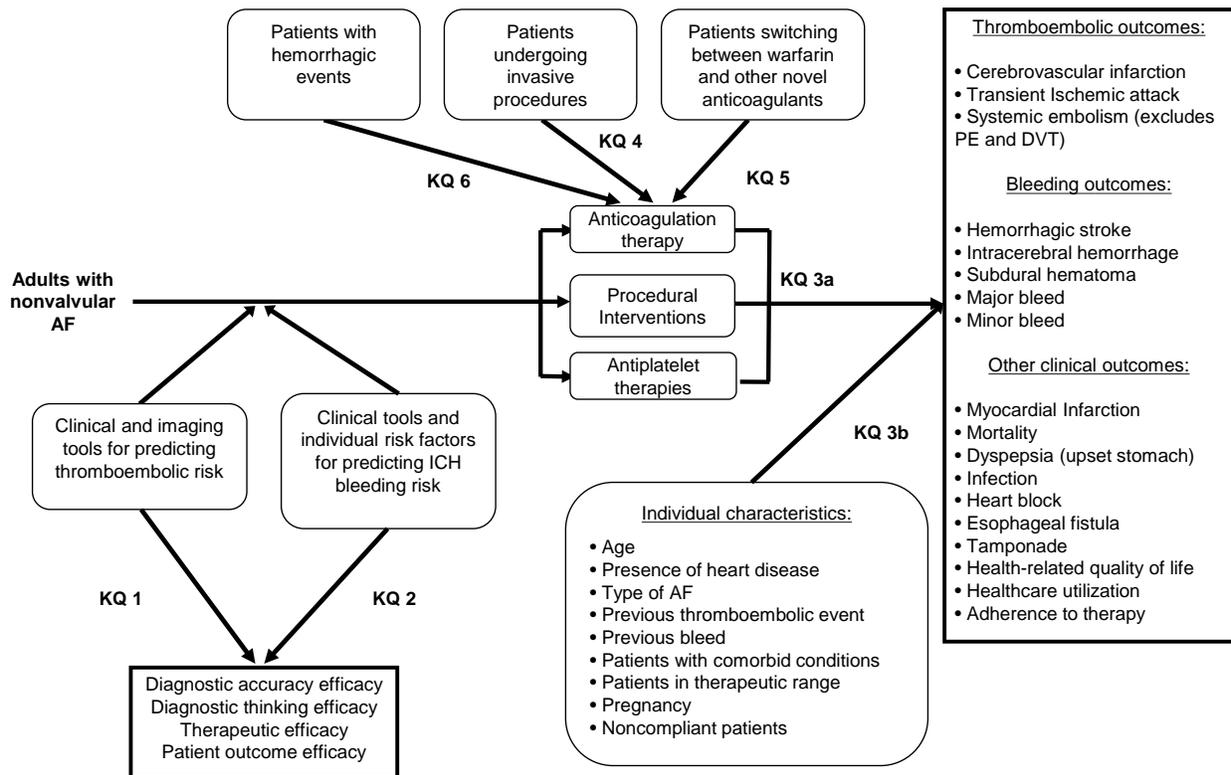
The KQs considered in this CER are:

- **KQ 1:** In patients with nonvalvular atrial fibrillation, what are the comparative diagnostic accuracy and impact on clinical decisionmaking (diagnostic thinking, therapeutic, and patient outcome efficacy) of available clinical and imaging tools for predicting thromboembolic risk?
- **KQ 2:** In patients with nonvalvular atrial fibrillation, what are the comparative diagnostic accuracy and impact on clinical decisionmaking (diagnostic thinking, therapeutic, and patient outcome efficacy) of clinical tools and associated risk factors for predicting bleeding events?
- **KQ 3:** What are the comparative safety and effectiveness of specific anticoagulation therapies, antiplatelet therapies, and procedural interventions for preventing thromboembolic events:
 - (c) In patients with nonvalvular atrial fibrillation?
 - (d) In specific subpopulations of patients with nonvalvular atrial fibrillation?
- **KQ 4:** What are the comparative safety and effectiveness of available strategies for anticoagulation in patients with nonvalvular atrial fibrillation who are undergoing invasive procedures?
- **KQ 5:** What are the comparative safety and effectiveness of available strategies for switching between warfarin and other novel oral anticoagulants, in patients with nonvalvular atrial fibrillation?
- **KQ 6:** What are the comparative safety and effectiveness of available strategies for resuming anticoagulation therapy or performing a procedural intervention as a stroke prevention strategy following a hemorrhagic event (stroke, major bleed, or minor bleed) in patients with nonvalvular atrial fibrillation?

Analytic Framework

Figure 1 depicts the analytic framework for this project.

Figure 1. Analytic framework



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

This figure depicts the KQs within the context of the PICOTS described elsewhere in this document. The patient population of interest is adults with nonvalvular AF. Interventions of interest are clinical and imaging tools for predicting thromboembolic risk (KQ 1); clinical tools and individual risk factors for predicting intracerebral hemorrhage bleeding risk (KQ 2); anticoagulation therapies, procedural interventions, and antiplatelet therapies in patients with nonvalvular AF (KQ 3a) and in specific subpopulations of patients with nonvalvular AF (e.g., age, presence of heart disease, type of AF, previous thromboembolic event, previous bleed, comorbid conditions, patients in therapeutic range, pregnant patients, and noncompliant patients) (KQ 3b); strategies for patients who are undergoing invasive procedures (KQ 4); strategies for patients who switch between warfarin and direct thrombin inhibitors (KQ 5); and strategies for patients with hemorrhagic events (KQ 6). The outcomes of interest are thromboembolic events (cerebrovascular infarction; TIA; and systemic embolism, excluding pulmonary embolism and deep vein thrombosis); bleeding outcomes (hemorrhagic stroke, intracerebral hemorrhage, subdural hematoma, major bleed, and minor bleed); other clinical outcomes (myocardial infarction, mortality, upset stomach, infection, heart block, esophageal fistula, tamponade, health-related quality of life, healthcare utilization, and adherence to therapy); and efficacy of the risk assessment tools (diagnostic accuracy, diagnostic thinking, therapeutic, and patient outcome efficacy).

Methods

The methods for this Comparative Effectiveness Review (CER) follow those suggested in the Agency for Healthcare Research and Quality (AHRQ) *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (hereafter referred to as the *Methods Guide*)²⁹ and *Methods Guide for Medical Test Reviews* (hereafter referred to as the *Medical Test Guide*).³⁰ The main sections in this chapter reflect the elements of the protocol established for the CER; certain methods map to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.³¹

Topic Refinement and Review Protocol

During the topic refinement stage, we solicited input from Key Informants representing medical professional societies/clinicians in the areas of general internal medicine, cardiology, cardiothoracic surgery, neurology, electrophysiology, and primary care; patients, scientific experts; and payers, to help define the Key Questions (KQs). The KQs were then posted for public comment for 4 weeks from September 19 to October 17, 2011, and the comments received were considered in the development of the research protocol. We next convened a Technical Expert Panel (TEP) comprising clinical, content, and methodological experts to provide input 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 at the AHRQ Effective Health Care Website.³²

Literature Search Strategy

Search Strategy

To identify relevant published literature, we searched PubMed[®], Embase[®], and the Cochrane Database of Systematic Reviews (CDSR), limiting the search to studies published from January 1, 2000, to the present. 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. Exact search strings are included in Appendix A. We supplemented the electronic searches with a manual search of citations from a set of key primary and systematic review articles.^{19,33-79} All citations were imported into an electronic database (EndNote[®] X4; Thomson Reuters, Philadelphia, PA).

As a mechanism to ascertain publication bias, we searched ClinicalTrials.gov to identify completed but unpublished studies. While the draft report is under peer review, we will update the literature search and include any eligible studies identified either during that search or through peer or public reviews in the final report.

We used several approaches to identify relevant grey 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. Grey literature databases included ClinicalTrials.gov; the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal; and ProQuest COS Conference Papers Index. Search terms used for these sources are provided in Appendix A.

Inclusion and Exclusion Criteria

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

Table 1. Inclusion and exclusion criteria

PICOTS Element	Inclusion Criteria	Exclusion Criteria
Populations	<ul style="list-style-type: none"> • Humans • Adults (age ≥18 years of age) • Patients with nonvalvular AF (including atrial flutter): <ul style="list-style-type: none"> ○ Paroxysmal AF (recurrent episodes that self-terminate in less than 7 days) ○ Persistent AF (recurrent episodes that last more than 7 days) ○ Permanent AF (an ongoing, long-term episode) ○ Patients with AF who experience acute coronary syndrome • Subgroups of potential interest include: <ul style="list-style-type: none"> ○ Patients who have comorbid conditions such as, dementia, or renal or hepatic failure ○ Patients with multiple coexisting conditions (e.g., combinations of hypertension, diabetes, congestive heart failure, coronary artery disease, and high cholesterol) ○ Patients with prior stroke (by type of event) ○ Patients with prior bleed (by type of bleed) ○ Patients in the therapeutic range (versus those not in range) ○ Type of AF (paroxysmal, persistent, and permanent) ○ Patients stratified by age ○ Pregnant patients ○ Patients stratified by race/ethnicity ○ Patients who are noncompliant with treatment. 	<ul style="list-style-type: none"> • Patients who have known reversible causes of AF (including but not limited to postoperative, hyperthyroidism) • All subjects are < 18 years of age, or some subjects are under < 18 years of age but results are not broken down by age
Interventions	<ul style="list-style-type: none"> • Clinical and imaging tools for assessment/evaluation of thromboembolic risk: <ul style="list-style-type: none"> ○ Clinical: <ul style="list-style-type: none"> ▪ CHADS₂ score ▪ CHA₂DS₂-VASc score ▪ Framingham risk score ○ Imaging: <ul style="list-style-type: none"> ▪ Transthoracic echo (TTE) ▪ Transesophageal echo (TEE) 	None

PICOTS Element	Inclusion Criteria	Exclusion Criteria
	<ul style="list-style-type: none"> ▪ CT scans ▪ Cardiac MRIs • Clinical tools and individual risk factors for assessment/evaluation of intracerebral hemorrhage bleeding risk: <ul style="list-style-type: none"> ○ Patient age ○ Prior stroke ○ Type of AF (paroxysmal, persistent, permanent) ○ International normalized ratio (INR) ○ Dementia/cognitive impairment ○ Falls risk ○ HAS-BLED score ○ CHADS2 score ○ CHA₂S₂-VASc score ○ Framingham risk score ○ HEMORR₂HAGES score ○ ATRIA score ○ Bleeding Risk Index (BRI) • Anticoagulation therapy (all oral anticoagulants): <ul style="list-style-type: none"> ○ Warfarin (Coumadin[®]) ○ Vitamin K antagonists (VKAs) ○ Dabigatran (Pradaxa[®]) ○ Rivaroxaban (Xarelto[®]) ○ Apixaban (Eliquis[®]) ○ Edoxaban (DU-176b) • Procedural interventions: <ul style="list-style-type: none"> ○ Surgical procedures (surgical resection/removal of left atrial appendage [LAA]) ○ Minimally invasive procedures (Atriclip device) ○ Transcatheter procedures (WATCHMAN device, AMPLATZER cardiac plug, PLAATO device) • Antiplatelet therapy: <ul style="list-style-type: none"> ○ Clopidogrel (Plavix[®]) ○ Aspirin (ASA) ○ ASA + dipyridamole (Aggrenox[®]) ○ Dipyridamole (Persantine[®]) ○ Combinations of antiplatelets • Anticoagulation bridging therapies: <ul style="list-style-type: none"> ○ FDA-approved low molecular weight heparins (e.g., bemiparin, certoparin, dalteparin, enoxaparin, nadroparin, parnaparin, reviparin, tinzaparin) ○ IV heparin ○ Dabigatran (off-label usage) 	
Comparators	<ul style="list-style-type: none"> • KQ 1: Other clinical or imaging tools listed for assessing thromboembolic risk • KQ 2: Other clinical tools listed for assessing bleeding risk • KQ 3: Other anticoagulation therapies, antiplatelet therapies, or procedural interventions for preventing thromboembolic events 	For KQs 3 and 4, studies that did not include an active comparator

PICOTS Element	Inclusion Criteria	Exclusion Criteria
	<ul style="list-style-type: none"> • KQ 4: Other anticoagulation therapies • KQ 5: Other anticoagulation bridging strategies • KQ 6: Other strategies for resuming anticoagulation therapy following a hemorrhagic event 	
Outcomes	<p>Study assesses a patient-centered outcome of interest:</p> <ul style="list-style-type: none"> • Assessment of thromboembolic outcomes: <ul style="list-style-type: none"> ○ Cerebrovascular infarction ○ Transient ischemic attack (TIA) ○ Systemic embolism (note: excludes pulmonary embolism and deep vein thrombosis) • Prevention of bleeding outcomes: <ul style="list-style-type: none"> ○ Hemorrhagic stroke ○ Intracerebral hemorrhage ○ Subdural hematoma ○ Major bleed (stratified by type and location) ○ Minor bleed (stratified by type and location) • Occurrence of other clinical outcomes: <ul style="list-style-type: none"> ○ Myocardial infarction ○ Mortality ○ Infection ○ Heart block ○ Esophageal fistula ○ Tamponade ○ Dyspepsia (upset stomach) ○ Health-related quality of life and functional capacity ○ Health services utilization (hospital admissions, office visits, prescription drug use) ○ Long term adherence to therapy • Assessment of clinical and imaging tool efficacy for predicting thromboembolic risk and bleeding events: <ul style="list-style-type: none"> ○ Diagnostic accuracy efficacy ○ Diagnostic thinking efficacy ○ Therapeutic efficacy ○ Patient outcome efficacy 	Study does not include any outcomes of interest
Timing	<ul style="list-style-type: none"> • Timing of followup not limited 	None
Settings	<ul style="list-style-type: none"> • Inpatient and outpatient 	None
Study design	<ul style="list-style-type: none"> • Original data • All sample sizes • RCTs, prospective and retrospective observational studies, or registries 	<ul style="list-style-type: none"> • Not a clinical study (e.g., editorial, nonsystematic review, letter to the editor, case series)
Publications	<ul style="list-style-type: none"> • English-language publications only • Relevant systematic reviews, meta-analyses, or methods articles (used for background only)^a • Published January 1, 2000, to present 	<ul style="list-style-type: none"> • Non-English-language publications^b

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

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

Abbreviations: AF=atrial fibrillation; ASA=aspirin; ATRIA=Anticoagulation and Risk Factors in Atrial Fibrillation; BRI=Bleeding Risk Index; 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 $\leq 40\%$, Hypertension, Age ≥ 75 (2 points), Diabetes mellitus, prior Stroke/transient ischemic attack/thromboembolism (2 points), Vascular disease, Age 65-74, Sex category female; CT=computed tomography; FDA=U.S. Food and Drug Administration; HAS-BLED=Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (> 65 years), Drugs/alcohol concomitantly; HEMORR₂HAGES=Hepatic or renal disease, Ethanol abuse, Malignancy, Older (age > 75 years), Reduced platelet count or function, Re-bleeding risk (2 points), Hypertension (uncontrolled), Anemia, Genetic factors, Excessive fall risk, Stroke; INR=international normalized ratio; IV=intravenous; KQ=Key Question; LAA=left atrial appendage; MRI=magnetic resonance imaging; PICOTS=Populations, Interventions, Comparators, Outcomes, Timings, and Settings of interest; RCTs=randomized controlled trials; TIA=transient ischemic attack; TEE=transesophageal echocardiography; TTE=transthoracic echocardiography; VKAs=vitamin K antagonists

Study Selection

Using the prespecified inclusion and exclusion criteria described in Table 1, two investigators independently reviewed titles and abstracts for potential relevance to the KQs. Articles included by either reviewer underwent full-text screening. At the full-text review stage, paired researchers independently reviewed the articles and indicated a decision to “include” or “exclude” the article for data abstraction. When the two reviewers arrived at different decisions about whether to include or exclude an article, they reconciled the difference through review and discussion, or through a third-party arbitrator if needed. Full-text articles meeting our eligibility criteria were included for data abstraction. Relevant systematic review articles, meta-analyses, and methods articles were flagged for manual searching of references and cross-referencing against the library of citations identified through electronic database searching.

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

Data Extraction

The research team created data abstraction forms and evidence table templates for abstracting data for each KQ. Based on clinical and methodological expertise, a pair of investigators was assigned to abstract data from each eligible article. One investigator abstracted the data, and the second reviewed the completed abstraction form alongside the original article to check for accuracy and completeness. Disagreements were resolved by consensus, or by obtaining a third reviewer’s opinion if consensus could not be reached. To aid in both reproducibility and standardization of data collection, researchers received data abstraction instructions directly on each form created specifically for this project within the DistillerSR database.

We designed the data abstraction forms to collect the data required to evaluate the specified eligibility criteria for inclusion in this review, as well as demographic and other data needed for determining outcomes (intermediate, final, and adverse events outcomes). We paid particular attention to describing the details of the treatment (e.g., pharmacotherapy dosing, methods of procedural therapies), patient characteristics (e.g., etiology of AF, history of prior bleed or stroke), and study design (e.g., randomized controlled trial [RCT] versus observational) that may be related to outcomes. In addition, we described comparators carefully, as treatment standards

may have changed during the period covered by this review. Data necessary for assessing quality and applicability, as described in the *Methods Guide*,²⁹ were abstracted. Before the data abstraction form templates were used, they were pilot-tested with a sample of included articles to ensure that all relevant data elements were captured and that there was consistency/reproducibility between abstractors. Forms were revised as necessary before full abstraction of all included articles. Some outcomes were reported only in figures. In these instances, we used the web-based software, EnGauge Digitizer (<http://digitizer.sourceforge.net/>) to convert graphical displays to numerical data. Appendix B provides a detailed listing of the elements included in the data abstraction forms.

Quality (Risk of Bias) Assessment of Individual Studies

We evaluated the quality of individual studies using the approach described in the *Methods Guide*.²⁹ To assess quality, we used the strategy to (1) classify the study design, (2) apply predefined criteria for quality and critical appraisal, and (3) arrive at a summary judgment of the study's quality. We applied criteria for each study type derived from core elements described in the *Methods Guide*. Criteria of interest for all studies included similarity of groups at baseline, extent to which outcomes were described, blinding of subjects and providers, blinded assessment of the outcome(s), intention-to-treat analysis, differential loss to followup between the compared groups or overall high loss to followup, and conflicts of interest. Criteria specific to RCTs included methods of randomization and allocation concealment. For observational studies, additional elements such as methods for selection of participants, measurement of interventions/exposures, addressing any design-specific issues, and controlling confounding were considered. To indicate the summary judgment of the quality of individual studies, we used the summary ratings of good, fair, or poor based on the study's adherence to well-accepted standard methodologies and adequate reporting (Table 2).

Table 2. Definitions of overall quality ratings

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

For studies of diagnostic tests (KQs 1 and 2), we used the Quality Assessment tool for Diagnostic Accuracy Studies (QUADAS)-2⁸⁰ to assess quality. QUADAS-2 describes risk of bias in four key domains: patient selection, index test(s), reference standard, and flow and timing. The questions in each domain are rated in terms of risk of bias and concerns regarding

applicability, with associated signaling questions to help with these bias and applicability judgments.

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

Data Synthesis

We began our data synthesis by summarizing key features of the included studies for each KQ. To the degree that data were available, we abstracted information on study design; patient characteristics; clinical settings; interventions; and intermediate, final, and adverse event outcomes.

We determined the feasibility of completing a quantitative synthesis (i.e., meta-analysis). 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 considered meta-analysis for comparisons where at least three studies reported the same outcome. We grouped interventions by prediction tool (KQs 1–2) 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). 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. For comparison, we also performed fixed-effect meta-analyses. We present summary estimates, standard errors, and confidence intervals in our data synthesis. When we were able to calculate hazard ratios (HRs), we assumed that a HR between 0.9 and 1.2 with a narrow confidence interval which 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 KQ 1 and KQ 2 we synthesized available c-statistics for the predictive 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.⁸¹ Of note, a risk score may have a statistically significant association with a clinical outcome, but the relationship may not discriminate 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 predictive accuracy in the patient data set used to develop the model than in independent sets of patients; we therefore indicate when studies being discussed were actually used to develop the models they describe.

We anticipated that intervention effects might be heterogeneous. We hypothesized that the methodological quality of individual studies, study type, the characteristics of the comparator, and patients’ underlying clinical presentation would be associated with the intervention effects. 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*.^{29,82} and *Medical Test Guide*.³⁰ In brief, the approach requires assessment of four domains: risk of bias, consistency, directness, and precision (Table 3).

Table 3. Strength of evidence—required domains

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

Abbreviation: RCT=randomized controlled trial

Additional domains were used when appropriate, namely, strength of association (magnitude of effect), and 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. For outcomes where confounding was not believed to be an issue (e.g. predictive value of stroke and bleeding risk tools in KQ1/2), evidence based on observational studies started with a “moderate” strength of evidence rating. We assumed outcomes based on only one study to be consistent.

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

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

Applicability

We assessed applicability across our KQs using the method described in the *Methods Guide*.^{29,83} 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 used checklists to guide the assessment of applicability (see relevant sections of Appendix B). We used these data to evaluate the applicability to clinical practice, paying special attention to study eligibility criteria, demographic features of the enrolled population in comparison to the target population, characteristics of the intervention used in comparison with care models currently in use, and clinical relevance and timing of the outcome measures. We summarized issues of applicability qualitatively.

Peer Review and Public Commentary

The peer review process is our principal external quality-monitoring device. Nominations for peer reviewers were solicited from several sources, including the TEP and interested Federal agencies. Experts in a range of pertinent fields (general cardiology, heart failure, electrophysiology, neurology, internal medicine, stroke prophylaxis, pharmacological treatments for AF, geriatrics, primary care, health services research, epidemiology, and biostatistics) along with individuals representing stakeholder and user communities have been invited to provide external peer review of this draft report; AHRQ and an associate editor will also provide comments. The draft report will be posted on the AHRQ Web site for 4 weeks to elicit public comment. We will address all reviewer comments, revising the text as appropriate, and will document everything in a disposition of comments report that will be made available 3 months after the Agency posts the final report on the AHRQ Web site. We will include a list of peer reviewers submitting comments on this draft in the final report.

Results

Introduction

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

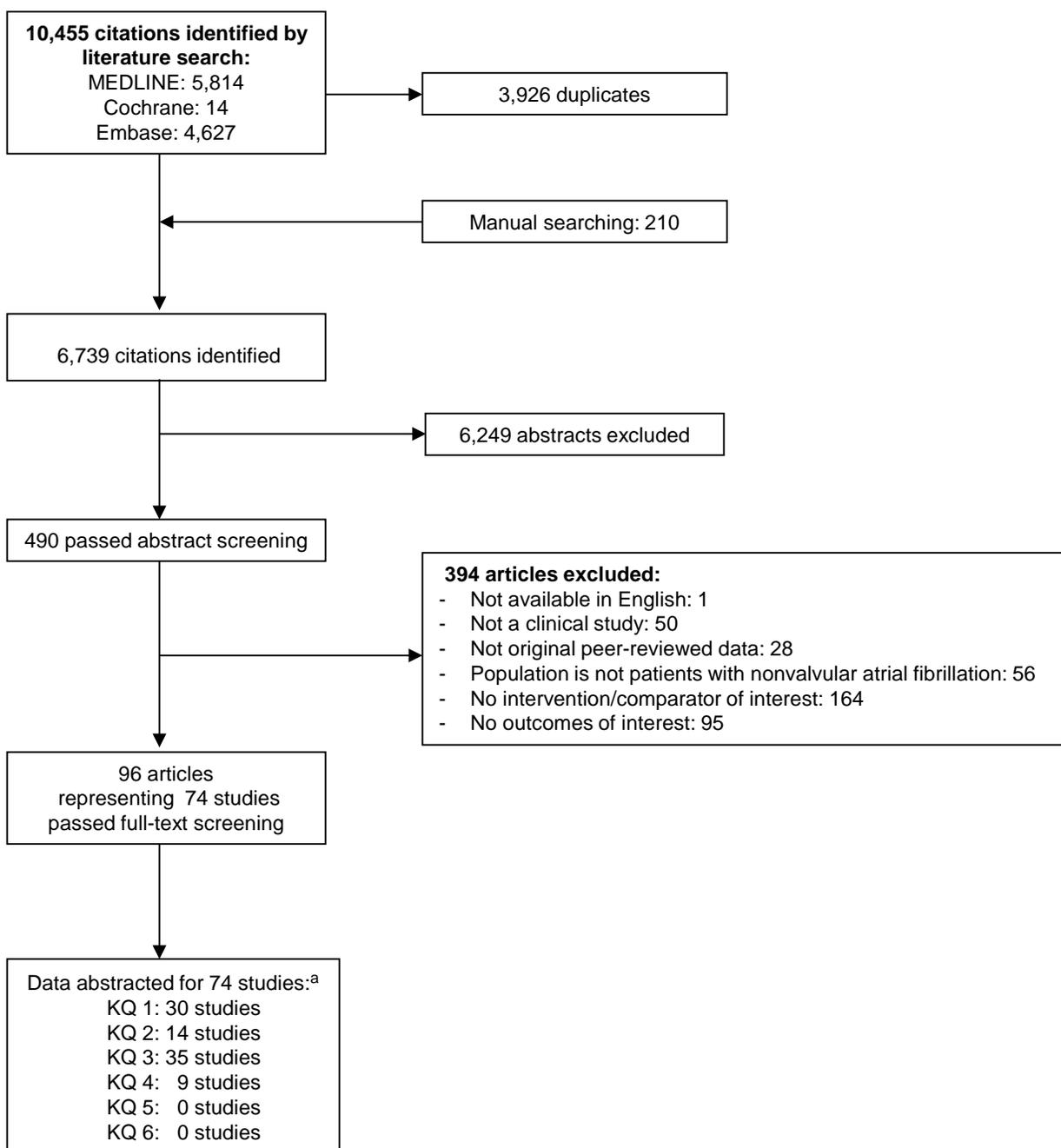
A list of abbreviations and acronyms used in this chapter is provided at the end of the report.

Results of Literature Searches

Figure 2 depicts the flow of articles through the literature search and screening process. Searches of PubMed®, Embase®, and CDSR yielded 10,455 citations, 3,926 of which were duplicate citations. Manual searching identified 210 additional citations, for a total of 6,739 citations. After applying inclusion/exclusion criteria at the title-and-abstract level, 490 full-text articles were retrieved and screened. Of these, 394 were excluded at the full-text screening stage, leaving 96 articles for data abstraction. These 96 articles described 74 unique studies. The relationship of studies to the review questions is as follows: 30 studies relevant to KQ 1, 14 studies relevant to KQ 2, 35 studies relevant to KQ 3, 9 studies relevant to KQ 4, 0 studies relevant to KQ 5, and 0 studies relevant to KQ 6 (some studies were relevant to more than one KQ).

Appendix C provides a detailed listing of included articles. Appendix D provides a complete list of articles excluded at the full-text screening stage, with reasons for exclusion. Appendix E provides a “study key” table listing the primary and companion publications for the 74 included studies.

Figure 2. Literature flow diagram



^aSome studies were relevant to more than one KQ.

Abbreviation: KQ=Key Question

Description of Included Studies

Overall, we included 74 studies represented by 96 publications: 30 studies were relevant to KQ 1, 14 studies to KQ 2, 35 studies to KQ 3, 9 studies to KQ 4, 0 studies to KQ 5, and 0 studies to KQ 6. Studies were conducted wholly or partly in continental Europe (47%), the United States

or Canada (31%), Asia (19%), the UK (15%), South or Central America (7%), Australia or New Zealand (7%), Africa (4%), and unspecified or other locations (7%). Further details on the studies included for each KQ are provided in the relevant results sections, below, and in Appendix F.

As described in the Methods chapter, we searched ClinicalTrials.gov to identify completed but unpublished studies as a mechanism for ascertaining publication bias. Our search yielded 170 trial records. A single reviewer identified 52 of these records as potentially relevant; 29 had been completed at least 1 year prior to our search of the database and review of the published literature. Of those 29, we identified and screened publications for 15. All of the 14 trial records for which we did not identify publications were relevant to KQ 3. These 14 trials could potentially provide additional evidence on the comparative safety and effectiveness of specific anticoagulation therapies, antiplatelet therapies, and procedural interventions for preventing thromboembolic events involving 9,230 patients. Note that our included 35 studies for KQ 3 involved approximately 114,000 patients.

Key Question 1. Predicting Thromboembolic Risk

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

Key Points

- Based on a meta-analysis of seven studies, there is low strength of evidence that the continuous CHADS₂ score provides modest stroke risk prediction (c-statistic of 0.71; 95% CI, 0.65 to 0.77).
- Based on a meta-analysis of four studies, there is low strength of evidence that the continuous CHA₂DS₂-VASc score provides modest stroke risk prediction (c-statistic of 0.71; 95% CI, 0.64 to 0.79).
- Based on a meta-analysis of four studies, the categorical Framingham score provides limited risk prediction with an estimated c-statistic of 0.62 (95% CI, 0.61 to 0.64) (moderate strength of evidence).
- There is insufficient evidence for the relationship between LA thrombus on echocardiograph and subsequent stroke based on five studies which reported discrepant results.
- Of the tools reviewed, the CHADS₂ and CHA₂DS₂-VASc continuous risk scores appear to be similar and the most predictive of stroke events when compared with the CHADS₂ categorical score, the CHA₂DS₂-VASc categorical score, and the Framingham categorical score. This finding was, however, statistically significant only when compared with the Framingham categorical score. Other comparisons were not possible given limited data.

Description of Included Studies

Overall, 31 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 (Appendix Table F-1). These articles explored tools in studies of diverse quality, design,

geographical location, and study characteristics. Fourteen included studies were of good quality,^{13,15,26,84-94} 15 of fair quality,⁹⁵⁻¹⁰⁹ and 2 of poor quality.^{110,111} Three studies enrolled patients from an inpatient setting;^{87,104,110} the majority (23) were from outpatient settings,^{13,15,26,84-86,88-94,96,97,99,102,105-109,111} and 2 studies enrolled patients from both types of settings.^{98,103} In three studies, the location of enrollment was not reported.^{95,100,101} The studies covered broad geographical locations with 12 studies conducted in Europe,^{15,84,86,90,94,95,99,103,107,109-111} 9 in the United States, 3 in the UK,^{96,104,105} 5 in Asia,^{85,87,93,102,108} and 1 in multiple nations;²⁶ 1 study did not report geography of enrollment.⁸⁹

Twelve studies were conducted at multiple sites,^{13,15,26,88-91,94,95,105,107,110} and 15 studies were conducted at a single center.^{85-87,93,97-104,106,108,109} In four studies, this information was unclear or not reported.^{84,92,96,111} Four studies were supported by industry.^{26,89,104,105} Two studies received solely government support,^{13,91} and in three studies funding was partially composed of government support.^{87,88,92} Two studies had no funding support,^{84,95} while in 17 studies funding was unclear or not reported.^{15,85,86,90,93,94,96,97,100,102,103,106-111}

Studies examined patients enrolled or with encounters between the years of 1948⁹² and 2008.⁹⁸ The number of patients included in studies ranged from fewer than 200^{87,98} to 132,372,¹¹⁰ with overlap in patient populations between some studies; altogether, the included studies analyzed data from over 400,000 unique patients. The mean age of study participants ranged from 53–81 years. None of the studies presented data on ethnicity of subjects. Male sex ranged from 44 percent¹⁰⁹ to 84 percent¹⁰⁶ in the included studies. Study followup duration ranged from 1–12 years.

Thirteen studies used prospective cohorts to identify patients,^{85,86,90,92,93,95,97,99,100,102,103,106,109} while 16 studies utilized retrospective cohorts,^{13,15,84,87,88,91,94,96,98,101,104,105,107,108,110,111} and 2 studies were RCTs.^{26,89} One study included only patients with paroxysmal AF,¹⁰⁸ one patients with paroxysmal or persistent AF,⁸⁹ one patients with permanent or paroxysmal AF,⁹⁰ one only patients with persistent AF,¹⁰⁹ two patients with permanent AF,^{99,105} and two studies that included patients with atrial flutter or fibrillation.^{84,110} The remaining studies did not report the type of AF examined.

Many studies examined multiple risk stratification scores concurrently. The tool most commonly examined for risk stratification was CHADS₂ score (22 studies^{13,15,26,84-86,88,89,94-97,99,101-105,107-110}) Six studies examined CHA₂DS₂-VASc;^{15,84,86,94,96,110} the Framingham risk score was evaluated in five studies.^{15,88,89,92,96} Five studies examined the use of TEE for evaluation of left atrial characteristics and stroke risk,^{87,90,93,100,106} and one study used MRI to examine this relationship.⁹⁸ Finally, three studies described the prediction role of INR values for stroke risk.^{88,90,109}

Detailed Synthesis

CHADS₂ Risk Tool

Twenty-two studies directly compared CHADS₂ risk score and its predictive ability for thromboembolic events (stroke or peripheral arterial, but excluding venous thrombus or pulmonary embolism; Table 4).^{13,15,26,84-86,88,89,94-97,99,101-105,107-110} Eighteen of the studies included patients on oral anticoagulant therapy.^{26,85,86,88,89,95-97,99,101-105,107-110} One study examined CHADS₂ risk and stroke outcomes among patients undergoing coronary revascularization with PCI,¹⁰⁷ one study in patients after surgical Maze procedure,⁹⁷ one in elderly patients (mean age 74 years),⁸⁶ two among Japanese patients,^{102,108} and one in Mediterranean patients.¹⁰⁹

The use of CHADS₂ to predict stroke risk varied among the studies. Four studies reported CHADS₂ score and stroke outcomes by individual CHADS₂ score.^{13,84,85,105} Seven studies investigated the classical CHADS₂ risk as categorical variables: low (CHADS₂=0), moderate (CHADS₂=1–2), and high (CHADS₂=3–6).^{15,86,88,89,95,96,103} Two studies examined the revised CHADS₂ score classification as continuous variables,^{86,110} and three studies did not report results by categorical or continuous CHADS₂ score.^{88,97,104} The remaining studies used varying categorical classifications.

Table 4. Thromboembolic events by CHADS₂ score and concomitant stroke prevention therapy (antiplatelet and/or anticoagulant) use

Study	No. of Patients	Results (Thromboembolic Rates)	Followup Period	Risk of Bias
<i>Patients on therapy</i>				
Olesen, 2012 ⁹⁴	47,576	CHADS ₂ =0: 1.59* CHADS ₂ =1: 4.92* * per 100 patients years	12 years	Low risk of bias
Poli, 2011 ⁹⁵	3,302	CHADS ₂ =0–1: 0.1%* CHADS ₂ =1–2: 0.7%* CHADS ₂ =3–6: 1.2%* * per 100 patients year	10019 patient-years	Low risk of bias
Poli, 2011 ⁸⁶	662	<u>Classic</u> CHADS ₂ = 0: 0% CHADS ₂ = 1–2: 3.9% CHADS ₂ =3–6: 6.7% <u>Revised</u> CHADS ₂ = 0: 0% CHADS ₂ = 1: 4.4% CHADS ₂ = 2–6: 5.3%	Mean 3.6 years	Low risk of bias
Ruiz-Nodar, 2011 ¹⁰⁷	604	CHADS ₂ ≤1: 4.8% CHADS ₂ >1: 5.4%	Mean 642.2 days	Low risk of bias
Van Staa, 2011 ⁹⁶	79,844	CHADS ₂ =Low: 1.0% CHADS ₂ =Moderate: 3.7% CHADS ₂ =High: 8.3%	Mean 4 years	High risk of bias
Ad, 2010 ⁹⁷	385	Mean CHADS ₂ 0.5	Mean 32.77 months	Low risk of bias

Study	No. of Patients	Results (Thromboembolic Rates)	Followup Period	Risk of Bias
Komatsu, 2010 ¹⁰⁸	344	CHADS ₂ =0: 0% CHADS ₂ =1: 0% CHADS ₂ =2: 1.4% CHADS ₂ =3: 4.4% CHADS ₂ =4: 13.5% CHADS ₂ =5: 0% CHADS ₂ =6: NR	Mean 60 months	Low risk of bias
Lip, 2010 ¹⁵	1,084	CHADS ₂ = 0: 1.4% CHADS ₂ = 1–2: 2.4% CHADS ₂ =3–6: 3.2%	1 year	Low risk of bias
Sadanaga, 2010 ⁸⁵	245	CHADS ₂ =0: 0% CHADS ₂ =1: 0.6% CHADS ₂ =2: 0.8% CHADS ₂ =3: 3.6% CHADS ₂ =4: 13.7% CHADS ₂ =5: 12.57% CHADS ₂ =6: 17.17%	Average 756 days	Low risk of bias
Connolly, 2009 ²⁶	18,113	CHADS ₂ =0–1: 0.93%* CHADS ₂ =2: 1.22%* CHADS ₂ =3–6: 2.44%* * per 100 patients year	2 years	Low risk of bias
Crandall, 2009 ¹⁰¹	343	CHADS ₂ =0: NR* CHADS ₂ =1: 1.29%* CHADS ₂ =2: 1.54%* CHADS ₂ =3: 2.07%* CHADS ₂ =4: 2.41%* CHADS ₂ =5: 2.68%* CHADS ₂ =6: NR* *reported as major cardiac events (stroke, myocardial infarction, death)	Mean 8.9 years	High risk of bias
Masaki, 2009 ¹⁰²	293	CHADS ₂ =0: 0% CHADS ₂ =1–2: 7.7% CHADS ₂ =3–4: 21.7% CHADS ₂ =5–6: 10%	703 days	Low risk of bias
Morgan, 2009 ¹⁰⁴	5,513	NR by risk score	1025 days	High risk of bias
Poli, 2009 ¹⁰³	662	CHADS ₂ =0–1: 0%* CHADS ₂ =1–2: 1.0%* CHADS ₂ =3–6: 1.9%* *per 100 patient-years	Mean 3.1 years, 2365 patient-years	Low risk of bias
Fang, 2008 ⁸⁸	10,932	NR by risk score	6 years	Low risk of bias

Study	No. of Patients	Results (Thromboembolic Rates)	Followup Period	Risk of Bias
Rietbrock, 2008 ¹⁰⁵	51,807	<u>Control</u> CHADS ₂ =0: 0.34% CHADS ₂ =1: 1.09% CHADS ₂ =2: 1.62% CHADS ₂ =3: 3.7% CHADS ₂ =4: 6.22% CHADS ₂ =5: 7.52% CHADS ₂ =6: 9.51% <u>Atrial Fibrillation</u> CHADS ₂ =0: 0.83% CHADS ₂ =1: 1.54% CHADS ₂ =2: 2.35% CHADS ₂ =3: 4.29% CHADS ₂ =4: 9.06% CHADS ₂ =5: 11.02% CHADS ₂ =6: 13.4%	Control: 2.74 years (median) AF: 2.46 years (median)	Low risk of bias
Ruiz Ortiz, 2008 ¹⁰⁹	1,137	CHADS ₂ =0: 2.88* CHADS ₂ =1: 5.8* CHADS ₂ =2: 5.16* CHADS ₂ =3: 14.78* CHADS ₂ ≥4: 22.02* * per 100 patient-years	21 months (484 patient-years)	Low risk of bias
Baruch, 2007 ⁸⁹	7,329	CHADS ₂ =0–1: 0%* CHADS ₂ =1–2: 1.0%* CHADS ₂ =3–6: 2.3%* * per patient-year	11245 patient-years Mean 1.5 years per patient	Low risk of bias
<i>Patients <u>off</u> therapy</i>				
Olesen, 2011 ⁸⁴	73,538	CHADS ₂ =0: 1.24% CHADS ₂ =1: 3.56% CHADS ₂ =2: 5.4% CHADS ₂ =3: 9.89% CHADS ₂ =4: 13.7% CHADS ₂ =5: 12.57% CHADS ₂ =6: 17.17%	10 years	Low risk of bias

Study	No. of Patients	Results (Thromboembolic Rates)	Followup Period	Risk of Bias
Gage, 2001 ¹³	1,733	<u>Unadjusted</u> CHADS ₂ =0: 1.2%* CHADS ₂ =1: 2.8%* CHADS ₂ =2: 3.6%* CHADS ₂ =3: 6.4%* CHADS ₂ =4: 8.0%* CHADS ₂ =5: 7.7%* CHADS ₂ =6: 44%* <u>Adjusted</u> CHADS ₂ =0: 1.9%* CHADS ₂ =1: 2.8%* CHADS ₂ =2: 4.0%* CHADS ₂ =3: 5.9%* CHADS ₂ =4: 8.5%* CHADS ₂ =5: 12.5%* CHADS ₂ =6: 18.5%* * per 100 patient-years	2121 patient-years	Low risk of bias
Patients on <u>and</u> off therapy				
Olesen, 2011 ¹¹⁰	132,372	<u>No Treatment</u> CHADS ₂ =0: 1.6% CHADS ₂ =1: 4.0% CHADS ₂ =2–6: 8.4% <u>Treatment (antiplatelet or anticoagulation)</u> CHADS ₂ =0: 1.4% CHADS ₂ =1: 2.8% CHADS ₂ =2–6: 6.0%	12 years	High risk of bias
Ruiz Ortiz, 2010 ⁹⁹	796	<u>On OAC</u> CHADS ₂ =0: 1% CHADS ₂ =1: 0.6% CHADS ₂ =2: 0.5% CHADS ₂ =3: 2.4% CHADS ₂ ≥ 4: 2.9% <u>No OAC</u> CHADS ₂ =0: 4.1% CHADS ₂ =1: 7.1% CHADS ₂ =2: 5.1% CHADS ₂ =3: 12.5% CHADS ₂ ≥4: 20%	Mean 2.4 years	Low risk of bias

Abbreviations: AF=atrial fibrillation; CHADS₂=Congestive heart failure, Hypertension, Age ≥75, Diabetes mellitus, prior Stroke/transient ischemic attack (2 points); No.=number; NR=not reported; OAC=oral anticoagulation

CHA₂DS₂-VASc Risk Tool

Six studies directly examined CHA₂DS₂-VASc risk score and its predictive ability for cerebral vascular events (Table 5).^{15,84,86,94,96,110} One study examined the predictive value in elderly patients (mean age 74 years).⁸⁶ Three studies had identical categorical classification of stroke risk by CHA₂DS₂-VASc score: low (score=0), moderate (score=1), and high (score=2–9).^{86,96,110} Two studies reported stroke outcomes by individual CHA₂DS₂-VASc score,^{15,84} while one reported stroke outcomes by CHA₂DS₂-VASc score from 0 to 4 points.⁹⁴ Three studies examined stroke risk among patients not treated with oral anticoagulant therapy.^{15,84,94}

Table 5. Thromboembolic events by CHA₂DS₂-VASc score and concomitant stroke prevention therapy (antiplatelet and/or anticoagulant) use

Study	No. of Patients	Results (Thromboembolic Event Rates per 100 Patient-Years)	Followup Period	Risk of Bias
<i>Patients on therapy</i>				
Olesen, 2012 ⁹⁴	47,576	CHA ₂ DS ₂ -VAsC=0: 0.76 CHA ₂ DS ₂ -VAsC=1: 1.44 CHA ₂ DS ₂ -VAsC=2: 2.89 CHA ₂ DS ₂ -VAsC=3: 4.22 CHA ₂ DS ₂ -VAsC=4: 4.93	12 years	Low risk of bias
Poli, 2011 ⁸⁶	662	CHA ₂ DS ₂ -VAsC=0: 0* CHA ₂ DS ₂ -VAsC=1: 2.8* CHA ₂ DS ₂ -VAsC ≥ 2: 5.0* * % patients with event during study	Mean 3.6 years	Low risk of bias
Van Staa, 2011 ⁹⁶	79,844	CHA ₂ DS ₂ -VAsC=0: 0.5 CHA ₂ DS ₂ -VAsC=1: 1.1 CHA ₂ DS ₂ -VAsC ≥ 2: 4.6	Mean 4 years	High risk of bias
Lip, 2010 ¹⁵	1,084	<u>Categorical</u> CHA ₂ DS ₂ -VAsC=0: 0* CHA ₂ DS ₂ -VAsC=1: 0.6* CHA ₂ DS ₂ -VAsC ≥ 2: 3.0* <u>Continuous</u> CHA ₂ DS ₂ -VAsC=0: 0.0* CHA ₂ DS ₂ -VAsC=1: 0.6* CHA ₂ DS ₂ -VAsC=2: 1.6* CHA ₂ DS ₂ -VAsC=3: 3.9* CHA ₂ DS ₂ -VAsC=4: 1.9* CHA ₂ DS ₂ -VAsC=5: 3.2* CHA ₂ DS ₂ -VAsC=6: 3.6* CHA ₂ DS ₂ -VAsC=7: 8.0* CHA ₂ DS ₂ -VAsC=8: 11.1* CHA ₂ DS ₂ -VAsC=9: 100.0* * % patients with event during study	1 year	Low risk of bias

Study	No. of Patients	Results (Thromboembolic Event Rates per 100 Patient-Years)	Followup Period	Risk of Bias
Patients off therapy				
Olesen, 2011 ⁸⁴	73,538	<u>Categorical</u> CHA ₂ DS ₂ -VASC=0: 0.66 CHA ₂ DS ₂ -VASC=1: 1.45 CHA ₂ DS ₂ -VASC ≥ 2: 5.72 <u>Continuous</u> CHA ₂ DS ₂ -VASC=0: 0.66 CHA ₂ DS ₂ -VASC=1: 1.45 CHA ₂ DS ₂ -VASC=2: 2.92 CHA ₂ DS ₂ -VASC=3: 4.28 CHA ₂ DS ₂ -VASC=4: 6.46 CHA ₂ DS ₂ -VASC=5: 9.97 CHA ₂ DS ₂ -VASC=6: 12.52 CHA ₂ DS ₂ -VASC=7: 13.96 CHA ₂ DS ₂ -VASC=8: 14.10 CHA ₂ DS ₂ -VASC=9: 15.89	10 years	Low risk of bias
Patients on <u>and</u> off therapy				
Olesen, 2011 ¹¹⁰	132,372	<u>VKA:</u> CHA ₂ DS ₂ -VASC=0: 0.7 CHA ₂ DS ₂ -VASC=1: 1.1 CHA ₂ DS ₂ -VASC ≥ 2: 3.1 <u>ASA:</u> CHA ₂ DS ₂ -VASC=0: 1.1 CHA ₂ DS ₂ -VASC=1: 1.8 CHA ₂ DS ₂ -VASC ≥ 2: 6.3 <u>No antithrombotic:</u> CHA ₂ DS ₂ -VASC=0: 0.9 CHA ₂ DS ₂ -VASC=1: 1.7 CHA ₂ DS ₂ -VASC ≥ 2: 6.3	12 years	High risk of bias

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

Framingham Risk Tool

Five studies reported the association of Framingham risk and stroke events among patients with AF (Table 6).^{15,88,89,92,96} All studies reported the individual risk factors associated with Framingham risk. Two studies reported stroke outcomes in patients without oral anticoagulant therapy,^{15,92} and one study where all patients were on oral anticoagulant therapy.⁸⁹

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

Study	No. of Patients	Results (Thromboembolic Rates)	Followup Period	Risk of Bias
<i>Patients on therapy</i>				
Van Staa, 2011 ^{9b}	79,844	Low - 1.8* Moderate - 4.3* High - 9.5* *Cases per 100 patient-years	4 years	High risk of bias
Fang, 2008 ⁸⁸	10,932	Low - 0.81%* Moderate - NR High - 3.9%* *Per 100 person-years	Median 6.0 years	Low risk of bias
Baruch, 2007 ⁸⁹	7,329	Low - 0.7%* Moderate - 1.4%* High - 2.7%* *Per patient-years	Mean 1.5 years	Low risk of bias
<i>Patients on and off therapy</i>				
Lip, 2010 ^{1b}	1,084	<u>Overall</u> Low - 1.2% Moderate - 3.2% High - 4.6% <u>On Treatment</u> Low - 1.0% Moderate - 1.2% High - 3.5%	1 year	Low risk of bias
<i>Use of therapy uncertain (no VKA, but antiplatelet use NR)</i>				
Wang, 2003 ^{9z}	705	NR by category	4.3 years	Low risk of bias

Abbreviations: NR=not reported; VKA= vitamin K antagonist

Imaging Risk Tool

Six studies examined specific anatomical findings on imaging studies and the association with stroke risk in patients with AF (Table 7).^{87,90,93,98,100,106} One study used magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) quantification of left atrial appendage (LAA) dimensions.⁹⁸ Four studies utilized transesophageal echocardiography to examine imaging parameters or findings associated with stroke risk in patients with AF,^{87,93,100,106} and one used both transesophageal echocardiography and transthoracic echocardiography.⁹⁰

In the study examining MRI/MRA characteristics, 144 patients with nonvalvular AF not on warfarin underwent MRI/MRA prior to catheter ablation for AF.⁹⁸ LAA volume, LAA depth, short and long axes of LAA neck, and numbers of lobes and their association with stroke risk were examined. In univariate analysis, LAA volume, LAA depth, and short and long axes of LAA neck were significantly associated with stroke risk. In multivariate analysis, the only

MRI/MRA characteristic significant in the stroke prediction model was product of the short and long axes of the LAA neck (odds ratio [OR] 3.59; 95% CI, 1.93 to 6.69; p<0.001).

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

Study	No. of Patients	Features Examined	Results	Risk of Bias
<i>Patients on and off therapy</i>				
Nair, 2009 ¹⁰⁰	226	1. Presence or absence of LA thrombus on TEE	1. No difference in stroke rates in patients with LA thrombus versus those without LA thrombus (7% vs. 4%, p=NS)	Low risk of bias
Okuyama, 2008 ⁸⁷	192	1. LAA spontaneous contrast 2. LAA thrombus 3. LAA peak flow velocity (cm/s) 4. LAA peak flow velocity ≤20cm/s 5. LAA area 6. LAA wall velocity 7. LAA intensity variation 8. LAA intensity variation ≤9.2 dB	Decreased LAA intensity variation (HR 5.24; 95% CI, 1.81 to16.4)	Low risk of bias
Stollberger, 2004 ⁹⁰	409	<u>TTE</u> 1. LV fractional shortening 2. Reduced LV systolic function 3. LA diameter 4. Valvular abnormalities <u>TEE</u> 1. LAA thrombus 2. Spontaneous echo contrast 3. LAA size 4. LAA length 5. LAA width 6. LAA area, mean	None significant in multivariate analysis	Low risk of bias

Study	No. of Patients	Features Examined	Results	Risk of Bias
Stoddard, 2003 ¹⁰⁶	272	<ol style="list-style-type: none"> 1. LA diameter 2. LVEF 3. LVEF<40% 4. LA SEC 5. Aortic plaque \geq5 mm 6. Mobile PFO \geq grade 2 7. MV/AV strands 8. Atrial septal aneurysm 9. Mitral stenosis 	LA thrombus (OR 7.7, 95% CI, 2.7-21.6)	Low risk of bias
Miyazaki, 2001 ⁹³	89	<ol style="list-style-type: none"> 1. LA dimension 2. LV end-diastolic dimension 3. LV fractional shortening 4. Moderate to severe MR LAA velocity (cm/s) 5. LAA size 6. LA SEC 7. LAA thrombus present 	<ol style="list-style-type: none"> 1. LAA thrombus (chi-square 5.5, p=0.019) 2. LAA dysfunction (chi-square 4.0, p=0.045) 	Low risk of bias

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

International Normalized Ratio (INR) Tool

Three studies evaluated the predictor role of INR and its association with stroke risk in patients with AF.^{91,104,111} One study considered the INR value on hospital admission,⁹¹ one study considered the time in therapeutic range (TTR) of INR,¹⁰⁴ and one study considered both TTR and the standard deviation of transformed INR.¹¹¹ In one study of 6,108 patients, the investigators examined the rate of stroke events on patients treated with warfarin after a mean follow-up 1025.1 days.¹⁰⁴ The study reported that only patients with CHADS₂ \geq 2 with a time in therapeutic range for warfarin (INR 2.0–3.0) of 71–100% during the study had a signification reduction in stroke risk (HR 0.20; 95% CI, 0.05 to 0.82; p =0.025). A second study of 13,559 patients on warfarin showed that an INR of less than 2.0 compared with an INR \geq 2.0 independently increased the odds of a severe stroke in a multivariate model (OR 1.9; 95% CI, 1.1 to 3.4).⁹¹ The third study examined 19,180 patients on warfarin to determine if INR variability (standard deviation of transformed INR [SDT_{INR}]) has better predictive value for stroke events than time in therapeutic range (TTR).¹¹¹ The HR for stroke events was higher for the SDT_{INR} than for the TTR (1.30; 95% CI, 1.22 to 1.39 vs. 1.06; 95% CI, 1.00 to 1.13).

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

A total of eight studies directly investigated at least two risk scores of interest in the same population. Two studies used the same population to examine the performance of the CHADS₂, Framingham, and CHA₂DS₂-VASc scores.^{89,96} These two studies showed similar performance of all three scores in the same population, with similar c-statistics ranging from 0.60–0.67. Three studies used the same population to assess the risk prediction of CHADS₂ and CHA₂DS₂-

VASc,^{84,86,94} with c-statistics ranging from 0.60 to 0.89 overall, but with similar performance of the two scores in the same population. Three studies used the same population of patients to examine the CHADS₂ and Framingham risk scores, with similar performance of the two risk scores in the same populations.^{15,88,92} No studies used the same population to assess the Framingham and CHA₂DS₂-VASc for stroke risk estimation. These findings suggest that all three of these risk scores perform similarly when used in the same populations.

Table 8 provides a summary of available c-statistics for predictive accuracy of the risk scores of interest. This table demonstrates both a range of scoring systems evaluated (continuous vs. categorical) as well as a range of c-statistics through the studies with the CHADS₂ score c-statistic estimates ranging from 0.52 to 0.82, the Framingham scores ranging from 0.62 to 0.69, and the CHA₂DS₂-VASc ranging from 0.52 to 0.89.

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

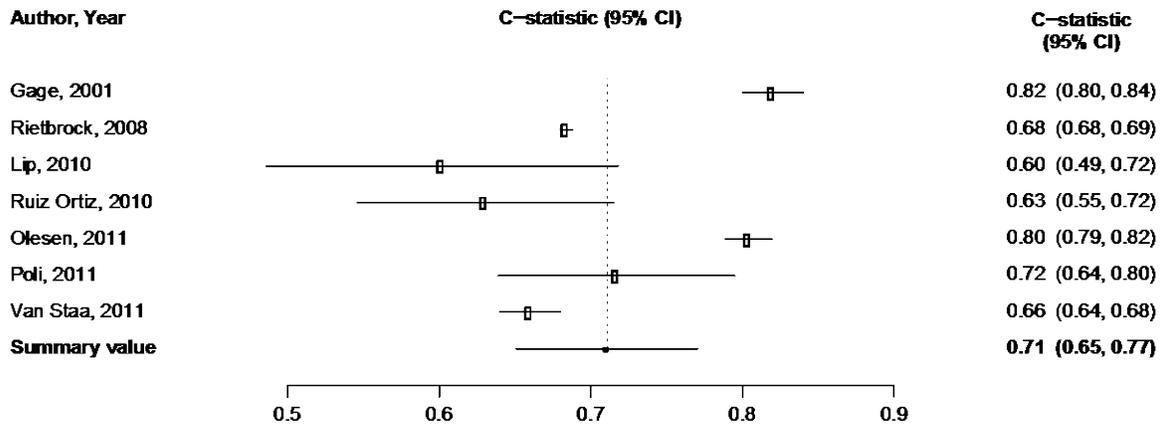
Study	CHADS ₂	Framingham	CHA ₂ DS ₂ -VASc
Poli, 2011 ⁸⁶	<u>Continuous (Revised):</u> 0.72 (95% CI, 0.64 to 0.80) <u>Categorical (Classic):</u> 0.68 (95% CI, 0.61 to 0.76) <u>Categorical Revised:</u> 0.60 (95% CI, 0.51 to 0.67)	-	<u>Continuous:</u> 0.72 (95% CI, 0.65 to 0.80) <u>Categorical:</u> 0.52 (95% CI, 0.44 to 0.61)
Ruiz Ortiz, 2010 ⁹⁹	<u>Continuous:</u> 0.63 (95% CI, 0.55 to 0.72)	-	-
Poli, 2009 ¹⁰³	<u>Categorical:</u> All patients: 0.68 On therapy: 0.52	-	-
Fang, 2008 ⁸⁸	<u>Continuous:</u> All patients: 0.60 <u>Categorical:</u> All patients: 0.58 Off therapy: 0.67	<u>Continuous:</u> All patients: 0.64 <u>Categorical:</u> All patients: 0.62 Off therapy: 0.69	-
Baruch, 2007 ⁸⁹	<u>Categorical (Classic):</u> 0.64 (95% CI, 0.61 to 0.67) <u>Categorical (Revised):</u> 0.64 (95% CI, 0.61 to 0.67)	<u>Categorical:</u> 0.62 (95% CI, 0.59 to 0.66)	<u>Categorical:</u> 0.65 (95% CI, 0.61 to 0.68)
Gage, 2001 ¹³	<u>Continuous:</u> 0.82 (95% CI, 0.80 to 0.84)	-	-

Study	CHADS ₂	Framingham	CHA ₂ DS ₂ -VASc
Olesen, 2011 ⁸⁴	<p><i>Covariates analyzed as categorical variables:</i></p> <p><u>Continuous:</u> 0.78 (95% CI, 0.76 to 0.80)</p> <p><u>Categorical:</u> 0.81 (95% CI, 0.80 to 0.83)</p> <p><i>Covariates analyzed as continuous variables:</i></p> <p><u>Continuous:</u> 0.80 (95% CI, 0.79 to 0.82)</p> <p><u>Categorical:</u> 0.81 (95% CI, 0.80 to 0.83)</p>	-	<p><i>Covariates analyzed as categorical variables:</i></p> <p><u>Continuous:</u> 0.78 (95% CI, 0.76 to 0.79)</p> <p><u>Categorical:</u> 0.89 (95% CI, 0.88 to 0.90)</p> <p><i>Covariates analyzed as continuous variables:</i></p> <p><u>Continuous:</u> 0.79 (95% CI, 0.78 to 0.81)</p> <p><u>Categorical:</u> 0.89 (95% CI, 0.88 to 0.90)</p>
Van Staa, 2011 ⁹⁶	<p><u>Continuous:</u> 0.66 (95% CI, 0.64 to 0.68)</p> <p><u>Categorical:</u> 0.65 (95% CI, 0.63 to 0.67)</p>	<p><u>Continuous:</u> 0.65 (95% CI, 0.63 to 0.68)</p> <p><u>Categorical:</u> 0.62 (95% CI, 0.60 to 0.64)</p>	<p><u>Continuous:</u> 0.67 (95% CI, 0.65 to 0.69)</p> <p><u>Categorical:</u> 0.60 (95% CI, 0.59 to 0.61)</p>
Lip, 2010 ¹⁵	<p><u>Continuous:</u> 0.60 (95% CI, 0.49 to 0.72)</p> <p><u>Categorical (Classic):</u> 0.56 (95% CI, 0.44 to 0.66)</p> <p><u>Categorical (Revised):</u> 0.59 (95% CI, 0.48 to 0.70)</p>	<p><u>Continuous:</u> 0.69 (95% CI, 0.60 to 0.78)</p> <p><u>Categorical:</u> 0.64 (95% CI, 0.53 to 0.74)</p>	-
Wang, 2003 ⁹²	<p><u>Categorical:</u> 0.62</p>	<p><u>Categorical:</u> 0.66 (SD 0.03)</p>	-
Olesen, 2012 ⁹⁴	<p><u>Categorical:</u> 0.63 (95% CI, 0.62 to 0.65)</p>	-	<p><u>Continuous:</u> 0.66 (95% CI, 0.65 to 0.68)</p>
Rietbrock, 2008 ¹⁰⁵	<p><u>Continuous (Classic):</u> 0.68 (95% CI, 0.68 to 0.69)</p> <p><u>Continuous (Revised):</u> 0.72 (95% CI, 0.72 to 0.73)</p>	-	-

Abbreviations: 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

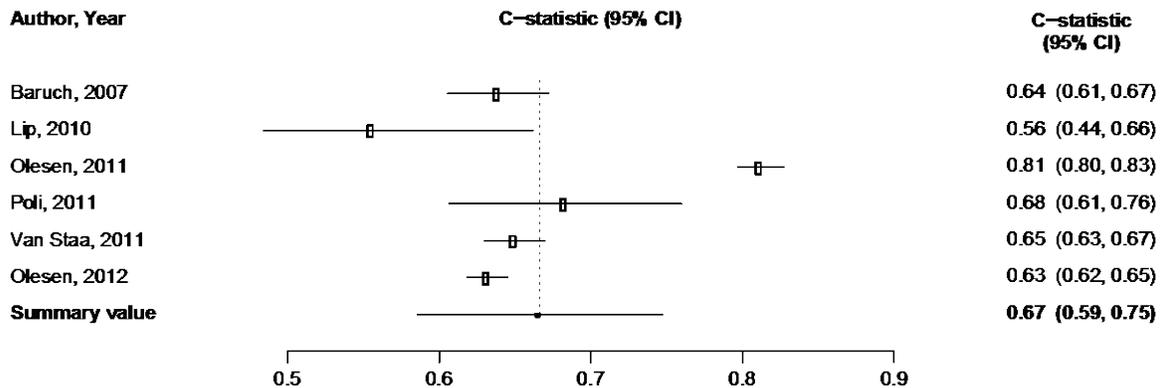
Sufficient data existed to permit meta-analysis of studies evaluating c-statistics for the CHADS₂ score using a continuous score (Figure 3) and categorical score (Figure 4), the Framingham categorical score (Figure 5), and the CHA₂DS₂-VASc continuous (Figure 6) and categorical score (Figure 7). Meta-analysis could not be completed for other risk scores of interest.

Figure 3. Summary estimate of c-statistics for predictive ability of CHADS₂ continuous stroke risk score



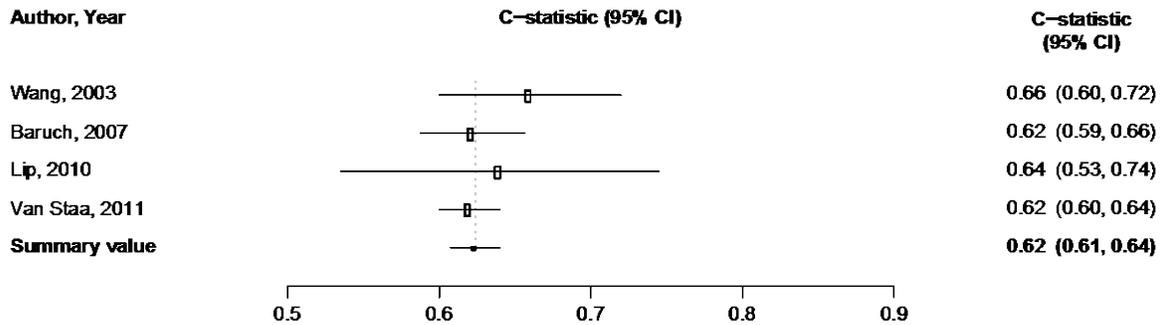
Abbreviations: CHADS₂=Congestive heart failure, Hypertension, Age ≥75, Diabetes mellitus, prior Stroke/transient ischemic attack (2 points); CI=confidence interval

Figure 4. Summary estimate of c-statistics for predictive ability of CHADS₂ categorical stroke risk score



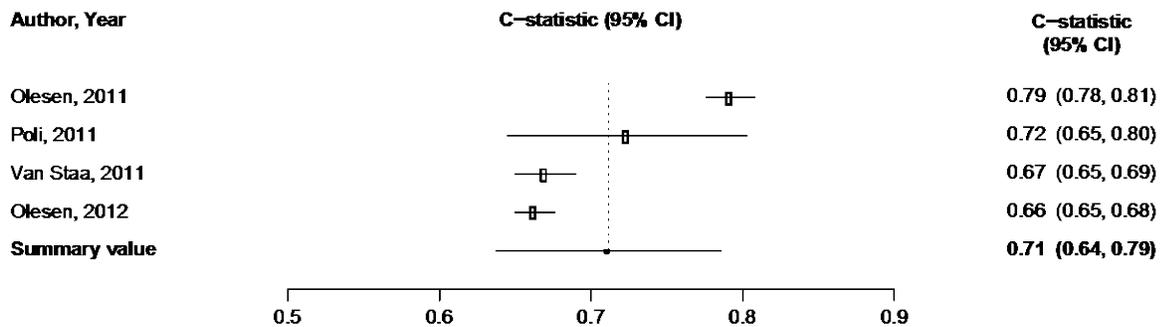
Abbreviations: CHADS₂=Congestive heart failure, Hypertension, Age ≥75, Diabetes mellitus, prior Stroke/transient ischemic attack (2 points); CI=confidence interval

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



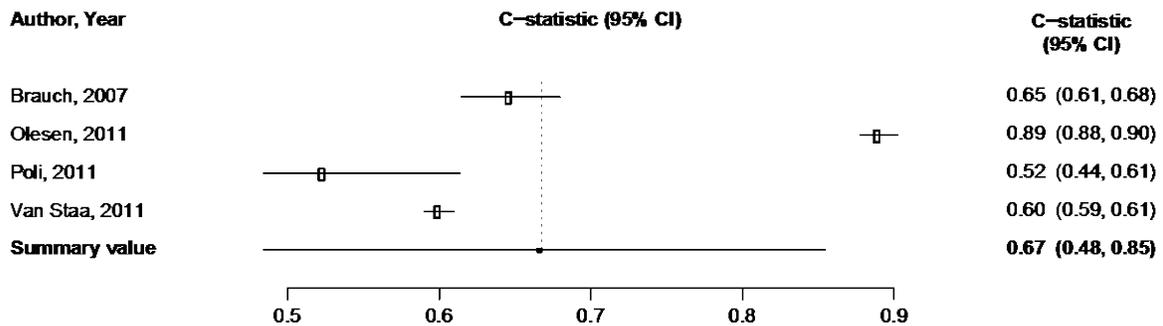
Abbreviation: CI=confidence interval

Figure 6. Summary estimate of c-statistics for predictive ability of CHA₂DS₂-VASc continuous stroke risk score



Abbreviations: 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

Figure 7. Summary estimate of c-statistics for predictive ability of CHA₂DS₂-VASc categorical stroke risk score



Abbreviations: 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

These analyses demonstrated that the CHADS₂ continuous score and the CHA₂DS₂-VASc continuous score have comparable predictive abilities for stroke risk (0.71 [95% CI, 0.65 to

0.77], Q=385.9 [p<0.001], I²=98.4; and 0.71 [95% CI, 0.64 to 0.79], Q=165.6 [p<0.001], I²=98.2, respectively) and greater predictive ability than other scores. These scores are not, however, statistically significantly different from either the CHADS₂ categorical score (0.67 [95% CI, 0.59 to 0.75], Q=338.3 [p<0.001], I²=98.5) or the CHA₂DS₂-VASc categorical score (0.67 [95% CI, 0.48 to 0.85], Q=1292.2 [p<0.001], I²=99.8). They do appear to be better predictors of risk than the Framingham categorical score (0.62 [95% CI, 0.61 to 0.64], Q=1.6 [p=0.65], I²=0.0) given our included studies. Note that only the Framingham categorical score has no heterogeneity, while all other scores have substantial heterogeneity reducing the strength of evidence.

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

Table 9. Strength of evidence domains for predicting thromboembolic risk

Outcome	Number of Studies (Subjects)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
CHADS ₂ (Categorical)	6 (210,033)	Observational/Moderate	Inconsistent	Direct	Imprecise	SOE=Insufficient
CHADS ₂ (Continuous)	7 (209,464)	Observational/Moderate	Inconsistent	Direct	Precise	SOE=Low c-statistic=0.71 (95% CI, 0.65 to 0.77)
CHA ₂ DS ₂ -VASc (Categorical)	4 (161,373)	Observational/Moderate	Inconsistent	Direct	Imprecise	SOE=Insufficient
CHA ₂ DS ₂ -VASc (Continuous)	4 (201,620)	Observational/Moderate	Inconsistent	Direct	Precise	SOE=Low c-statistic=0.71 (95% CI, 0.64 to 0.79)
Framingham (Categorical)	4 (88,962)	Observational/Moderate	Consistent	Direct	Precise	SOE=Moderate c-statistic=0.62 (95% CI, 0.61 to 0.74)
Framingham (Continuous)	2 (80,928)	Observational/Moderate	Inconsistent	Direct	Imprecise	SOE=Insufficient
Imaging	0	NA	NA	NA	NA	SOE=Insufficient
INR	0	NA	NA	NA	NA	SOE=Insufficient

Abbreviations: CI=confidence interval; 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; INR=international normalized ratio; NA=not applicable; SOE=strength of evidence

Key Question 2. Predicting Bleeding Events

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

Key Points

- Based on five studies comparing the Bleeding Risk Index (BRI), HEMORR₂HAGES, HAS-BLED, and ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation), in predicting major bleeding rates among patients with AF on warfarin, the HAS-BLED tool appears to have the highest predictive accuracy for bleeding events in this population, although no study directly compared HAS-BLED with ATRIA (low strength of evidence).
- Based on three studies comparing BRI, HEMORR₂HAGES, and HAS-BLED, in predicting major bleeding rates among patients with AF off of antithrombotic therapy, the HAS-BLED tool appears to have the highest predictive accuracy for bleeding events in this population (low strength of evidence).
- Based on two studies comparing BRI, HEMORR₂HAGES, and HAS-BLED, in predicting major bleeding rates among patients with AF on aspirin alone, the HAS-BLED tool appeared to have the highest predictive accuracy for bleeding events in this population (low strength of evidence).
- Although six studies generally suggested increasing rates of major bleeding with increasing CHADS₂ among patients on warfarin, aspirin, and off antithrombotic therapy, data were not provided to fully evaluate the predictive accuracy of CHADS₂ for major bleeding events (insufficient strength of evidence).
- Although one study suggested increasing rates of major bleeding with increasing CHA₂DS₂-VASc among patients on warfarin, aspirin, and off antithrombotic therapy, data were not provided to fully evaluate the predictive accuracy of CHA₂DS₂-VASc for major bleeding events (insufficient strength of evidence).

Description of Included Studies

Fifteen studies met our inclusion criteria (Appendix Table F-2).^{16,26,89,91,95,97,99,110-117} Apart from a shared focus on outpatient settings, the included studies represented variation in geographical location, study design, quality, and patient characteristics. Seven studies analyzed prospective data (including data from RCTs),^{16,26,89,95,97,99,113} while eight analyzed retrospective data (including registries).^{91,110-112,114-117} Seven studies were conducted in Europe,^{16,95,99,110,111,113,117} six in the United States,^{91,97,112,114-116} one was multinational,²⁶ and the location was not reported for one.⁸⁹ Ten studies were multicenter,^{16,26,89,91,95,110,112,114,115,117} four were single-site,^{97,99,113,116} and study site data were not reported for one study.¹¹¹ All studies were conducted primarily in the outpatient setting, although one study did not report setting.⁹⁵ Of the 15 studies, 5 did not report funding source,^{97,110,111,113,117} 3 used exclusively industry funding,^{16,26,89} 2 used exclusively government funding,^{91,114} 2 were unfunded,^{95,116} 1 used exclusively foundation funding,⁹⁹ and 2 used funding from multiple sources.^{112,115} Nine studies

were of good methodological quality,^{16,26,89,91,112-114,116,117} four were of fair quality,^{95,97,99,115} and two were of poor quality.^{110,111}

Studies enrolled patients between 1995 and 2008. The number of patients included in studies ranged from fewer than 300¹¹³ to 132,372,¹¹⁰ with overlap in patient populations between some studies; altogether, the included studies analyzed data from approximately 219,363 unique patients. The mean age of study participants ranged from 65–80 years. The proportion of male patients ranged from approximately 40–60 percent. None of the studies presented data on ethnicity of subjects, and only two presented data on race; 1 of these studies was 87 percent “Caucasian,”⁹⁷ and one was 81 percent white.¹¹⁶ Study followup duration ranged from 1–12 years. Each of the study populations included patients with paroxysmal, persistent, and permanent AF, except for one study that included only patients with permanent AF.⁹⁹

Regarding the outcomes assessed, 14 studies reported the diagnostic accuracy and impact on clinical decisionmaking of bleeding risk scores with respect to major bleeding,^{16,26,89,95,97,99,110-117} two reported these outcomes with respect to intracranial hemorrhage,^{26,91} and a single study reported these outcomes with respect to minor bleeding.¹¹⁶ Clinical tools of interest included risk scores and INR indices (INR, time in therapeutic range [TTR], and standard deviation of transformed INR [SDT_{INR}]; Table 10). The individual factors comprising the risk scores of interest (Table 10) are also generally associated with a higher risk of bleeding in patients with AF based on available data, but for the purposes of this analysis, we focused on risk scores typically utilized for prospective estimation of bleeding risk in clinical settings.

Table 10. Description and interpretation of included bleeding risk scores

Bleeding Risk Score	Reference	Risk Factors Included	Interpretation
ATRIA	Fang, 2011 ¹¹²	Anemia, renal disease (CrCl <30) (3 points each); age ≥75 (2 points); any prior bleeding, hypertension (1 point each)	Low (0-3), moderate (4), high (5-10)
BRI	Beyth, 1998 ¹¹⁸	Age ≥65, GI bleed in past 2 weeks, previous stroke, comorbidities (recent MI, hematocrit <30%, diabetes, creatinine >1.5), with 1 point for presence of each condition and 0 if absent	low (0), moderate (1-2), high (3-4)
CHADS ₂	Gage, 2001 ¹³	Congestive heart failure, hypertension, age ≥75, diabetes (1 point each); previous stroke or TIA (2 points)	Classic: low (0), moderate (1-2), high (>2) Revised: low (0), moderate (1), high (≥2)
CHA ₂ DS ₂ -VASc	Lip, 2010 ¹⁵	Congestive heart failure, hypertension, diabetes, vascular disease, age 65-74, and female sex (1 point each); previous thromboembolism, age ≥75 years (2 points each)	Low (0), moderate (1), high (≥2)
HAS-BLED	Pisters, 2010 ¹⁶	Hypertension, abnormal renal (CrCl <50) or liver function (1 point each); stroke, bleeding history or predisposition, labile INR (TTR <60%), age >65, drugs/alcohol (1 point each)	Low (0), moderate (1-2), high (≥3)

Bleeding Risk Score	Reference	Risk Factors Included	Interpretation
HEMORR ₂ HAGES	Gage, 2006 ¹¹⁵	Liver/renal disease, ethanol abuse, malignancy, age >75, low platelet count or function, re-bleeding risk, uncontrolled hypertension, anemia, genetic factors (CYP2C9), risk of fall or stroke (1 point for each risk factor present with 2 points for previous bleed)	low (0-1), moderate (2-3), high (≥4)

Abbreviations: ATRIA=Anticoagulation and Risk Factors in Atrial Fibrillation; BRI=Bleeding Risk Index; 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; CrCl=creatinine clearance; GI=gastrointestinal; HAS-BLED=Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (> 65 years), Drugs/alcohol concomitantly; HEMORR₂HAGES=Hepatic or renal disease, Ethanol abuse, Malignancy, Older (age >75 years), Reduced platelet count or function, Re-bleeding risk (2 points), Hypertension (uncontrolled), Anemia, Genetic factors, Excessive fall risk, Stroke; INR=international normalized ratio; MI=myocardial infarction; TTR=time in therapeutic range

Detailed Synthesis

Major Bleeding

Overview

A total of 14 studies evaluated various risk scores or factors for estimating major bleeding risk in patients with AF, including patients on warfarin, aspirin, both warfarin and aspirin, and no antithrombotic therapy.^{16,26,89,95,97,99,110-117} Different studies compared different risk scores and utilized different statistics to describe their findings. Results are presented below by risk score with additional information regarding comparisons. The final subsection below presents a summary table of available c-statistics for predictive accuracy of the risk scores of interest among patients on different antithrombotic therapies. Due to the limited number of studies available, meta-analysis was possible for just one risk score, HEMORR₂HAGES, among patients on warfarin only; summary tables comparing c-statistics for risk scores of interest and meta-analysis results are provided at the end of this section.

Bleeding Risk Index (BRI)

The Bleeding Risk Index (BRI), also known as the Outpatient Bleeding Risk Index, was evaluated in six included studies among patients with AF with and without anticoagulation.^{89,95,112,114-116} Four of these studies compared BRI with other risk scores of interest, while two did not provide comparisons with other risk scores of interest. Multiple studies presented major bleeding event rate data for BRI stratified by risk level among patients on warfarin (Table 11). Event rates for the low-risk group ranged from 0.39–1.1 events per 100 patient-years, and 0–2.1 percent of individuals experienced a bleeding event. Event rates for the moderate-risk group ranged from 1.26–4.9 events per 100 patient-years, and 1–3.9 percent of individuals experienced a bleeding event. Event rates for the high-risk group ranged from 1.74–8.8 events per 100 patient-years, and 2.5–11.1 percent of individuals experienced a bleeding event. Event rate data were not provided for patients not taking warfarin.

Among patients on warfarin, c-statistics for the categorical BRI ranged from 0.56-0.65 (Table 11);^{89,112,114,115} one study found a c-statistic of 0.68 for the BRI as a continuous variable.¹¹² Two studies presented c-statistics for the BRI in other populations; for patients not

on antithrombotic therapy, c-statistics ranged from 0.50⁸⁹–0.65,¹¹⁵ while among patients on aspirin, one study reported a c-statistic of 0.69.¹¹⁵

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

Study	N	Followup	Bleeding event rates	C-statistic
Fang, 2011 ¹¹²	3,063	Median 3.5 years	Low=0.39 events/100 patient-years Moderate=1.31 High=3.96	0.59 (95% CI, 0.58 to 0.61)
Poli, 2011 ⁹⁵	3,302	Median 2.3 years	Low=0.95 events/100 patient-years Moderate=1.26 High=1.74	NR
Lip, 2011 ¹¹⁹	7,329	Mean 499 days	Low=2.1% with bleeding event Moderate=3.9 High=4.0	0.56 (95% CI, 0.51 to 0.60)
Shireman, 2006 ¹¹⁴	26,345	90 days	Low=0% with bleeding event Moderate=1 High=2.5	0.61
Gage, 2006 ¹¹⁵	3,791	Mean 0.82 years	Low=1.1 events/100 patient-years Moderate=4.9 High=8.8	0.65 (SE 0.03)
Aspinall, 2005 ¹¹⁶	543 with A-fib	Mean 1.02 years	Low=0% with bleeding event Moderate=2.3 High=11.1	NR

Abbreviations: BRI=Bleeding Risk Index; CI=confidence interval; N=number of participants; NR=not reported; SE=standard error

HEMORR₂HAGES

HEMORR₂HAGES was evaluated in five included studies among patients with AF with and without anticoagulation.^{16,89,112,115,117} Each of these studies compared HEMORR₂HAGES with at least one other risk score of interest. Multiple studies presented major bleeding event rate data for HEMORR₂HAGES stratified by risk level among patients on warfarin (Table 12). Event rates for the low-risk group ranged from 0.72¹¹²–3.06¹¹⁷ events per 100 patient-years, and in one study⁸⁹ 3.0 percent of individuals experienced a bleeding event. Event rates for the moderate-risk group ranged from 2.49¹¹²–6.33¹¹⁷ events per 100 patient-years, and in one study⁸⁹ 6.1 percent of individuals experienced a bleeding event. Event rates for the high-risk group ranged from 3.96¹¹²–12.16¹¹⁷ events per 100 patient-years, and in one study⁸⁹ 2.0 percent of individuals experienced a bleeding event (though the high-risk group contained only 2.7 percent of the study cohort in this study). One study presented data regarding major bleeding events per 100 patient-years based on the continuous HEMORR₂HAGES score;¹¹⁵ rates ranged from 1.9 for those with 0 points to 12.3 for those with ≥5 points. Event rate data were not provided for patients not taking warfarin.

Among patients on warfarin, c-statistics for HEMORR₂HAGES ranged from 0.61–0.78 (Table 12);^{16,89,112,115,117} two studies evaluated HEMORR₂HAGES as a continuous variable and found c-statistics of 0.71¹¹² and 0.771.¹¹⁷ Four studies presented c-statistics for HEMORR₂HAGES in other populations; for patients not on antithrombotic therapy, c-statistics

ranged from 0.62–0.81,^{16,89,115,117} while two studies provided c-statistics for patients on aspirin alone of 0.72¹¹⁵ and 0.83.¹⁶

Table 12. Summary of results for studies evaluating HEMORR₂HAGES among patients on warfarin

Study	N	Followup	Bleeding event rates	C-statistic
Fang, 2011 ¹¹²	3,063	Median 3.5 years	Low=0.72 events/100 patient-years Moderate=2.49 High=3.96	0.67 (95% CI, 0.65 to 0.70)
Pisters, 2010 ¹⁶	3,456	Mean 1 year	NR	0.64 (95% CI, 0.53 to 0.75)
Lip, 2011 ¹¹⁹	7,329	Mean 499 days	Low=3.0% with bleeding event Moderate=6.1 High=2.0 (based on only 2.7% of population)	0.61 (95% CI, 0.56 to 0.65)
Gage, 2006 ¹¹⁵	3,791	Mean 0.82 years	0=1.9 events/100 patient-years 1=2.5 2=5.3 3=8.4 4=10.4 ≥5=12.3	0.67 (SE 0.04)
Olesen, 2011 ¹¹⁷	118,584	Mean 10 years	Low=3.06 events/100 patient-years Moderate=6.33 High=12.16	0.78 (95% CI, 0.75 to 0.82)

Abbreviations: CI=confidence interval; HEMORR₂HAGES=Hepatic or renal disease, Ethanol abuse, Malignancy, Older (age >75 years), Reduced platelet count or function, Re-bleeding risk (2 points), Hypertension (uncontrolled), Anemia, Genetic factors, Excessive fall risk, Stroke; N=number of participants; SE=standard error

HAS-BLED

HAS-BLED was evaluated in three included studies among patients with AF with and without anticoagulation.^{16,89,117} Each of these studies compared HAS-BLED with at least one other risk score of interest. Multiple studies presented major bleeding event rate data for HAS-BLED stratified by risk level among patients on warfarin (Table 13). One study indicated that the major bleeding event rate was 2.66 events per 100 patient-years for the low-risk group, 5.54 events per 100 patient-years for the moderate-risk group, and 8.11 events per 100 patient-years for the high-risk group,¹¹⁷ while another indicated that the percentage of individuals experiencing major bleeding was 0.9 percent in the low-risk group, 3.7 percent in the moderate-risk group, and 6.7 percent in the high-risk group.⁸⁹ One study presented data regarding major bleeding based on the continuous HAS-BLED score; major bleeding event rates ranged from 1.13 per 100 patient-years for those with 0 points to 12.50 per 100 patient-years for those with ≥ 5 points.¹⁶ Event rate data were not provided for patients not taking warfarin.

Among patients on warfarin, c-statistics for HAS-BLED ranged from 0.66–0.80^{16,89,117} one study evaluated HAS-BLED as a continuous variable and found a c-statistic of 0.80.¹¹⁷ Three studies presented c-statistics for HAS-BLED in other populations; for patients not on antithrombotic therapy, c-statistics ranged from 0.62–0.81,^{16,89,117} while one study provided a c-statistic of 0.91 for patients on aspirin alone.¹⁶ Of note, another study provided hazard ratios for HAS-BLED ≤2 and ≥3 using a complicated matrix in which results were stratified by CHADS₂, CHA₂DS₂-VASc, and treatment status.¹¹⁰ Because the primary goal of this analysis was to

evaluate the net clinical benefit of antithrombotic treatment versus no treatment in different subgroups, these data are not presented here.

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

Study	N	Followup	Bleeding event rates	C-statistic
Pisters, 2010 ¹⁶	3,456	Mean 1 year	0=1.13 events/100 patient-years 1=1.02 2=1.88 3=3.74 4=8.70 5=12.50 6=0.0 7-9=no patients	0.69 (95% CI, 0.59 to 0.80)
Lip, 2011 ¹¹⁹	7,329	Mean 499 days	Low=0.9% with bleeding event Moderate=3.7 High=6.7	0.66 (95% CI, 0.61 to 0.70)
Olesen, 2011 ¹¹⁷	118,584	Mean 10 years	Low=2.66 events/100 patient-years Moderate=5.54 High=8.11	0.80 (95% CI, 0.76 to 0.83)

Abbreviations: CI=confidence interval; HAS-BLED=Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (> 65 years), Drugs/alcohol concomitantly; N=number of participants

ATRIA

ATRIA was evaluated in one study among patients with AF on anticoagulation.¹¹² This study compared ATRIA with two other risk scores of interest, the BRI and HEMORR₂HAGES. Among patients on warfarin, the available study indicated that the major bleeding event rate in the validation cohort was 0.83 events per 100 patient-years for the low-risk group, 2.41 events per 100 patient-years for the moderate-risk group, and 5.32 events per 100 patient-years for the high-risk group. This study also presented data regarding major bleeding based on ATRIA stratified by points; major bleeding event rates ranged from 0.48 per 100 patient-years for those with 0 points to 16.34 per 100 patient-years for those with 10 points. Event rate data were not provided for patients not taking warfarin.

The c-statistic for ATRIA among patients on warfarin ranged was 0.69. ATRIA was also evaluated as a continuous variable and found to have a c-statistic of 0.74.

CHADS₂

Six studies provided data on the impact of CHADS₂ on diagnostic thinking with respect to estimating the likelihood of major bleeding in AF.^{26,95,97,99,110,113} These studies did not provide c-statistics for CHADS₂ with respect to bleeding risk, so the predictive accuracy of CHADS₂ in this situation could not be fully evaluated. However, data regarding event rates were provided. Multiple studies presented major bleeding event rate data for CHADS₂ stratified by risk level, but different studies often defined low, moderate, and high risk in different ways. In some studies, event rate according to standard CHADS₂ risk levels could be calculated from available data.

Among patients on warfarin, event rates for the CHADS₂ revised score low-risk group ranged from 0.4–3.3^{95,99,110} events per 100 patient-years (Table 14). Event rates for the moderate-

risk group ranged from 0.8–4.4 (4.4,¹¹⁰ 1.3,⁹⁵ 0.8,⁹⁹ 1.9¹¹³) events per 100 patient-years. Event rates for the high-risk group ranged from 1.3–5.3^{95,110,113} events per 100 patient-years. One study stratified event rates according to the CHADS₂ classic score in addition to the revised score, but event rates by group did not differ.⁹⁵ Another study presented event rate data for the continuous CHADS₂ score only;⁹⁹ event rates were low and did not appear to show consistent trends with CHADS₂ (0=3, 1=0.8, 2=1.3, 3=0.4, ≥4=2.9 events per 100 patient-years). Another study presented event rate data for patients on warfarin according to an atypical CHADS₂ stratification system;²⁶ this showed that the number of patients experiencing major bleeding events was 2.84 percent per year for CHADS₂ 0–1, 3.3 percent per year for CHADS₂ 2, and 4.6 percent per year for CHADS₂ ≥3 (p-value for three-way comparison <0.001). One study provided relative risks (RRs) comparing the revised CHADS₂ risk strata, indicating that the RR for major bleeding was 3.1 (95% CI, 1.1 to 11.8) for moderate-risk versus low-risk patients, and 1.0 (0.7 to 1.5) for high-risk versus moderate-risk patients.⁹⁵

One study presented event rate data for a mixed population of patients on warfarin and dabigatran according to the revised CHADS₂;²⁶ this showed that the number of patients experiencing major bleeding events during a median of 2 years followup was 3.3 percent for the low-risk group, 4.7 percent for the moderate-risk group, and 7.3 percent for the high-risk group.

Among patients not on antithrombotic therapy, one study evaluated event rates for the CHADS₂ revised score;¹¹⁰ the low-risk group experienced 1.4 events per 100 patient-years, the moderate-risk group experienced 3.4 events per 100 patient-years, and the high-risk group experienced 4.7 events per 100 patient-years. This study also evaluated event rates for the CHADS₂ revised score among patients on aspirin alone;¹¹⁰ the low-risk group experienced 2.3 events per 100 patient-years, the moderate-risk group experienced 3.8 events per 100 patient-years, and the high-risk group experienced 5.0 events per 100 patient-years. Another study presented event rate data by continuous CHADS₂ score for a mixed population of patients on aspirin and off antithrombotic therapy (“off oral anticoagulants”);⁹⁹ event rates were low and did not appear to show consistent trends with CHADS₂ (0=0.8, 1=0.7, 2=0.7, 3=0, ≥4=5 events per 100 patient-years).

Finally, one study presented limited data regarding use of the continuous CHADS₂ in predicting bleeding events following AF ablation. Continuous CHADS₂ was a significant predictor of bleeding following ablation, with an odds ratio (OR) of 1.33 (95% CI, 1.02 to 1.73). Though most studies generally suggested increasing rates of major bleeding with increasing CHADS₂, data were not provided to fully evaluate the predictive accuracy of CHADS₂ for major bleeding events among patients on warfarin, aspirin, or no antithrombotic therapy (e.g., c-statistics).

Table 14. Summary of results for studies evaluating CHADS₂ (revised scoring system unless otherwise specified) among patients on warfarin

Study	N	Followup	Bleeding event rates	C-statistic
Olesen, 2011 ¹¹⁰	132,372	Up to 12 years	Low=3.3 events/100 patient-years Moderate=4.4 High=5.3	NR
Poli, 2011 ⁹⁵	3,302	Median 2.3 years	Low=0.4 events/100 patient-years Moderate=1.3 High=1.3	NR
Ad, 2010 ⁹⁷	347	Mean 32.77 months	NR	NR
Ruiz Ortiz, 2010 ⁹⁹	796	Mean 2.4 years	Low=0.4 events/100 patient-years Moderate=1.3 High=NR for CHADS ₂ ≥2 <i>Continuous score:</i> 0=3 events per 100 patient-years 1=0.8 2=1.3 3=0.4 ≥4=2.9	NR
Connolly, 2009 ²⁶	18,113	Median 2 years	<i>Atypical scoring system:</i> 0-1=2.84 percent per year 2=3.3 ≥3=4.6	NR
Poli, 2007 ¹¹³	290*	Mean 2.8 years	Low=NR (all patients >75 years old) Moderate=1.9 events/100 patient-years High=2.1	NR

Abbreviations: CHADS₂=Congestive heart failure, Hypertension, Age ≥75, Diabetes mellitus, prior Stroke/transient ischemic attack (2 points); N=number of participants; NR = not reported

CHA₂DS₂-VASc

One study provided data regarding the impact of the categorical CHA₂DS₂-VASc on diagnostic thinking with respect to estimating the likelihood of major bleeding in patients with AF.¹¹⁰ This study did not provide c-statistics for CHA₂DS₂-VASc with respect to bleeding risk in any population, so the predictive accuracy of CHA₂DS₂-VASc could not be fully evaluated. Among patients on warfarin, the low-risk group experienced 2.6 events per 100 patient-years, the moderate-risk group experienced 3.5 events per 100 patient-years, and the high-risk group experienced 4.9 events per 100 patient-years. Among patients not on antithrombotic therapy, the low-risk group experienced 1.0 event per 100 patient-years, the moderate-risk group experienced 1.8 events per 100 patient-years, and the high-risk group experienced 3.9 events per 100 patient-years. Among patients on aspirin alone, the low-risk group experienced 1.8 events per 100 patient-years, the moderate-risk group experienced 2.5 events per 100 patient-years, and the high-risk group experienced 4.5 events per 100 patient-years. Though the observed trends appear to suggest increased major bleeding with increased CHA₂DS₂-VASc, predictive accuracy cannot be fully evaluated based on the available data.

INR

A single, large, retrospective study evaluated the use of two INR-related statistics, TTR (% time in therapeutic INR range of 2.0–3.0) and SDT_{INR} (standard deviation of transformed INR values), in terms of impact on diagnostic thinking with respect to estimating the likelihood of major bleeding in patients with AF.¹¹¹ This study presented hazard ratios (HRs) associated with a 1 SD change in each risk variable; the HR for the SDT_{INR} variable was 1.27 (95% CI, 1.20 to 1.35) and the HR for TTR was 1.07 (95% CI, 1.01 to 1.14). These available data appear to suggest that SDT_{INR} would have better predictive accuracy for major bleeding than TTR, but no prospective confirmatory data were available.

Comparison of Bleeding Risk Scores and Meta-Analysis Results

Table 15 provides a summary of available c-statistics for predictive accuracy of the risk scores of interest among patients on warfarin. Tables 16 and 17 provide the same for patients on no antithrombotic therapy and aspirin alone, respectively. The c-statistic, or area under the receiver operating characteristic curve, may not be optimal in assessing models that predict future risk or stratify individuals into risk categories, but it is the most commonly reported statistic for assessing a model's performance in predicting risk of future disease.¹²⁰ Because the c-statistic is the most widely available means for characterizing the risk scores described in the studies included in this section, we have used it as the basis for comparing these scores. Studies evaluating CHADS₂, CHA₂DS₂-VASc, and INR indices did not provide c-statistics or other indicators of predictive accuracy, so we were unable to include these bleeding risk assessment tools in this comparison.

Among patients on warfarin, three of the risk scores—BRI, HEMORR₂HAGES, and HAS-BLED—were evaluated in studies where direct comparison with another of these three scores was possible (Table 15). Although differences in c-statistics were not statistically significant in every case, these comparisons generally indicated that HAS-BLED performed better than HEMORR₂HAGES, which in turn performed better than BRI. Therefore, based on available data, HAS-BLED would appear to be the most accurate bleeding risk prediction score for use among patients on warfarin (low strength of evidence). It should be noted that one of the studies comparing HAS-BLED with HEMORR₂HAGES was the study from which the HAS-BLED score was derived.¹⁶ Also, the ATRIA bleeding risk score has only been compared with other scores in one study, which was the study from which ATRIA was derived. The results of this review should be interpreted with some caution for these reasons.

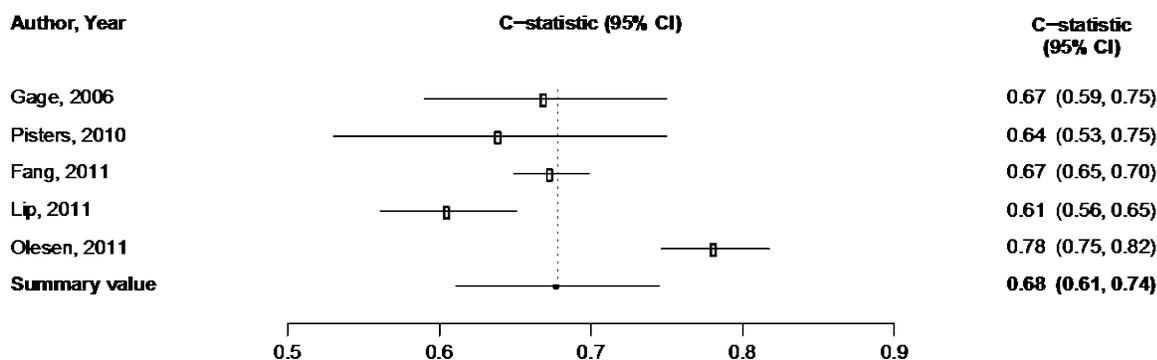
Sufficient data existed to permit meta-analysis of studies evaluating HEMORR₂HAGES among patients on warfarin (Figure 8), but meta-analysis could not be completed for other risk scores of interest due to insufficient data. Therefore, meta-analysis did not add to our ability to compare available bleeding risk scores in this population. The HEMORR₂HAGES synthesis demonstrated a summary c-statistic of 0.68 (95% CI, 0.61 to 0.74, $Q=41.8$ [$p<0.001$], $I^2=90.4$) with substantial heterogeneity.

Table 15. C-statistics from studies comparing risk scores of interest among patients on warfarin

Study	BRI	HEMORR ₂ HAGES	HAS-BLED	ATRIA
Fang, 2011 ¹¹²	0.59 (95% CI, 0.58 to 0.61)	0.67 (95% CI, 0.65 to 0.70)	-	0.69 (95% CI, 0.66 to 0.71)
Gage, 2006 ¹¹⁵	0.65 (SE 0.03)	0.67 (SE 0.04)	-	-
Baruch, 2007 ⁸⁹	0.56 (95% CI, 0.51 to 0.60)	0.61 (95% CI, 0.56 to 0.65)	0.66 (95% CI, 0.61 to 0.70)	-
Pisters, 2010 ¹⁶	-	0.64 (95% CI, 0.53 to 0.75)	0.69 (95% CI, 0.59 to 0.80)	-
Olesen, 2011 ¹¹⁷	-	0.78 (95% CI, 0.75 to 0.82)	0.80 (95% CI, 0.77 to 0.83)	-

Abbreviations: ATRIA=Anticoagulation and Risk Factors in Atrial Fibrillation; BRI=Bleeding Risk Index; CI=confidence interval; HAS-BLED=Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (> 65 years), Drugs/alcohol concomitantly; HEMORR₂HAGES=Hepatic or renal disease, Ethanol abuse, Malignancy, Older (age >75 years), Reduced platelet count or function, Re-bleeding risk (2 points), Hypertension (uncontrolled), Anemia, Genetic factors, Excessive fall risk, Stroke; SE=standard error

Figure 8. Meta-analysis results for studies evaluating the HEMORR₂HAGES bleeding risk score



Abbreviations: CI=confidence interval; HEMORR₂HAGES=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

Tables 16 and 17 show data comparing bleeding risk scores among patients off antithrombotic therapy and on aspirin alone, respectively. Although differences in c-statistics were not statistically significant in every case, these comparisons also indicated that HAS-BLED performed better than HEMORR₂HAGES, which in turn performed better than BRI, in these populations. Insufficient data existed to allow meta-analysis in these populations.

Table 16. C-statistics from studies comparing risk scores of interest among patients off antithrombotic therapy

Study	BRI	HEMORR ₂ HAGES	HAS-BLED
Gage, 2006 ¹¹⁵	0.65 (SE 0.03)	0.66 (SE 0.04)	-
Baruch, 2007 ⁸⁹	0.50 (95% CI, 0.44 to 0.57)	0.62 (95% CI, 0.52 to 0.72)	0.66 (95% CI, 0.55 to 0.74)
Pisters, 2010 ¹⁶	-	0.81 (95% CI, 0.00 to 1.00)	0.85 (95% CI, 0.00 to 1.00)

Abbreviations: BRI=Bleeding Risk Index; CI=confidence interval; HAS-BLED=Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (> 65 years), Drugs/alcohol concomitantly; HEMORR₂HAGES=Hepatic or renal disease, Ethanol abuse, Malignancy, Older (age >75 years), Reduced platelet count or function, Re-bleeding risk (2 points), Hypertension (uncontrolled), Anemia, Genetic factors, Excessive fall risk, Stroke; SE=standard error

Table 17. C-statistics from studies comparing risk scores of interest among patients on aspirin alone

Study	BRI	HEMORR ₂ HAGES	HAS-BLED
Gage, 2006 ¹¹⁵	0.69 (SE 0.05)	0.72 (SE 0.05)	-
Pisters, 2010 ¹⁶	-	0.83 (95% CI, 0.68 to 0.98)	0.91 (95% CI, 0.83 to 1.00)

Abbreviations: BRI=Bleeding Risk Index; CI=confidence interval; HAS-BLED=Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (> 65 years), Drugs/alcohol concomitantly; HEMORR₂HAGES=Hepatic or renal disease, Ethanol abuse, Malignancy, Older (age >75 years), Reduced platelet count or function, Re-bleeding risk (2 points), Hypertension (uncontrolled), Anemia, Genetic factors, Excessive fall risk, Stroke; SE=standard error

Intracranial Hemorrhage

Overview

Most available studies for KQ 2 included intracranial hemorrhage (ICH) within the outcome “major bleeding,” but two studies presented this outcome separately, one evaluating CHADS₂,²⁶ and the other evaluating INR.⁹¹ Because of the small number of studies, meta-analysis was not considered for this outcome.

CHADS₂

A single study provided data on the impact of CHADS₂ on diagnostic thinking with respect to estimating the likelihood of ICH in AF, but did not provide c-statistics for CHADS₂ with respect to ICH risk, so the predictive accuracy of CHADS₂ in this situation could not be fully evaluated.²⁶ This study presented event rate data for patients on warfarin according to an atypical CHADS₂ stratification system; this showed that the number of patients experiencing ICH was 0.54 percent per year for CHADS₂ 0–1, 0.69 percent per year for CHADS₂ 2, and 1.07 percent per year for CHADS₂ >3 (p-value for three-way comparison =0.02). This study also presented event rate data for a mixed population of patients on warfarin and dabigatran according to the revised CHADS₂; this showed that the number of patients experiencing ICH events during a median of 2 years followup was 0.2 percent for the low-risk group, 0.7 percent for the moderate-risk group, and 0.8 percent for the high-risk group.

INR

A single study conducted among patients with AF presenting with stroke evaluated the incidence of ICH by INR at the time of stroke.⁹¹ This study suggested that at supratherapeutic INR ranges, ICH incidence was higher, but the study was not designed to truly evaluate the predictive accuracy of this risk factor. ICH rates per 100 patient-years were 0.5 for INR <1.5, 0.3 for INR 1.5–1.9, 0.3 for INR 2.0–2.5, 0.5 for INR 2.6–3.0, 0.6 for INR 3.1–3.5, 0.4 for INR 3.6–3.9, 2.7 for INR 4.0–4.5, and 9.4 for INR >4.5.

Minor Bleeding

Overview

A single study evaluated the impact of the BRI on estimating the risk of minor bleeding (not requiring transfusion, no major associated morbidity) in patients with AF on warfarin.¹¹⁶

BRI

A single study provided event rate data for incidence of minor bleeding by BRI risk category among patients on warfarin.¹¹⁶ In this study, 8.3 percent of the low-risk group, 4.4 percent moderate-risk group, and 6.9 percent of the high-risk group experienced minor bleeding per patient-year. The BRI was not felt to be predictive of minor bleeding in this analysis.

Table 18 summarizes the strength of evidence for the predictive abilities of the included tools. This summary table represents only those studies that evaluated the predictive abilities of the tools using a c-statistic.

Table 18. Strength of evidence domains for predicting bleeding events

Outcome	Number of Studies (Subjects)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Summary c-Statistic						
ATRIA	1 (3,063)	Observational/ Moderate	NA	Direct	Imprecise	SOE=Insufficient
Bleeding Risk Score	3 (14,183)	Observational/ Moderate	Consistent	Direct	Precise	SOE=Moderate Limited risk prediction (c-statistic ranging from 0.56 to 0.65)
HAS-BLED	3 (129,369)	Observational/ Moderate	Consistent	Direct	Precise	SOE=Moderate Modest risk prediction (c-statistic ranging from 0.66 to 0.80)
HEMORR ₂ HAGES	5 (135,233)	Observational/ Moderate	Consistent	Direct	Precise	SOE=Moderate Limited risk prediction (c-statistic=0.68; 95% CI, 0.61 to 0.74)
CHADS ₂	6 (155,220)	Observational/ Moderate	xxx	Direct	Imprecise	SOE=Insufficient
CHA ₂ DS ₂ -VASC	1 (132,372)	Observational/ Moderate	NA	Direct	Imprecise	SOE=Insufficient

Outcome	Number of Studies (Subjects)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Comparative Predictive Abilities						
Major bleeding rates among patients with AF on warfarin	5 (142,346)	Observational/ Moderate	Consistent	Direct	Imprecise	SOE=Low HAS-BLED tool appears to have the highest predictive accuracy
Major bleeding rates among patients with AF off of antithrombotic therapy	3 (14,576)	Observational/ Moderate	Consistent	Direct	Imprecise	SOE=Low HAS-BLED tool appears to have the highest predictive accuracy
Major bleeding rates among patients with AF on aspirin alone	2 (7,247)	Observational/ Moderate	Consistent	Direct	Imprecise	SOE=Low HAS-BLED tool appears to have the highest predictive accuracy

Abbreviations: AF=atrial fibrillation; ATRIA=Anticoagulation and Risk Factors in Atrial Fibrillation; 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; HAS-BLED=Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (> 65 years), Drugs/alcohol concomitantly; HEMORR₂HAGES=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

Key Question 3. Interventions for Preventing Thromboembolic Events

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

- a) In patients with nonvalvular AF?
- b) In specific subpopulations of patients with nonvalvular AF?

Key Points

- Warfarin reduces the risk of non-fatal and fatal ischemic stroke when compared with aspirin (moderate strength of evidence); on the other hand, warfarin is associated with increased annual rates of severe bleeding complications (moderate strength of evidence). These findings are based on two retrospective studies (one good quality and one poor quality) involving 99,061 patients.
- The combination of aspirin + clopidogrel demonstrated similar rates of stroke when compared with aspirin alone in one trial involving 7,554 patients, but showed a significant reduction in stroke in the aspirin + clopidogrel arm in a smaller study of 593 patients (low strength of evidence for similar rates of stroke between treatments); in both

RCTs, the combination was associated with higher rates of major bleeding (high strength of evidence).

- Clopidogrel monotherapy is associated with increased risk of non-fatal and fatal ischemic stroke when compared with warfarin monotherapy, with no differences in major bleeding (moderate strength of evidence). This is based on one large retrospective good-quality study involving 54,636 patients.
- Warfarin is superior to aspirin plus clopidogrel for the prevention of stroke, systemic embolism, MI, or vascular death, with similar rates of major bleeding (moderate strength of evidence). This finding is based on one large good-quality RCT of 6,706 patients which was stopped early and a retrospective good-quality study of 53,778 patients.
- Adding clopidogrel to warfarin has no benefits on stroke prevention (low strength of evidence) and is associated with increased risk of non-fatal and fatal bleeding when compared with warfarin alone (moderate strength of evidence). This finding is based on one good-quality retrospective study involving 52,349 patients
- Triple therapy with warfarin + ASA + clopidogrel substantially increases the risk of non-fatal and fatal bleeding (moderate strength of evidence) with no benefits on preventing ischemic stroke when compared with warfarin alone (low strength of evidence). This finding is based on one good-quality retrospective study involving 52,180 patients
- A Factor II inhibitor (dabigatran) at a 150 mg is superior to warfarin in reducing the incidence of composite of stroke (including hemorrhagic) or systemic embolism, with no significant difference in the occurrence of major bleeding (high strength of evidence). Dabigatran increased MI risk (moderate strength of evidence). This finding is based on one large good-quality RCT involving 12,098 patients from the larger RE-LY trial of 18,113 patients.
- A Factor II inhibitor (dabigatran) at a 110 mg dose is non-inferior to warfarin for the outcome of the composite of stroke or systemic embolism and is associated with a reduction in major bleeding when compared with warfarin. Dabigatran increased MI risk (moderate strength of evidence). The rates of intracerebral hemorrhage are significantly lower with both dabigatran doses compared with warfarin (high strength of evidence). This finding is based on one large good-quality RCT involving 12,037 patients from the larger RE-LY trial of 18,113 patients.
- The direct Xa inhibitor apixaban compared with aspirin was superior in reducing the incidence of stroke and systemic embolism, with similar hemorrhagic events, including major bleeding in patients who are not suitable for oral anticoagulation (high strength of evidence). This finding is based on one good-quality RCT involving 5,599 patients.
- The Xa inhibitor apixaban is superior in reducing the incidence of stroke, systemic embolism, major bleeding, and all-cause mortality when compared with warfarin (high strength of evidence). This finding is based on one good-quality RCT involving 18,201 patients.
- The Xa inhibitor rivaroxaban is non-inferior to warfarin in preventing stroke and systemic embolism, with similar rates of major bleeding and death. Among patients receiving the drug, rivaroxaban is superior to warfarin for the prevention of stroke (high strength of evidence). This finding is based on one good quality RCT involving 14,264 patients.
- Percutaneous left atrial appendage (LAA) closure is non-inferior to warfarin on the primary composite outcome of stroke, cardiovascular death, and systemic embolism, with

less risk of hemorrhagic stroke (low strength of evidence). Adverse safety events occur at a higher rate with the procedure. This is based on one good-quality RCT involving 707 patients.

- Patients with renal impairment, with different INR control, and with prior stroke seem to benefit equally from the new anticoagulant agents when compared with warfarin (low strength of evidence). This finding is based on one study of patients with renal impairment, two studies of patients with different INR control, and seven studies of patients with prior stroke.

Description of Included Studies

Thirty-six studies published between 2000 and 2011 were identified (Appendix Table F-3). The majority of studies (24) were multicenter,^{14,26,27,91,110,121-139} 11 were single-center,^{99,140-149} and in 1 the study site was unclear.¹⁵⁰ A total of 20 RCTs,^{26,27,121,122,124-126,128-131,133,136-139,143,144,147,148} 9 retrospective studies,^{91,110,123,132,135,141,142,149,150} and 7 prospective cohorts^{14,99,127,134,140,145,146} were included in our analyses. Eight studies enrolled only inpatients,^{110,125,127,130,131,135,138,148} 15 included only outpatients,^{26,27,91,99,122-124,126,137,139,142-144,147,150} 5 included both inpatients and outpatients,^{134,136,145,146,149} and 8 studies included patients from unclear settings.^{14,121,128,129,132,133,140,141} The number of patients included in studies ranged from 30¹⁴⁷ to 132,372,¹¹⁰ with a total of 245,828 patients.

In regards to funding, 16 studies were sponsored by industry,^{26,27,121-126,128-130,133,136,139,142,147} 3 by government,^{91,137,150} and 17 had either no sponsorship or this information was unclear.^{14,99,110,127,131,132,134,135,138,140,141,143-146,148,149} Fourteen studies enrolled consecutive patients,^{27,99,122,125,130,134,138-140,145-149} and one used a convenience sample.²⁶ The remaining studies either did not report the enrollment approach or the approach used was unclear.^{14,91,110,121,123,124,126-129,131-133,135-137,141-144,150}

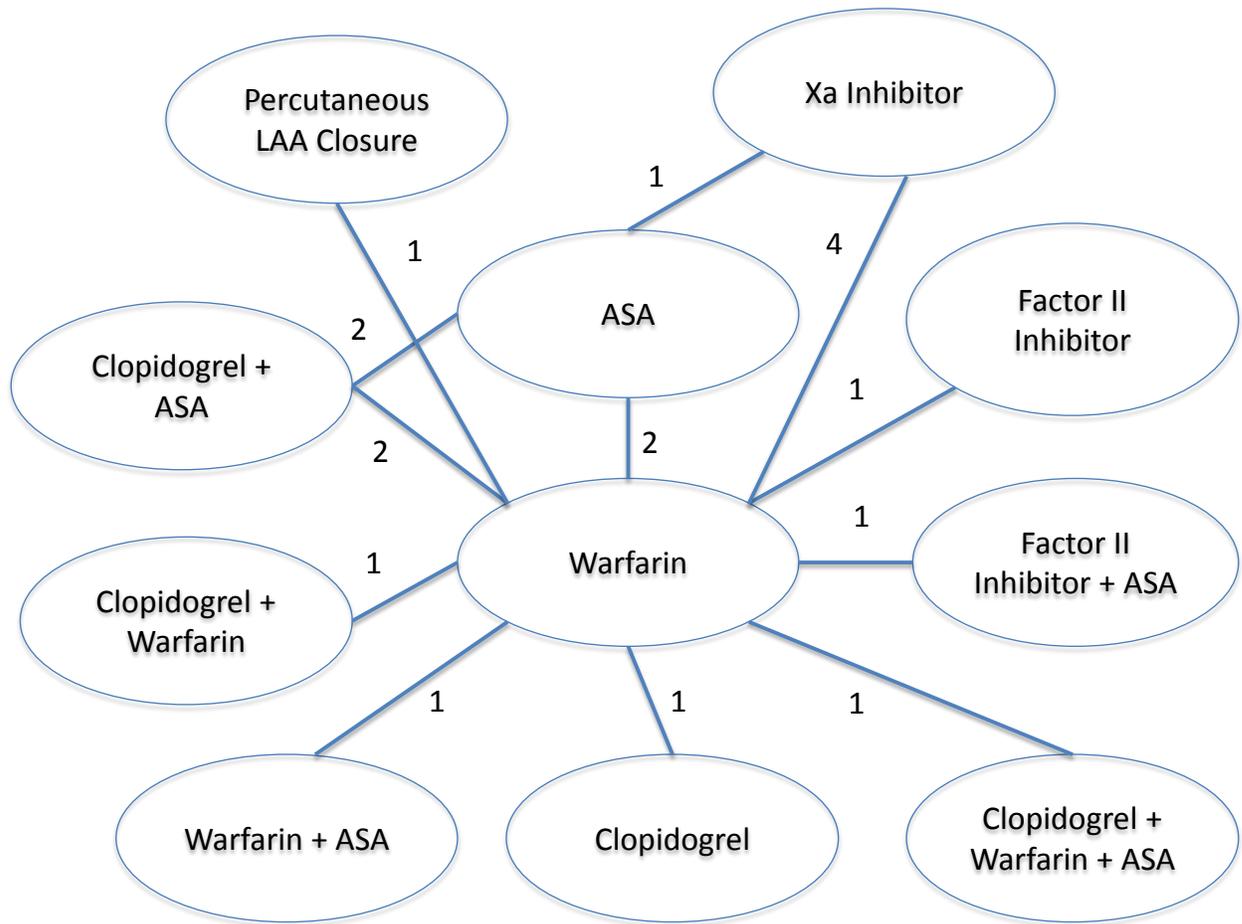
The mean age of included patients varied from 62.6¹⁴⁸ to 77.2¹³⁵ years. Only three studies reported the overall mean CHADS₂ score, which varied from 2.1¹²⁶ to 3.5.²⁷ Three studies included only patients with persistent AF,^{124,132,148} while three studies included only patients with permanent AF.^{99,127,143} In two studies, only patients with prior stroke were enrolled.^{91,138} Among the studies in which comorbidities were reported these varied widely, 6.6–40 percent of the population had diabetes mellitus, 15.4–90.5 percent had systemic hypertension, 14–62.5 percent had congestive heart failure, 9–67.4 percent had coronary artery disease, and 6.2–17 percent had a history of prior MI.

Among the multicenter studies, two were performed exclusively in the UK,^{131,132} five in Europe,^{110,123,127,134,138} two in Asia,^{14,137} three in the United States,^{91,128,135} two in both the United States and Europe,^{125,130} and the remaining in multiple continents.^{26,27,121,122,124,126,129,133,136,139} Among the single-center studies, one was conducted in the United States,¹⁴² one in the UK¹⁴³ two in Asia,^{140,141} and seven in Europe.^{99,144-149}

Nineteen studies were considered of good quality,^{26,27,91,121-126,128-131,133,134,138,139,143,146} 10 of fair quality,^{135,136,140,141,144,145,147,148,150} and 7 were of poor quality.^{14,110,127,132,137,142,149}

Figure 9 represents the treatment comparisons evaluated for this KQ.

Figure 9. Overview of treatment comparisons evaluated for KQ 3



Abbreviations: ASA=aspirin; KQ=Key Question; LAA=left atrial appendage

As Figure 9 shows, most comparisons were only explored in a limited number of studies, although many of these were good-quality RCTs involving over 5,000 patients. The Xa inhibitor versus warfarin comparison was the only comparison for which we identified more than two studies.

Detailed Synthesis

Fourteen of our included studies looked explicitly at the comparative safety and effectiveness of specific anticoagulation therapies, antiplatelet therapies, and procedural interventions for preventing thromboembolic events in patients with nonvalvular AF. Below we describe each of these studies categorized by the treatment comparisons represented. An additional 21 unique studies (and 12 substudies of included RCTs) focused on specific subgroups of interest. These studies are not combined with the more general AF population studies, but instead are discussed separately at the end of this section categorized by specific subgroup.

As described above, for all comparisons other than Xa inhibitor versus warfarin, we only identified one or two studies per comparison of interest. The data for these comparisons therefore was deemed inappropriate for meta-analysis. Although we identified four studies for the Xa inhibitors versus warfarin comparison, the specific Xa inhibitors and the trials differed

substantially, and a quantitative synthesis of these data was also considered inappropriate. We therefore describe results for outcomes of interest qualitatively below.

Aspirin (ASA) Versus Warfarin

We identified one good-quality retrospective study involving 98,460 patients¹²³ and one poor-quality retrospective study involving 601 patients¹³² that compared ASA with warfarin. A third retrospective study¹⁵⁰ also evaluated ASA versus warfarin, but study investigators were not able to distinguish patients who were on a combination of warfarin and ASA and counted these patients as warfarin only. This third study was therefore excluded from our analysis and not synthesized with the other two.

Ischemic Stroke

In one study,¹²³ treatment with ASA was associated with increased risk of non-fatal and fatal ischemic stroke when compared with warfarin (HR 1.83; 95% CI, 1.73 to 1.94). Similarly, in the second study,¹³² there were increased rates of stroke among patients receiving ASA compared with warfarin (3.57% per patient-year in the ASA group vs. 1.64% per patient-year in the warfarin group).

Bleeding

In one study,¹²³ the risk of non-fatal and fatal bleeding was lower in the aspirin group (HR 0.93; 95% CI, 0.88 to 0.98). Similarly, in the second study,¹³² annual rates of severe bleeding complications were higher in the warfarin group (1.90% per patient-year in the ASA group vs. 2.6% per patient-year in the warfarin group). Overall, bleeding rates were also higher in the warfarin group (4.7% per patient-year in the ASA group vs. 9.0% per patient-year in the warfarin group).

All-Cause Mortality

One study¹³² reported on rates of all-cause mortality and found that they were lower among patients receiving warfarin (13.3% per patient-year in the ASA group vs. 7.3% per patient-year in the warfarin group).

Warfarin + ASA Versus Warfarin Alone

One good-quality retrospective cohort study compared warfarin + ASA (18,345 patients) with warfarin monotherapy (50,919 patients).¹²³ This study demonstrated increased risks of both stroke and bleeding in the combination arm compared with warfarin monotherapy.

Ischemic Stroke

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

Bleeding

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

Clopidogrel + ASA Versus ASA Alone

Two good-quality RCTs involving 8,147 patients analyzed the combination of clopidogrel + ASA compared with ASA therapy alone in patients with AF.^{126,128} Although the smaller study involving 593 patients did not demonstrate any difference in the main outcomes of interest,¹²⁸ the larger trial of 7,554 patients demonstrated a reduction in stroke for patients on clopidogrel + ASA, while showing an increase in bleeding events as compared with ASA alone.¹²⁶

Any Stroke

The findings of these two studies differed in terms of the impact of treatment on all strokes. Rates of any stroke did not differ between groups in one study (2.2% per year vs. 2.1% per year for clopidogrel + ASA and ASA alone, respectively; HR 1.03; 95% CI, 0.49 to 2.13; $p=0.94$).¹²⁸ The other showed lower rates of stroke in the group treated with clopidogrel + ASA (2.4% per year vs. 3.3% per year for clopidogrel + ASA and ASA alone, respectively; HR 0.72; 95% CI, 0.62 to 0.83; $p<0.001$).¹²⁶

Ischemic Stroke

Rates of ischemic stroke were also similar in one study when the two groups were compared (2.0% per year for clopidogrel + ASA vs. 2.1% per year for ASA alone; HR 0.96; 95% CI, 0.46 to 2.01; $p=0.91$),¹²⁸ and higher in the ASA group in the other study (1.9% per year for clopidogrel + ASA vs. 2.8% per year for ASA alone; HR 0.68; 95% CI, 0.57 to 0.80).¹²⁶

Systemic Embolism

Only one study reported the rates of systemic embolism, which were similar between the groups (0.4% per year for clopidogrel + ASA vs. 0.4% per year for ASA alone; HR 0.96; 95% CI, 0.66 to 1.40; $p=0.84$).¹²⁶

Hemorrhagic Stroke

Rates of hemorrhagic stroke were similar between the groups in both studies.

Major Bleeding

The combination of clopidogrel + ASA was associated with higher rates of major bleeding when compared with ASA alone in one study (2.0% per year for clopidogrel + ASA vs. 1.3% per year for ASA alone; HR 1.57; 95% CI, 1.29 to 1.92; $p<0.001$).¹²⁶ The other study did not report rates of major bleeding.¹²⁸

Minor Bleeding

Overall, the rates of minor bleeding were higher in the clopidogrel + ASA group compared with ASA alone in one study (3.5% per year for clopidogrel + ASA vs. 1.4% per year for ASA alone; HR 2.42; 95% CI, 2.03 to 2.89; $p<0.001$).¹²⁶ The other study did not report this information.

Intracranial Bleeding

Rates of intracranial bleeding were similar in one study when the two groups were compared (3 patients in the clopidogrel + ASA group vs. 1 patient in the ASA alone group; $p=0.62$),¹²⁸ and higher in the clopidogrel + ASA group in the other study (0.4% per year for clopidogrel + ASA vs. 0.2% per year for ASA alone; HR 1.87; 95% CI, 1.19 to 2.94; $p=0.006$).¹²⁶

Extracranial Bleeding

Rates of extracranial bleeding between the groups were similar in one study (2% in the clopidogrel + ASA group vs. 1% patients in the ASA alone group, $p=0.51$),¹²⁸ and higher in the clopidogrel + ASA group in the other study (1.6% per year for clopidogrel + ASA vs. 1.1% per year for ASA alone; HR 1.51; 95% CI, 1.21 to 1.88; $p<0.001$).¹²⁶

All-Cause Mortality

All-cause mortality did not differ between the groups in either study (6.4% per year for clopidogrel + ASA vs. 6.6% per year for ASA alone; HR 0.98; 95% CI, 0.89 to 1.08; $p=0.69$;¹²⁶ and 29 patients in the clopidogrel + ASA vs. 25 patients in ASA alone group; HR 1.12; 95% CI, 0.65 to 1.90; $p=0.69$ ¹²⁸).

Death From Vascular Causes

Death from vascular causes also did not differ between the groups in either study (4.7% per year for clopidogrel + ASA vs. 4.7% per year for ASA alone; HR 1.00; 95% CI, 0.89 to 1.12; $p=0.97$;¹²⁶ and 21 patients in the clopidogrel + ASA vs. 12 patients in ASA alone group; HR 1.68; 95% CI, 0.83 to 3.42; $p=0.15$ ¹²⁸).

Myocardial Infarction

Both studies reported similar rates of MI between groups (0.7% per year for clopidogrel + ASA vs. 0.9% per year for ASA alone; HR 0.78; 95% CI, 0.59 to 1.03; $p=0.08$;¹²⁶ and 9 patients in the clopidogrel + ASA group vs. 6 patients in the ASA alone group; HR 1.43; 95% CI, 0.51 to 4.01; $p=0.50$ ¹²⁸).

Hospitalization

One study reported rates of rehospitalization, which were similar between the two groups (41 patients in the clopidogrel + ASA group vs. 43 patients in the ASA alone group; HR 0.89; 95% CI, 0.58 to 1.37; $p=0.60$).¹²⁸

Clopidogrel Versus Warfarin

One good-quality retrospective cohort study compared clopidogrel (3,717 patients) with warfarin (50,919 patients).¹²³

Ischemic Stroke

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

Bleeding

This study found that the risk of non-fatal and fatal bleeding was similar between groups (HR 1.06; 95% CI, 0.87- to 1.29).

Clopidogrel + ASA Versus Warfarin

Two studies compared clopidogrel + ASA with warfarin.^{123,133} One study was a good-quality retrospective analysis involving 2,859 patients on clopidogrel + ASA treatment and 50,919 patients on warfarin monotherapy.¹²³ The other study was a good-quality RCT involving 6,706

patients which was stopped early because of the clear evidence of superiority of the warfarin strategy.¹³³

Stroke or Systemic Embolism

In both studies, treatment with ASA + clopidogrel was associated with increased risk of non-fatal and fatal ischemic stroke when compared with warfarin (HR 1.56; 95% CI, 1.17 to 2.10;¹²³ and 1.72; 95% CI, 1.24 to 2.37; p=0.001¹³³).

Hemorrhagic Stroke

Only one study reported rates of hemorrhagic stroke, which were higher in the warfarin group (0.12% per year vs. 0.36% per year for clopidogrel + ASA and warfarin, respectively; HR 0.34; 95% CI, 0.12 to 0.93; p=0.036).¹³³

Major Bleeding

One study reported no differences in major bleeding rates, including severe and fatal (2.42% per year vs. 2.21% per year for clopidogrel + ASA and warfarin, respectively; HR 1.10; 95% CI, 0.83 to 1.45; p=0.53).¹³³ The other study reported that the risk of non-fatal and fatal bleeding was higher in the ASA + clopidogrel group (HR 1.66; 95% CI, 1.34 to 2.04).¹²³

Minor Bleeding

Only one study reported rates of minor bleeding, which were higher in the clopidogrel + ASA group (13.58% per year vs. 11.45% per year for clopidogrel + ASA and warfarin, respectively; HR 1.23; 95% CI, 1.09 to 1.39; p=0.0009).¹³³

Intracranial Bleeding

Intracranial bleeding including subdural hematoma was reported by only one study and was more common with warfarin therapy; however, this difference did not reach statistical significance (p=0.08).¹³³

All-Cause Mortality

All-cause mortality was reported by only one study, and there was no difference between the two groups (3.8% per year vs. 3.76% per year for clopidogrel + ASA and warfarin, respectively; HR 1.01; 95% CI, 0.81 to 1.26; p=0.91).¹³³

Death From Vascular Causes

Death from vascular causes was reported by only one study. Rates were slightly higher with clopidogrel + ASA, however, the difference did not reach statistical significance (2.87% per year vs. 2.52% per year for clopidogrel + ASA and warfarin, respectively; HR 1.14; 95% CI, 0.88 to 1.48; p=0.34).¹³³

Myocardial Infarction

Within the RCT,¹³³ MI occurred at rates of less than one percent per year in both groups and was not significantly different between the treatments. Rates of MI were not reported in the other study.¹²³

Clopidogrel + Warfarin Versus Warfarin

One good-quality retrospective study compared warfarin + clopidogrel (1,430 patients) with warfarin monotherapy (50,919 patients).¹²³ Although potentially showing a trend towards reducing ischemic stroke, the risk of bleeding was greatly increased in patients receiving clopidogrel + warfarin compared with warfarin monotherapy.

Ischemic Stroke

In the one included study, the rates non-fatal and fatal ischemic stroke were similar between groups (HR 0.70; 95% CI, 0.35 to 1.40).

Bleeding

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

Warfarin Versus Warfarin + ASA + Clopidogrel

One good-quality retrospective study compared warfarin monotherapy (50,919 patients) with the triple therapy of warfarin + ASA + clopidogrel (1,261 patients).¹²³

Ischemic Stroke

The rates of non-fatal and fatal ischemic stroke were similar between groups (HR 1.45; 95% CI, 0.84 to 2.52), although there was a nonstatistically significant trend towards an increase in the triple therapy arm.

Bleeding

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

Factor II Inhibitor Versus Warfarin

One large, good-quality, noninferiority RCT of 18,113 patients (RE-LY) compared a Factor II inhibitor (dabigatran) with warfarin in nonvalvular AF patients.²⁶ Patients receiving dabigatran were randomized to one of two doses (110 mg and 150 mg). Patients receiving the 110 mg dose had rates of stroke and systemic embolism that were similar to those associated with warfarin, but lower rates of major hemorrhage. Patients who received 150 mg of dabigatran had lower rates of stroke and systemic embolism than patients in the warfarin group, but similar rates of major hemorrhage.

Stroke or Systemic Embolism

Dabigatran at a 110 mg dose was non-inferior to warfarin in preventing stroke and systemic embolism (1.53% per year vs. 1.69% per year for dabigatran and warfarin, respectively; HR 0.91; 95% CI, 0.74 to 1.11; $p < 0.001$ for non-inferiority and 0.34 for superiority). Dabigatran at 150 mg was superior to warfarin in reducing the incidence of stroke (including hemorrhagic stroke) and systemic embolism by 34 percent (1.11% per year vs. 1.69% per year; HR 0.66; 95% CI, 0.53 to 0.82, $p < 0.001$).

Ischemic or Uncertain Stroke

The rates of ischemic or uncertain stroke were not different between dabigatran 110 mg and warfarin (1.34% per year for dabigatran 110 mg vs. 1.20% per year for warfarin; HR 1.11; 95% CI, 0.89 to 1.40; $p=0.35$). Dabigatran 150 mg was associated with lower rates of ischemic or uncertain stroke when compared with warfarin (0.92% per year for dabigatran 150 mg vs. 1.20% per year for warfarin; HR 0.76; 95% CI, 0.60 to 0.98; $p=0.03$).

Hemorrhagic Stroke

Both doses of dabigatran were associated with lower rates of hemorrhagic stroke (0.12% per year for dabigatran 110 mg vs. 0.38% per year for warfarin; HR 0.31; 95% CI, 0.17 to 0.56; $p<0.001$; 0.10% per year for dabigatran 150 mg versus 0.38% per year for warfarin; HR 0.26; 95% CI, 0.14 to 0.49; $p<0.001$).

Major Bleeding

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

Minor Bleeding

Overall, the rates of minor bleeding were higher in the warfarin group compared with both doses of dabigatran (13.16% per year for dabigatran 110 mg vs. 16.37% per year for warfarin; HR 0.79; 95% CI, 0.74 to 0.84; $p<0.001$; 14.84% per year for dabigatran 150 mg vs. 16.37% per year for warfarin; HR 0.91; 95% CI, 0.85 to 0.97; $p=0.005$). Gastrointestinal bleeding was more common with higher dose dabigatran than with warfarin.

Intracranial Bleeding

Both doses of dabigatran were associated with lower rates of intracranial bleeding (0.23% per year for dabigatran 110 mg vs. 0.74% per year for warfarin; HR 0.31; 95% CI, 0.20 to 0.47; $p<0.001$; 0.30% per year for dabigatran 150 mg vs. 0.74% per year for warfarin; HR 0.40; 95% CI, 0.27 to 0.60; $p<0.001$).

All-Cause Mortality

All-cause mortality did not differ between warfarin and either dose of dabigatran (3.75% per year for dabigatran 110 mg vs. 4.13% per year for warfarin; HR 0.91; 95% CI, 0.80 to 1.03; $p=0.13$; 3.64% per year for dabigatran 150 mg vs. 4.13% per year for warfarin; HR 0.88; 95% CI, 0.77 to 1.00; $p=0.051$).

Death From Vascular Causes

Death from vascular causes was lower with the higher dose of dabigatran (2.43% per year for dabigatran 110 mg vs. 2.69% per year for warfarin; HR 0.90; 95% CI, 0.77 to 1.06; $p=0.21$; 2.28% per year for dabigatran 150 mg vs. 2.69% per year for warfarin; HR 0.85; 95% CI, 0.72 to 0.99; $p=0.04$).

Myocardial Infarction

The rates of MI were higher with both dabigatran doses as compared with warfarin (0.72% per year for dabigatran 110 mg vs. 0.53% per year for warfarin; HR 1.35; 95% CI, 0.98 to 1.87; $p=0.07$; 0.74% per year for dabigatran 150 mg vs. 0.53% per year for warfarin; HR 1.38; 95% CI, 1.00 to 1.91; $p=0.048$).

Hospitalization

Hospitalization rates were lower with dabigatran 110 mg, and there was no difference between the higher dose and warfarin (19.4% per year for dabigatran 110 mg vs. 20.8% per year for warfarin; HR 0.92; 95% CI, 0.87 to 0.97; $p=0.003$; 20.2% per year for dabigatran 150 mg vs. 20.8% per year for warfarin; HR 0.97; 95% CI, 0.92 to 1.03; $p=0.34$).

Adverse Events

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

Factor II Inhibitor + ASA Versus Warfarin

One good-quality RCT (PETRO) involving 502 patients evaluated different doses of the Factor II inhibitor dabigatran with and without concomitant ASA at different doses and compared with warfarin alone.¹³⁰

Thromboembolic Events

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

Major Bleeding

Major hemorrhages were limited to the group treated with 300 mg dabigatran twice daily + ASA (4 of 64), and the rate was statistically different compared with the group treated with dabigatran 300 mg twice daily without ASA (0 of 105; $p < 0.02$). There was a significant difference in major and clinically relevant bleeding episodes (11 of 64 vs. 6 of 105; $p=0.03$) and total bleeding episodes (25 of 64 versus 14 of 105; $p=0.0003$) between 300 mg dabigatran twice daily + ASA and 300 mg dabigatran twice daily without ASA. The frequency of bleeding in the group treated with 50 mg dabigatran twice daily was significantly lower than that in the warfarin group (7 of 107 vs. 12 of 70; $p=0.044$). When the doses of dabigatran were compared with each other, irrespective of ASA assignment, there were differences in total bleeding episodes in the 300 mg twice daily and 150 mg twice daily groups versus the 50 mg twice daily group (37 of 169 and 30 of 169 vs. 7 of 107; $p=0.0002$ and $p=0.01$, respectively). Total bleeding events were more frequent in the 300 mg (23%) and 150 mg (18%) dabigatran groups compared with the 50 mg groups (7%).

Myocardial infarction

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

Adverse Events

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

Xa Inhibitor Versus ASA

One good-quality RCT involving 5,599 patients compared the efficacy and safety of the direct Xa inhibitor apixaban with ASA in AF patients in whom warfarin therapy was unsuitable.¹²² This study demonstrated that apixaban reduced the risk of stroke or systemic embolism without significantly increasing the risk of major bleeding or intracranial hemorrhage.

Stroke or Systemic Embolism

Apixaban was superior to ASA in reducing the incidence of stroke and systemic embolism (1.6% per year vs. 3.7% per year; HR 0.45; 95% CI, 0.32 to 0.62; $p < 0.001$). Systemic embolism was more frequent in the ASA group (0.1% per year for apixaban vs. 0.4% per year for ASA; HR 0.157; 95% CI, 0.03 to 0.68; $p = 0.01$).

Ischemic Stroke

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

Hemorrhagic Stroke

Rates of hemorrhagic stroke did not differ between groups (0.2% per year for apixaban vs. 0.3% per year for ASA; HR 0.67; 95% CI, 0.24 to 1.88; $p = 0.45$).

Major Bleeding

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

Minor Bleeding

There were no significant differences in minor bleeding (6.3% per year for apixaban vs. 5.0% per year for ASA; HR 1.24; 95% CI, 1.00 to 1.53; $p = 0.05$).

Intracranial Bleeding

In both groups, 0.4 percent of patients per year developed intracranial bleeding (HR 0.85; 95% CI, 0.38 to 1.90, $p = 0.69$).

All-Cause Mortality

All-cause mortality did not differ between the groups (3.5% per year for apixaban vs. 4.4% per year for ASA; HR 0.79; 95% CI, 0.62 to 1.02; $p = 0.07$).

Death From Vascular Causes

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

Myocardial Infarction

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

Hospitalization

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

Adverse Events

No differences in liver function or other adverse events were seen between the groups.

Xa Inhibitor Versus Warfarin

Four studies compared different factor Xa inhibitors to warfarin. One good-quality RCT (ARISTOTLE) involving 18,201 patients compared apixaban to warfarin;¹²¹ one good-quality RCT involving 1,146 patients compared edoxaban to warfarin;¹²⁴ one good-quality RCT (ROCKET-AF) involving 14,264 patients compared rivaroxaban to warfarin;²⁷ and one good-quality RCT (AMADEUS) involving 4,576 patients compared idraparinux with warfarin.¹²⁹

Although each of these RCTs compared a novel Xa inhibitor with warfarin, they differed in significant ways, making a quantitative synthesis of the findings inappropriate. Specifically, the ROCKET-AF and ARISTOTLE studies were both Phase III trials of oral anticoagulants. The study by Wietz and colleagues,¹²⁴ however, was a Phase II trial. The corresponding Phase III study (ENGAGE-AF) will be completed in early 2013,¹⁵¹ and at that time a synthesis of its findings with the ROCKET-AF and ARISTOTLE studies would be appropriate. Finally, in the AMADEUS trial, treatment was given subcutaneously and once a week, having a very different pharmacokinetics and pharmacodynamics profile from the oral anticoagulants. We therefore do not combine the data from these four trials through meta-analysis, but instead describe their impact on the outcomes of interest qualitatively below.

Stroke or Systemic Embolism

Three studies explored the impact of Xa inhibitors versus warfarin on stroke or systemic embolism. In one study,¹²¹ apixaban was shown to be superior to warfarin in preventing stroke and systemic embolism (1.27% per year vs. 1.60% per year for apixaban and warfarin, respectively; HR 0.79; 95% CI, 0.66 to 0.95; $p=0.01$). Similarly, in a second study,²⁷ in the per-protocol population, rivaroxaban was shown to be non-inferior to warfarin in preventing stroke and systemic embolism (1.7% per year vs. 2.2% per year for rivaroxaban and warfarin, respectively; HR 0.79; 95% CI, 0.66 to 0.96; $p<0.001$ for non-inferiority; 1.7% per year vs. 2.2% per year for rivaroxaban and warfarin, respectively; HR 0.79; 95% CI, 0.65 to 0.95; $p=0.01$ for superiority). Among all randomized patients in the intention-to-treat analysis, primary events occurred in 2.1 percent per year in the rivaroxaban group and in 2.4 percent per year in the warfarin group (HR 0.88; 95% CI, 0.74 to 1.03; $p<0.001$ for non-inferiority; $p=0.12$ for superiority). Finally, in the third study,¹²⁹ idraparinux was non-inferior to warfarin in preventing stroke and systemic embolism (0.9% and 1.2% in the idraparinux and warfarin groups, respectively; HR 0.71; 95% CI, 0.39 to 1.30; $p=0.007$ for non-inferiority). Idraparinux was also non-inferior to warfarin in the per-protocol analysis (HR 0.74; 95% CI, 0.38 to 1.43; $p=0.018$ for non-inferiority).

Ischemic or Uncertain Stroke

One study¹²¹ reported rates of ischemic or uncertain stroke that were not different between apixaban and warfarin (0.97% per year for apixaban vs. 1.05% per year for warfarin; HR 0.92; 95% CI, 0.74 to 1.13; p=0.42).

Hemorrhagic Stroke

Two studies evaluated rates of hemorrhagic stroke.^{121,129} In one study,¹²¹ apixaban was associated with lower rates of hemorrhagic stroke (0.24% per year for apixaban vs. 0.47% per year for warfarin; HR 0.51; 95% CI, 0.35 to 0.75; p<0.001). In the other study,¹²⁹ hemorrhagic stroke occurred in 0.2 percent of patients in both the idraparinux and warfarin groups.

Any Stroke or TIA

In one study,¹²⁴ any stroke or TIA were observed in 0.4, 0.8, 0.4, 1.1, and 1.6 percent of patients in the edoxaban 30 mg qd, 30 mg bid, 60 mg qd, 60 mg bid, and warfarin treatment groups, respectively.

Systemic Embolism

Three studies specifically reported the impact of therapy on systematic embolism separated out from stroke. In one study,¹²¹ the rates of systemic embolism did not differ between groups (0.09% per year for apixaban vs. 0.10% per year for warfarin; HR 0.87; 95% CI, 0.44 to 1.75; p=0.70.) Similar findings were seen in two other studies. In one, systemic embolism was observed in 0.4, 0.4, 0, 0, and 0 percent of patients in the edoxaban 30 mg qd, 30 mg bid, 60 mg qd, 60 mg bid, and warfarin treatment groups, respectively,¹²⁴ and in the other, there was no difference between the groups (0% of patients in the idraparinux group vs. 0.1% in the warfarin group).¹²⁹

Major Bleeding

All four studies reported on the impact of Xa inhibitors versus warfarin on the outcome of major bleeding. In one study,¹²¹ apixaban was associated with lower rates of major bleeding when compared with warfarin (2.13% per year for apixaban vs. 3.09% per year for warfarin; HR 0.69; 95% CI, 0.60 to 0.80; p<0.001). In another study,²⁷ there was no difference in rates of any major bleeding between the two groups (3.6% per year for rivaroxaban vs. 3.4% per year and warfarin; HR 1.04; 95% CI, 0.90 to 1.20; p=0.58). Decreases in hemoglobin levels of 2 g/dL or more and transfusions were more common among patients in the rivaroxaban group, whereas fatal bleeding and bleeding at critical anatomical sites were less frequent. Conversely, in a third study,¹²⁴ major bleeding events were observed in 0, 2.0, 0.4, 3.3, and 0.4 percent of patients in the edoxaban 30 mg qd, 30 mg bid, 60 mg qd, 60 mg bid, and warfarin treatment groups, respectively. Compared with warfarin, the incidence of major bleeding was significantly higher with edoxaban doses of 30 mg bid or 60 mg bid. With the 30 mg or 60 mg qd edoxaban regimens, the incidence of major bleeding was similar to that in patients randomized to warfarin. Finally, in the fourth study¹²⁹ rates of major bleeding were significantly higher in the idraparinux group when compared with warfarin (3.9% vs. 1.4%). Fatal bleeding was also more frequent with idraparinux (0.7% vs. <0.1%). Major bleeding other than intracranial hemorrhage occurred in 2.8 percent of patient-years in the idraparinux group and in 0.9 percent patient-years in the warfarin group. A post hoc analysis showed that patients receiving combination antithrombotic

therapy had a 2.5 fold increase risk of major bleeding events compared with those receiving anticoagulation therapy only.¹⁵²

All-Cause Mortality

Three of the studies reported on all-cause mortality. In one,¹²¹ apixaban was associated with lower rates of death from any cause (3.52% per year for apixaban vs. 3.94% per year for warfarin; HR 0.89; 95% CI, 0.80 to 0.998; p=0.047). In the other two studies, evaluating rivaroxaban and idraparinix, mortality rates were similar. Specifically, in one study,²⁷ the rates of death from any cause were similar between groups (1.9% per year for rivaroxaban vs. 2.2% per year for warfarin; HR 0.85; 95% CI, 0.70 to 1.02; p=0.07). In the intention-to-treat analysis, deaths occurred in 4.5 percent and 4.9 percent per year in the rivaroxaban and warfarin groups, respectively (HR 0.92; 95% CI, 0.82 to 1.03; p=0.15). In the third study,¹²⁹ there was no difference in mortality between treatment groups (3.2% per year in the idraparinix group vs. 2.9% per year in the warfarin group; p=0.49).

Death From Cardiovascular Causes

Two studies assessed death from cardiovascular causes.^{121,124} Both showed similar rates of cardiovascular deaths in treatment arms (1.80% per year for apixaban vs. 2.02% per year for warfarin; HR 0.89; 95% CI, 0.76 to 1.04¹²¹; and death from cardiovascular causes occurring in 0.9, 1.6, 0, 0, and 0.8 percent of patients in the edoxaban 30 mg qd, 30 mg bid, 60 mg qd, 60 mg bid, and warfarin treatment groups, respectively¹²⁴).

Myocardial Infarction

All four studies reported on the rates of MI across the therapies. There were no significant differences across treatment groups in any of the four studies. Specifically, in one study,¹²¹ the rates of MI were lower in the apixaban group, but this difference was not statistically significant (0.53% per year for apixaban vs. 0.61% per year for warfarin; HR 0.88; 95% CI, 0.66 to 1.17; p=0.37). In the second study,¹²⁴ MI occurred in 0.9, 0.4, 0.9, 0, and 0 percent of patients in the edoxaban 30 mg qd, 30 mg bid, 60 mg qd, 60 mg bid, and warfarin treatment groups, respectively. In the third study,²⁷ rates of MI were similar between groups (0.9% and 1.1% per year for rivaroxaban and warfarin, respectively; HR 0.81; 95% CI, 0.63 to 1.06; p=0.12). And similarly, in the fourth study,¹²⁹ the rates of MI were similar between groups (0.8% for idraparinix vs. 0.6% for warfarin).

Intracranial Bleeding

Three studies assessed intracranial bleeding. In two, the use of apixaban and rivaroxaban lowered such bleeding (apixaban: HR 0.42; 95% CI, 0.30 to 0.58; p<0.001;¹²¹ rivaroxaban: HR 0.67; 95% CI, 0.47 to 0.93; p=0.02²⁷). In the third study,¹²⁹ rates of intracranial bleeding were higher with idraparinix than with warfarin (1.1% vs. 0.4%; HR 2.58; 95% CI, 1.18 to 5.64; p=0.014).

Hospitalization

One study¹²⁴ assessed hospitalization rates and found these to be similar between treatment arms: 0.9, 0.8, 3.0, 0, and 0.4 percent of patients in the edoxaban 30 mg qd, 30 mg bid, 60 mg qd, 60 mg bid, and warfarin treatment groups, respectively.

Adverse Events

Only the studies evaluating apixaban and edoxaban specifically looked at adverse events.^{121,124} In one,¹²¹ adverse events occurred in almost equal proportions of patients in the apixaban group and in the warfarin group (81.5% and 83.1%, respectively). The rates of abnormalities on liver function testing and liver-related serious adverse events were also similar in the two groups. In the other study,¹²⁴ there were 11.1, 13.5, 11.5, 22.2, and 18.4 percent drug-related treatment-emergent adverse events in the edoxaban 30 mg qd, 30 mg bid, 60 mg qd, 60 mg bid, and warfarin treatment groups, respectively. Of these, the percentage of subjects with serious treatment-emergent adverse events was similar in the edoxaban (5.9%) and warfarin (4.4%) treatment groups. There were no differences in the incidence of abnormal hepatic function tests across treatment groups.

Percutaneous Left Atrial Appendage (LAA) Closure Versus Warfarin

One good-quality RCT (PROTECT AF) involving 707 patients compared the safety and efficacy of percutaneous left atrial appendage (LAA) closure to warfarin in patients with nonvalvular AF.¹²⁵

Composite of Stroke, Cardiovascular Death, and Systemic Embolism

The primary endpoint in the trial was a composite endpoint of stroke, cardiovascular death, and systemic embolism. This composite outcome was lower in the LAA group (3 per 100 patient-years vs. 4.9 per 100 patient-years; rate ratio 0.62; 95% CI, 0.35 to 1.25), which reached the non-inferiority criteria. At 2 years, the cumulative event rate for the LAA group was 5.9 percent compared with 8.3 percent for the warfarin group. The efficacy results were consistent across all subgroups apart from sex (the HR was lower in men than for women; $p=0.03$).

Ischemic Stroke

After the periprocedural timeframe, 9 patients in the LAA group (1.3 events per 100 patient-years) and 6 patients in the warfarin group had ischemic stroke (1.6 events per 100 patient-years).

All Strokes

The rate of all strokes was lower in the LAA group, although the difference did not reach statistical significance (RR 0.71; 95% CI, 0.35 to 1.64).

All-Cause Mortality

The cumulative mortality rates were similar between the groups in the first year (3% in the LAA group and 3.1% in the warfarin group) and lower in the LAA group at 2 years (9.1% vs. 5.9%; RR 0.62; 95% CI, 0.34 to 1.24).

Major Bleeding

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

Adverse Events

The primary composite endpoint for safety consisted of excessive bleeding or procedure-related complications. This outcome was more frequent in the LAA group (RR 1.69; 95% CI,

1.01 to 3.19). At 2 years the cumulative primary safety rate was 10.2 percent and 6.8 percent for the LAA and warfarin groups, respectively. This was driven by two procedure-related complications: pericardial effusion (4.8% in the LAA group and none in the warfarin group) and device embolization (0.6% in the LAA group and none in the warfarin group).

Results in Specific Subgroups of Interest

Thirty-three of our included studies focused on the comparative safety and effectiveness of specific anticoagulation therapies, antiplatelet therapies, and procedural interventions for preventing thromboembolic events in specific subgroups of interest within patients with nonvalvular AF. Below we describe these studies and the qualitative synthesis of their findings.

Patients not Eligible for Warfarin Use

Only two studies have specifically looked at effectiveness of therapy in patients who were considered unsuitable for warfarin therapy.^{122,126} The ACTIVE-A trial¹²⁶ was designed to determine whether the combination of clopidogrel (75 mg daily) plus aspirin (75 to 100 mg daily) was better than aspirin alone for prevention of stroke and cardiovascular events (non-central nervous system embolism, MI, or vascular death) in patients with AF and at least one additional risk factor for vascular events who were considered unsuitable for warfarin therapy. A total of 7,554 patients were enrolled in a double-blind fashion from 580 centers in 33 countries, and the median followup was 3.6 years. The combination of clopidogrel plus aspirin compared with aspirin alone significantly reduced the primary outcome by 11 percent, primarily due to a 28 percent reduction in stroke (ischemic or unknown origin) (RR 0.72; 95% CI, 0.62 to 0.83, $p < 0.001$). MI occurred in 90 patients in the clopidogrel group (0.7% per year) and in 115 in the placebo group (0.9% per year; RR 0.78; 95% CI, 0.59 to 1.03, $p = 0.08$). Importantly, clopidogrel plus aspirin compared with aspirin alone significantly increased the rate of major bleeding, including intracranial and extracranial bleeding, from 1.3 percent to 2.0 percent per year (RR 1.57; 95% CI, 1.29 to 1.92, $p < 0.001$). The rates of bleeding in the clopidogrel plus aspirin group were very similar to those observed in the warfarin arm from the ACTIVE-W study. One should also keep in mind that among the reasons for enrolling in this trial, 50 percent of the time this was due to physician assessment that the patient was inappropriate for warfarin and therefore could be in the study, which is a subjective decision. On the other hand, it is known that this subjective decision from physicians is common in clinical practice, and the results of this trial might be applicable to daily practice. In summary, if we treat 1,000 AF patients that “cannot be put on warfarin” during 3 years, clopidogrel plus aspirin would prevent 28 strokes and 6 MIs, but it would cause 20 major bleeding events, 3 of them fatal. Thus, caution is warranted when considering clopidogrel plus aspirin for patients with AF for stroke prevention.

In the light of the ACTIVE-A results, another recent study deserves special attention. In patients with AF who failed, or were unsuitable for VKA treatment, apixaban (5 mg orally twice daily) was compared with aspirin (81–324 mg daily) in the AVERROES trial, a randomized, double-blind, and multicenter study.¹²² This trial enrolled about 5,600 patients. The primary efficacy outcome was the composite of stroke or systemic embolism, and secondary outcomes include the composite of: stroke, systemic embolism, MI, or vascular death (major vascular events). The study was terminated early by the data safety and monitoring board (DSMB) due to the superiority of apixaban over aspirin. This finding was more or less expected, since an oral anticoagulant was compared with aspirin, which is known to be less effective than VKAs for the prevention of stroke in patients with AF. However, the most impressive results were the similar

rates of bleeding between aspirin and apixaban, which illustrates that often times the risk of bleeding associated with aspirin is underestimated. Finally, apixaban was better tolerated than aspirin, leading to a lower rate of drug discontinuation than aspirin during the course of the trial. This finding also highlights that aspirin has side effects which are sometimes underappreciated in clinical practice.

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

Patients With AF and Renal Impairment

One substudy¹⁵³ of the ROCKET-AF RCT²⁷ analyzed the results of the 2,950 patients (20.7%) with renal impairment (creatinine clearance 30–49 mL/min) using rivaroxaban 15 mg/d (n=1,434) or warfarin (n=1,462). Among those patients, the primary endpoint of stroke or systemic embolism occurred in 2.32 per 100 patient-years using rivaroxaban versus 2.77 per 100 patient-years with warfarin (HR 0.84; 95% CI, 0.57 to 1.23) in the per-protocol population. Intention-to-treat analysis yielded similar results (HR 0.86; 95% CI, 0.63 to 1.17). Rates of the principal safety endpoint (major and clinically relevant non-major bleeding: 17.82 vs. 18.28 per 100 patient-years; p=0.76) and intracranial bleeding (0.71 vs. 0.88 per 100 patient-years; p=0.54) were similar with rivaroxaban or warfarin. Fatal bleeding (0.28 vs. 0.74% per 100 patient-years; p=0.047) occurred less often with rivaroxaban. This study suggested that patients with AF and moderate renal insufficiency have higher rates of stroke and bleeding than those with normal renal function. Rivaroxaban preserved the benefit of warfarin in preventing stroke and systemic embolus and produced lower rates while on treatment. Bleeding rates with the reduced dose of rivaroxaban were similar to those on warfarin therapy, and there were fewer fatal bleeds with rivaroxaban.

Patients With Paroxysmal Versus Sustained AF

One substudy¹⁵⁴ of the ACTIVE W RCT¹³³ analyzed the results in patients with paroxysmal AF (n=1,202) as compared with those who had sustained (persistent or permanent) AF (n=5,495). Patients with paroxysmal AF were younger, had a shorter AF history, more hypertension, and less valvular disease, heart failure, and diabetes mellitus than patients with sustained AF. The incidence of stroke and non-CNS embolism was lower for patients treated with oral anticoagulation irrespective of type of AF. There were more bleedings of any type in patients receiving clopidogrel plus aspirin, irrespective of the type of AF, but major bleedings events were similar in all groups (paroxysmal vs. sustained, and oral anticoagulants vs. ASA + clopidogrel).

Patients With AF Undergoing Cardioversion

Four studies explored stroke prevention in AF patients undergoing cardioversion.^{136,147,148,155} One very small study¹⁴⁷ compared aspirin-plus-clopidogrel versus warfarin in the prevention of thromboembolic events in a group of patients with non-high-risk AF. Thirty patients (11 women, 45 to 75 years of age) with non-high-risk permanent (n=12) or persistent AF awaiting

cardioversion (n=18) underwent transesophageal echocardiography to exclude left heart thrombi and were then randomly assigned to receive warfarin (INR 2–3 for 3 weeks) or aspirin (100 mg/d alone for 1 week) plus clopidogrel (75 mg/d added to aspirin for 3 weeks). Seven of nine patients receiving warfarin and seven of nine patients receiving aspirin + clopidogrel, undergoing electrical cardioversion achieved sinus rhythm. No thromboembolic or hemorrhagic events occurred in either arm throughout the 3-week treatment and a further 3-month followup.

A second study¹³⁶ was an RCT comparing the safety and efficacy of enoxaparin administered subcutaneously with intravenous unfractionated heparin (UFH) followed by the oral anticoagulant phenprocoumon in 496 patients scheduled for cardioversion of AF of >48 hours and ≤1 year's duration. Patients were stratified to cardioversion with (n=431) and without (n=65) guidance by transesophageal echocardiogram (TEE). The study aimed to demonstrate noninferiority of enoxaparin compared with UFH + phenprocoumon with regard to the incidence of embolic events, all-cause death, and major bleeding complications. Of 496 randomized patients, 428 were analyzed per protocol. Enoxaparin was non-inferior to UFH + phenprocoumon with regard to the incidence of the composite primary outcome in a per-protocol analysis (7 of 216 patients vs. 12 of 212 patients, respectively; p=0.016) and in an intention-to-treat analysis (7 of 248 patients vs. 12 of 248 patients, respectively; p=0.013). Analyzing the events separately, none of them (cerebral embolic infarct, minor and major hemorrhagic events, and death) were statistically different between the groups. There was also no significant difference between the two groups in the number of patients reverted to sinus rhythm.

A third study¹⁴⁸ was an RCT comparing the difference in the rate of thromboembolic events of TEE-guided early cardioversion with short-term low molecular weight heparin (LMWH) use in patients with nonvalvular persistent AF. The study group consisted of 172 consecutive patients with nonvalvular AF. Before TEE, 90 patients received LMWH (dalteparin 2 × 5,000 U) and 82 patients received standard heparin (UFH; 5,000 U bolus followed by infusion to raise APTT to 1.5 times control). TEE was performed, and the left atrium and LAA were examined thoroughly for the presence of thrombus. One patient from each group was excluded due to detection of a left atrial thrombus by TEE. Immediately after TEE, cardioversion was attempted and warfarin was initiated. All patients received warfarin for one month after cardioversion. In the LMWH group, 89 of 90 patients (98.9%) were successfully cardioverted. Cardioversion was successful in 97.5 percent of the patients in the UFH group. None of the patients experienced thromboembolic events during the 4 weeks after cardioversion.

The fourth study¹⁵⁵ was a subgroup analysis of the RE-LY trial²⁶ evaluating patients that were submitted to cardioversion therapy during the trial. Data from before, during, and 30 days after cardioversion were analyzed. A total of 1,983 cardioversions were performed in 1,270 patients: 647, 672, and 664 in the dabigatran 110 mg, dabigatran 150 mg, and warfarin groups, respectively. For dabigatran 110 mg, dabigatran 150 mg, and warfarin, TEE was performed before 25.5, 24.1, and 13.3 percent of cardioversions, respectively, of which 1.8, 1.2, and 1.1 percent, respectively, were positive for left atrial thrombi. Continuous treatment with study drug for ≥3 weeks before cardioversion was lower in dabigatran 110 mg (76.4%) and dabigatran 150 mg (79.2%) compared with warfarin (85.5%; p<0.01 for both). Stroke and systemic embolism rates at 30 days were 0.77, 0.3, and 0.6 percent in dabigatran 110 mg, dabigatran 150 mg, and warfarin, respectively (dabigatran 110 mg vs. warfarin, p =0.71; dabigatran 150 mg vs., p=0.40) and similar in patients with and without TEE. Major bleeding rates were 1.7, 0.6, and 0.6 percent, respectively (dabigatran 110 mg vs. warfarin, p=0.06; dabigatran 150 mg vs. warfarin, p=0.99).

Patients With AF After Stroke

Seven studies explored stroke prevention treatment in patients with AF who had previously suffered a stroke^{134,138,139,145,156-158}

The Heparin in Acute Embolic Stroke Trial (HAEST)¹³⁸ was a multicenter, RCT on the effect of LMWH (dalteparin 100 IU/kg subcutaneously twice a day) or aspirin (160 mg every day) for the treatment of 449 patients with acute ischemic stroke and AF. The primary aim was to test whether treatment with LMWH, started within 30 hours of stroke onset, is superior to aspirin for the prevention of recurrent stroke during the first 14 days. The frequency of recurrent ischemic stroke during the first 14 days was 19/244 (8.5%) in dalteparin-allocated patients versus 17/225 (7.5%) in aspirin-allocated patients (OR 1.13; 95% CI, 0.57 to 2.24). The OR remained unchanged after adjusting for sex in logistic-regression analysis (1.19 [0.60 to 2.36]). The secondary events during the first 14 days also revealed no benefit of dalteparin compared with aspirin. There were no significant differences in functional outcome or death at 14 days or 3 months.

A recent ROCKET AF RCT substudy¹³⁹ of 14,264 patients from 1,178 centers in 45 countries, investigated whether the efficacy and safety of rivaroxaban compared with warfarin was consistent among patients with and without previous stroke or TIA. Patients with AF who were at increased risk of stroke (CHADS₂ score >2) were randomly assigned (1:1) in a double-blind manner to rivaroxaban 20 mg daily or adjusted dose warfarin (to maintain INR 2.0–3.0). Patients and investigators were masked to treatment allocation. The primary endpoint was the composite of stroke or non-CNS systemic embolism as a safety endpoint. The treatment effects of rivaroxaban and warfarin were compared among patients with and without previous stroke or TIA. The safety analyses were done in the on-treatment population. Efficacy analyses were analyzed by intention to treat, and 7,468 (52%) patients had a previous stroke (n=4,907) or TIA (n=2,561). The number of events per 100 person-years for the primary endpoint in patients treated with rivaroxaban compared with warfarin was consistent among patients with previous stroke or TIA (2.79% rivaroxaban vs. 2.96% warfarin; HR 0.94; 95% CI, 0.77 to 1.16) and those without (1.44% vs. 1.88%; HR 0.77; 95% CI, 0.58 to 1.01; comparison interaction p=0.23). Similarly, the number of major and non-major clinically relevant bleeding events per 100 person-years in patients treated with rivaroxaban compared with warfarin was consistent among patients with previous stroke or TIA (13.31% rivaroxaban vs. 13.87% warfarin; HR 0.96; 95% CI, 0.87 to 1.07) and those without (16.69% vs. 15.19%; HR 1.10; 95% CI, 0.99 to 1.21; comparison interaction p=0.08).

One observational study¹⁴⁵ followed a consecutive series of AF patients with first-ever ischemic stroke, and evaluated prospectively those with moderate to severe disability (grade 4–5 on the modified Rankin Scale) who were treated during a 5-year followup period with either warfarin or aspirin. Death and recurrent vascular events were documented. Out of a pool of 438 AF patients, 191 were prospectively assessed. During a mean followup of 50.4 months, the cumulative 5-year mortality was 76.7% (95% CI, 69.0 to 84.3), and the 5-year recurrence rate was 33.7% (95% CI, 23.3 to 44.1). Additionally, two non-cerebral major bleeding events requiring hospital admission and blood transfusion were recorded in the warfarin group. Only one non-cerebral bleeding event was documented in the aspirin group. The annual event rates for all major bleeding complications in aspirin and warfarin groups were 0.7 and 3.3 percent, respectively. Aspirin versus warfarin was an independent predictor of mortality. Prior TIA and aspirin versus warfarin were predictors of vascular recurrence. Anticoagulation was associated with a decreased risk of death (HR 0.44; 95% CI, 0.27 to 0.70; p<0.001) and recurrent

thromboembolism (HR 0.36; 95% CI, 0.17 to 0.77; $p < 0.01$). The results of this observational study suggest that chronic anticoagulation therapy may be effective in lengthening survival and preventing recurrent thromboembolism in AF patients who have suffered a severely disabling ischemic stroke.

An observational study¹³⁴ analyzed recurrent cerebral and non-cerebral ischemic vascular events, major intracerebral and extracerebral bleeding, and vascular death in 401 consecutive patients with ischemic stroke or TIA and AF who were discharged with oral anticoagulation (OAC), antiplatelet agents (AA), or heparin only in a clinical routine setting. Patients on OAC at time of discharge were significantly younger and had suffered a major stroke less often than patients who received AA or heparin at discharge. One year after discharge, adherence to therapy was higher in patients discharged on OAC (72%) than in those on AA (46%; $p < 0.001$). The majority of patients discharged on heparin were subsequently treated with OAC. During a median followup of 25 months (IQR, 15–38), 103 (26%) patients experienced a complication: 91 (88%) patients an ischemic complication and 12 (12%) a bleeding complication. The rate of ischemic complications and the overall rate of complications were lowest in patients discharged on OAC. Patients on AA at discharge suffered from ischemic complications significantly more often during the follow-up period than patients on OAC or heparin at discharge (30% vs. 16% vs. 23%, $p = 0.031$). Patients on AA suffered their first vascular complication significantly sooner after discharge than patients on OAC. Safety endpoints showed that three percent of the patients on AA and four percent of those on OAC suffered from major bleeding complications during follow-up ($p = 0.028$). The rate of intracranial bleeding was higher in patients on OAC (3% vs. 1%), but the total numbers were too small to allow a valid statistical comparison. Total mortality was lowest in patients discharged on OAC, and vascular mortality also seemed somewhat lower in this group but the difference was not significant.

A predefined analysis¹⁵⁶ was conducted of the outcomes of the RE-LY trial²⁶ in subgroups of patients with or without previous stroke or transient ischemic attack. The primary efficacy outcome was stroke or systemic embolism, and the primary safety outcome was major hemorrhage. Within the subgroup of patients with previous stroke or TIA, 1,195 patients were from the 110 mg dabigatran group, 1,233 from the 150 mg dabigatran group, and 1,195 from the warfarin group. Stroke or systemic embolism occurred in 65 patients (2.78% per year) on warfarin compared with 55 (2.32% per year) on 110 mg dabigatran (relative risk [RR] 0.84; 95% CI, 0.58 to 1.20) and 51 (2.07% per year) on 150 mg dabigatran (RR 0.75, 95% CI, 0.52 to 1.08). The rate of major bleeding was significantly lower in patients on 110 mg dabigatran (RR 0.66; 95% CI, 0.48 to 0.90) and similar in those on 150 mg dabigatran (RR 1.01; 95% CI, 0.77 to 1.34) compared with those on warfarin. The effects of both doses of dabigatran compared with warfarin were not significantly different between patients with previous stroke or TIA and those without for any of the outcomes from RE-LY apart from vascular death (110 mg group compared with warfarin group, interaction $p = 0.038$). By these results, the effects of 110 mg dabigatran and 150 mg dabigatran twice daily in patients with previous stroke or TIA are consistent with those of other patients in RE-LY, for whom, compared with warfarin, 150 mg dabigatran reduced stroke or systemic embolism and 110 mg dabigatran was non-inferior.

A prespecified subgroup analysis¹⁵⁷ of AVERROES¹⁵⁹ included 5,599 patients (mean age 70 years) with AF who were at increased risk of stroke and unsuitable for warfarin therapy. These patients were randomly assigned to receive apixaban 5 mg twice daily ($n = 2,808$) or aspirin 81–324 mg per day ($n = 2,791$). The primary efficacy outcome was stroke or systemic embolism; the primary safety outcome was major bleeding. In this subanalysis of patients with previous stroke

or TIA, the effects of apixaban in patients with and without previous stroke or TIA were compared. The cumulative HR for stroke or systemic embolism at 1 year was 5.73% (95% CI, 4.10 to 8.02) in patients with previous stroke or TIA and 2.36% (1.93 to 2.89) in those without. In patients with previous stroke or TIA treated with apixaban, the rates of stroke or systemic embolism, ischemic stroke, and disabling or fatal stroke were consistently lower than those in patients treated with aspirin. In patients with previous stroke or TIA, 10 events of stroke or systemic embolism occurred in the apixaban group (n=390, cumulative hazard 2.39% per year) compared with 33 in the aspirin group (n=374, 9.16% per year; HR 0.29; 95% CI, 0.15 to 0.60). In those without previous stroke or TIA, 41 events occurred in the apixaban group (n=2,417, 1.68% per year) compared with 80 in the aspirin group (n=2,415, 3.06% per year; HR 0.51; 95% CI, 0.35 to 0.74). Compared with those treated with aspirin, the 1-year risk of stroke or systemic embolism decreased by 73 percent in patients treated with apixaban and with previous stroke or TIA (1-year absolute risk reduction of 6.4%; 95% CI, 2.8 to 10.0) and by 45 percent in patients treated with apixaban and without previous stroke or TIA (1-year absolute risk reduction of 1.4%, 95% CI, 0.4 to 2.3). The p values for interaction between history of previous stroke or TIA and treatment were not significant, indicating that the results in the subgroups were consistent with the overall result of the study. Major bleeding, the primary safety outcome, was more frequent in patients with history of previous stroke or TIA than in patients without this history (HR 2.88; 95% CI, 1.77 to 4.55) but risk of this event did not differ between treatment groups. The effect of apixaban versus aspirin for bleeding complications was consistent in the two subgroups, with non-significant interaction p values.

A prespecified subgroup analysis¹⁵⁸ from the ARISTOTLE trial¹²¹ evaluated the efficacy and safety of apixaban compared with warfarin in subgroups of patients with and without previous stroke or TIA. The primary efficacy outcome was stroke or systemic embolism, analyzed by intention to treat. The primary safety outcome was major bleeding in the on-treatment population. Outcomes in patients with and without previous stroke or TIA were compared. Of the trial population, 3,436 (19%) had a previous stroke or TIA. In the subgroup of patients with previous stroke or TIA, the rate of stroke or systemic embolism was 2.46 per 100 patient-years of followup in the apixaban group and 3.24 in the warfarin group (HR 0.76; 95% CI, 0.56 to 1.03); in the subgroup of patients without previous stroke or TIA, the rate of stroke or systemic embolism was 1.01 per 100 patient-years of followup with apixaban and 1.23 with warfarin (HR 0.82; 95% CI, 0.65 to 1.03). The relative risk reduction of stroke or systemic embolism with apixaban versus warfarin was similar among patients with and those without previous stroke or TIA (p for interaction=0.71). The reduction in rates of cardiovascular death, disabling or fatal stroke, and all-cause mortality with apixaban versus warfarin was similar in patients with and without previous stroke or TIA (p for interaction=0.53, 0.18, and 0.89, respectively). Compared with patients without previous stroke or TIA, patients with previous stroke or TIA were more likely to have major bleeding (HR 1.37; 95% CI, 1.17 to 1.62) and intracranial bleeding (2.15, 95% CI, 1.57 to 2.96). The relative risk reductions in major bleeding and total bleeding with apixaban versus warfarin were similar in both groups (p for interaction=0.69 and 0.0, respectively). Intracranial bleeding was reduced in the apixaban groups from 1.49 per 100 patient-years of followup on warfarin to 0.55 per 100 patient-years on apixaban in those with previous stroke or TIA (HR 0.37; 95% CI, 0.21 to 0.67) and from 0.65 per 100 patient-years of followup on warfarin to 0.29 per 100 patient-years on apixaban in those without previous stroke or TIA (0.44, 95% CI, 0.30 to 0.66). Based on these results, the effects of apixaban versus warfarin were consistent in patients with AF with and without previous stroke or TIA.

Patients With AF and Different Thromboembolic Risks

Six studies explored the comparative safety and effectiveness of stroke prevention therapy in patients at different thromboembolic risks.^{14,99,110,141,160,161}

An observational study¹¹⁰ sought to determine the efficacy and safety of warfarin and aspirin in patients with nonvalvular AF, with separate analyses according to predicted thromboembolic and bleeding risk. Nationwide registries allowed the identification of all patients discharged with nonvalvular AF in Denmark (n=132,372). For every patient, the risk of stroke and bleeding was calculated by CHADS₂, CHA₂DS₂-VASc, and HAS-BLED. In different groups according to thromboembolic risks, warfarin consistently lowered the risk of thromboembolism compared with aspirin; the combination of warfarin + ASA did not yield any additional benefit. In patients at high thromboembolic risk, HRs (95% CIs) for thromboembolism were (adjusted for all baseline characteristics): CHA₂DS₂-VASc ≥2: HR 1.81 (1.73 to 1.90), 1.14 (1.06 to 1.23) for ASA and warfarin + ASA, respectively, compared with warfarin; CHADS₂ ≥2: HR 1.73 (1.64 to 1.83), 1.05 (0.96 to 1.15), for ASA and warfarin + ASA, respectively, compared with warfarin. The risk of bleeding was increased with warfarin, ASA, and warfarin + ASA compared with no treatment; the HRs were 1.0 (warfarin; reference), 0.93 (ASA; 0.89–0.97), 1.64 (warfarin + ASA; 1.55–1.74), and 0.84 (no treatment; 0.81–0.88), respectively. This large cohort study corroborates the effectiveness of warfarin and no effect of ASA treatment on the risk of stroke/thromboembolism. Also, the risk of bleeding was increased with both warfarin and ASA treatment, but the net clinical benefit was clearly positive, in favor of warfarin in patients with increased risk of stroke/thromboembolism.

A post hoc analysis¹⁴ was performed to determine the relationship of risk levels (quantified using the CHADS₂) and thromboembolic events in patients with nonvalvular AF. A total of 509 patients with nonvalvular AF were analyzed, and the CHADS₂ score of 0 was classified as low risk, 1–2 a moderate risk, and ≥3 high risk. Warfarin was given to 263 patients (mean INR at enrollment, 1.86), antiplatelets (aspirin or ticlopidine) to 163 patients, and no antithrombotic therapy to 83. The event rate increased as the risk level estimated with CHADS₂ score increased in patients in the non-warfarin group, although the difference did not reach the significance level (p=0.11). In contrast, the event rate differed significantly between the three different risk level groups of patients receiving warfarin (p=0.015), but paradoxically the event rate of the low-risk group was higher than that of the moderate-risk group (3.9% vs. 1.9%). Surprisingly, the event rate was 7.7 percent per year for high-risk patients receiving warfarin. INR levels at the time of enrollment did not differ among the three groups of warfarin-treated patients (low risk, 1.82 ± 0.81; moderate risk, 1.92 ± 0.87; high risk, 1.78 ± 0.70). The unpredictable results shown above could be attributed to the fact that patients with hypertrophic cardiomyopathy but without any clinical risk factors for thromboembolism were defined as low risk, but they actually experienced thromboembolic events frequently. When patients with hypertrophic cardiomyopathy were excluded from the analyses, the event rates increased in patients receiving warfarin as the risk level increased (p=0.033).

A prospective cohort study⁹⁹ analyzed the effectiveness and safety of oral anticoagulants in 796 outpatients with nonvalvular AF in daily clinical practice, according to embolic risk evaluated by means of CHADS₂ score. Oral anticoagulation was prescribed to 564 (71%) patients. After 2.4 ± 1.9 years of followup, the embolic event (TIA, ischemic stroke, peripheral embolism) rates (per 100 patient-years) for each stratum of the CHADS₂ score for patients with/without oral anticoagulants were: 1/4.1, p=0.23 (CHADS₂=0); 0.6/7.1, p=0.0018 (CHADS₂=1); 0.5/5.1, p=0.0014 (CHADS₂=2); 2.4/12.5, p=0.0017 (CHADS₂=3) and 2.9/20,

$p=0.013$ ($\text{CHADS}_2 \geq 4$). The severe bleeding rates for the same CHADS_2 score strata were 3/0.8, 0.8/0.7, 1.3/0.7, 0.4/0, and 2.9/5 in patients with/without oral anticoagulants (non-significant.). This study demonstrated that oral anticoagulants appeared safe and effective in patients with $\text{CHADS}_2 \geq 1$.

Another observational study¹⁴¹ compared warfarin versus aspirin therapy for the prevention of stroke in AF patients with CHADS_2 score =1. Among 1,502 patients (mean 62.4 ± 13.8 years old, male 65.4%) who were treated for nonvalvular AF without previous stroke, the number of patients with CHADS_2 score =1 was 422 (62.9 ± 10.7 years old, male 290 [68.7%]) and their antithrombotic therapies were as follows: warfarin ($n=143$), aspirin ($n=124$), other antiplatelet ($n=45$), and no antithrombotic therapy (none: $n=110$). During 22.3 ± 17.8 months of followup, the incidence of ischemic stroke was significantly lower in warfarin (6 patients, 4.2%, mean INR 2.0 ± 0.5 IU) than in aspirin (16 patients, 12.9%, $p=0.008$) than none (23 patients, 20.9%, $p < 0.001$) without differences in all-cause mortality. The incidence of major bleeding (decrease in hemoglobin ≥ 2 g/dL, requiring hospitalization or red blood cell transfusion ≥ 2 pints) was not different between warfarin (2.1%) and aspirin (0.8%, $p=\text{NS}$), but minor bleeding was more common in warfarin (10.5%) than in aspirin (2.4%, $p=0.007$).

In ACTIVE W,¹³³ oral anticoagulation was more efficacious than combined clopidogrel plus aspirin in preventing vascular events in patients with AF. A subanalysis of ACTIVE W¹⁶¹ evaluated the findings according to risk stratification using the CHADS_2 score. Treatment-specific rates of stroke and major bleeding were calculated for patients with a $\text{CHADS}_2=1$ and compared with those with a $\text{CHADS}_2 >1$. The ACTIVE W primary outcome (stroke, noncentral nervous system systemic embolism, all-cause mortality, and MI) occurred more frequently in patients on clopidogrel + aspirin, both with $\text{CHADS}_2=1$ (3.28% per year versus 1.92% per year, $\text{RR}=1.72$, $p=0.01$) and with $\text{CHADS}_2 >1$ (7.14% per year versus 5.18% per year, $\text{RR} 1.40$, $p=0.0035$). CHADS_2 status did not significantly affect the relative benefit of oral anticoagulants for this outcome (P for interaction=0.41). Observed stroke rates for those with a $\text{CHADS}_2=1$ were 1.25 percent per year on clopidogrel + aspirin and 0.43 percent per year on oral anticoagulants ($\text{RR} 2.96$; 95% CI, 1.26 to 6.98, $p=0.01$). Among patients with a $\text{CHADS}_2 >1$, the stroke rates were 3.15 percent per year on clopidogrel + aspirin and 2.01 percent per year on oral anticoagulants ($\text{RR} 1.58$; 95% CI, 1.11 to 2.24; $p=0.01$; p for interaction between stroke risk category and efficacy of oral anticoagulants =0.19). The risk of major bleeding during oral anticoagulants was significantly lower among patients with $\text{CHADS}_2=1$ (1.36% per year) compared with $\text{CHADS}_2 >1$ (2.75% per year) ($\text{RR} 0.49$; 95% CI, 0.30 to 0.79, $p=0.003$). For patients with $\text{CHADS}_2=1$, the rate of major bleeding was 2.09 percent per year on clopidogrel + aspirin, which was higher than the rate of 1.36 percent per year on oral anticoagulants ($\text{RR} 1.55$; 95% CI, 0.91 to 2.64, $p=0.11$). For patients with $\text{CHADS}_2 >1$, major bleeding occurred at a rate of 2.63 percent per year on clopidogrel + aspirin and 2.75 percent per year on oral anticoagulants ($\text{RR} 0.97$; 95% CI, 0.69 to 1.35; $p=0.84$). The relative risk of major bleeding with clopidogrel + aspirin, compared with oral anticoagulants was not significantly different between patients with high and low CHADS_2 scores (p for interaction=0.15); however, the absolute risk of major bleeding on oral anticoagulants was significantly lower among patients with $\text{CHADS}_2=1$ compared with $\text{CHADS}_2 >1$ ($\text{RR}=0.49$; 95% CI, 0.30 to 0.79; $p=0.0003$). Based on these results, patients with a $\text{CHADS}_2=1$ had a low risk of stroke, yet still derived a modest (<1% per year) but statistically significant absolute reduction in stroke with oral anticoagulants compared with clopidogrel + aspirin and had low rates of major hemorrhage on oral anticoagulants.

Finally, a subgroup analysis¹⁶⁰ of the RE-LY trial²⁶ evaluated the prognostic importance of CHADS₂ risk score in patients with AF receiving oral anticoagulants, including warfarin and the direct thrombin inhibitor dabigatran. Of the 18,112 patients, the distribution of CHADS₂ scores were as follows: 0–1, 5,775 patients; 2, 6,455 patients; and 3–6, 5,882 patients. Annual rates of the primary outcome of stroke or systemic embolism among all participants were 0.93 percent in patients with a CHADS₂ score of 0–1, 1.22 percent in those with a score of 2, and 2.24 percent in those with a score of 3–6. Annual rates of other outcomes among all participants with CHADS₂ scores of 0–1, 2, and 3–6, respectively, were the following: major bleeding, 2.26, 3.11, and 4.42 percent; intracranial bleeding, 0.31, 0.40, and 0.61 percent; and vascular mortality, 1.35, 2.39, and 3.68 percent ($p < 0.001$ for all comparisons). Rates of stroke or systemic embolism, major and intracranial bleeding, and vascular and total mortality each increased in the warfarin and dabigatran groups as CHADS₂ score increased. The reduction in stroke or systemic embolism with dabigatran 150 mg twice daily versus warfarin was consistent across the CHADS₂ risk groups. The rates of stroke or systemic embolism were similar with dabigatran, 110 mg twice daily and warfarin across CHADS₂ risk groups. The rates of intracranial bleeding with dabigatran 150 mg or 110 mg twice daily were lower than those with warfarin; there was no significant heterogeneity in subgroups defined by CHADS₂ scores.

Patients With AF According to INR Control

Two studies evaluated treatment safety and effectiveness according to patient INR control.^{91,137} In the first study,⁹¹ incident ischemic strokes were evaluated in a cohort of 13,559 patients with nonvalvular AF. Of 596 ischemic strokes, 32 percent occurred during warfarin therapy, 27 percent during aspirin therapy, and 42 percent during neither type of therapy. Among patients who were taking warfarin, an INR of < 2.0 at admission, as compared with an INR of ≥ 2.0 , independently increased the odds of a severe stroke in a proportional odds logistic-regression model (OR 1.9; 95% CI, 1.1 to 3.4) across three severity categories of stroke and the risk of death within 30 days (HR 3.4; 95% CI, 1.1 to 10.1). The proportion of patients who had a severe or fatal stroke did not differ significantly between those with an admission INR of 1.5–1.9 and those with an INR of < 1.5 . After adjustment for potential confounders in the proportional odds model, the medication group remained an independent risk factor for the severity of stroke when patients who had an INR ≥ 2.0 were compared with those who had an INR of < 2.0 or those who were taking neither aspirin nor warfarin. An INR of 1.5–1.9 at admission was associated with a mortality rate similar to that for an INR of < 1.5 (18% and 15%, respectively). The 30-day mortality rate among patients who were taking aspirin at the time of the stroke was similar to that among patients who were taking warfarin and who had an INR < 2.0 . The rate of ischemic stroke was highest at INR values < 2.0 , especially values < 1.5 . By contrast, there was no marked absolute increase in the rate of intracranial hemorrhage at INR values < 4.0 . Based on these results, anticoagulation that results in an INR ≥ 2.0 in patients with nonvalvular AF reduces not only the frequency of ischemic stroke but also its severity and the risk of death from stroke.

A second study¹³⁷ analyzed the efficacy and safety of conventional and low-intensity warfarin therapy in a prospective, randomized, multicenter trial. The study population consisted of patients with nonvalvular AF who had a stroke or TIA. The patients were randomly allocated into a conventional-intensity group (INR 2.2–3.5) and a low-intensity group (INR 1.5–2.1). A total of 115 patients were enrolled (mean age 66.7/66.5 years): Fifty-five and 60 patients were allocated into the conventional- and low-intensity groups, respectively. The trial was stopped when major hemorrhagic complications occurred in 6 patients of the conventional-intensity

group and the frequency (6.6% per year) was significantly higher than that in the low-intensity group (0% per year, $p=0.01$, Fisher's exact test). All of the 6 patients with major bleeding were elderly (mean age 74 years), and their mean INR before the major hemorrhage was 2.8. The annual rate of ischemic stroke was low in both groups (1.1% per year in the conventional-intensity group and 1.7% per year in the low-intensity groups) and did not differ significantly.

Elderly Patients With AF

Ten studies specifically explored the safety and effectiveness of stroke prevention therapies in the elderly.^{127,131,135,142-144,146,149,162,163}

A single-center, retrospective, observational study¹⁴² included data from patients aged ≥ 65 years with chronic nonvalvular AF treated at an urban academic geriatrics practice over a 1-year period. Eligible patients were receiving noninvasive management of AF with warfarin or ASA. A total of 112 patients (mean age, 82 years) were identified; 106 were included in this analysis (80 women, 26 men). Warfarin was prescribed in 85 percent (90 patients); ASA in 15 percent (16). The distributions of both the CHADS₂ and Outpatient Bleeding Risk Index scores were not significantly different between the warfarin and ASA groups. The proportions of patients treated with warfarin were not significantly different between the groups with a high risk for hemorrhage and the groups at lower risk. At 12 months in the 90 patients initially treated with warfarin, the rate of stroke was 2 percent (2 patients); major hemorrhage, 6 percent (5); and death, 20 percent (18). The number of patients who received ASA was too small to provide sufficient power to detect significant treatment differences.

A prospective clinical study¹²⁷ of four clinical services of geriatric medicine included 209 inpatients, (mean age 84.7 ± 7 years; women 60.8%) with chronic AF. The patients were distributed into two groups (anticoagulant or aspirin) according to medical decision. The evolution of the patients was recorded after 3 months. One hundred and two patients (48.8%) received anticoagulant and 107 patients received aspirin. Patients in the aspirin group were significantly older (86.5 ± 6.5 vs. 82.9 ± 7.1 years), with more frequent social isolation, higher systolic blood pressure, and had more important subjective bleeding risk and risk of falls. Patients in the anticoagulant group had significantly more valvulopathies (17.6% vs. 2.8%) and a more important subjective thromboembolic risk. Thrombophlebitis antecedents, dementia, denutrition, and walking alterations were only slightly more frequent in patients in the aspirin group. After 3 months, the two groups did not significantly differ for death, bleeding or ischemic events.

A prospective RCT¹³¹ included 973 patients aged 75 years or over (mean age 81.5 years, SD 4.2) with AF from primary care who were randomly assigned to warfarin (target INR 2–3) or aspirin (75 mg per day). The primary endpoint was fatal or disabling stroke (ischemic or hemorrhagic), intracranial hemorrhage, or clinically significant arterial embolism. Analysis was by intention to treat. There were 24 primary events (21 strokes, 2 other intracranial hemorrhages, and 1 systemic embolus) in people assigned to warfarin, and 48 primary events (44 strokes, 1 other intracranial hemorrhage, and 3 systemic emboli) in people assigned to aspirin (yearly risk 1.8% vs 3.8%, relative risk 0.48; 95% CI, 0.28 to 0.80; $p=0.003$). Yearly risk of extracranial hemorrhage was 1.4 percent (warfarin) versus 1.6 percent (aspirin) (relative risk 0.87, 95% CI, 0.43 to 1.73).

An RCT¹⁴³ of primary thromboprophylaxis for AF included patients aged >80 and <90 randomized to receive dose-adjusted warfarin (INR 2.0–3.0) or aspirin 300 mg. The primary outcome measure was a comparative frequency of combined endpoints comprising death,

thromboembolism, serious bleeding, and withdrawal from the study. Seventy-five patients (aspirin 39; warfarin 36) were entered (mean age 83.9, 47% male). There were significantly more adverse events with aspirin (13/39; 33%) than with warfarin (2/36; 6%), $p=0.002$. Ten of 13 aspirin adverse events were caused by side effects and serious bleeding; there were three deaths (two aspirin, one warfarin).

Another RCT¹⁴⁴ recruited patients over 75 years of age without previous stroke or systemic embolism. Patients were randomized into three groups, with group A receiving aspirin 100 mg/day, group B fixed-dose warfarin 1 mg/day; and group C adjusted-dose warfarin with a target range of INR between 1.6 and 2.5. Primary endpoints (ischemic strokes and systemic embolisms) and secondary endpoints (deaths, MIs, and major bleeding events) were prospectively documented. The study was discontinued 6 months after the enrollment of the first patient for safety reasons. During this period, 45 patients were recruited (15 patients in group A, 14 in group B, and 16 in group C). Over a mean followup period of 3.7 months (range: 1–6 months), two patients from group B developed a dangerous prolongation of the INR (7.0 and 4.2), which led to the discontinuation of fixed-dose warfarin. Another patient from the same group experienced a major bleeding event 1 month after enrollment in the study (INR 5.5). The percentage of INR measurements within the target range was significantly ($p < 0.001$) lower in group B (48.7%) than in group C (83.7%).

A prospective observational study¹⁴⁶ included 207 older people (>75 years) with AF and first ever ischemic stroke. During the followup period (mean 88.4 months, range 3–120), the study population was under either oral anticoagulants ($n=72$) or aspirin ($n=135$). The cumulative 10-year mortality and recurrence rates were 92.5 percent (95% CI, 85.7 to 99.3) and 66.1 percent (95% CI, 43.1 to 89.1), respectively. Increasing age, functional dependency at hospital discharge, and antiplatelet versus anticoagulation therapy were independent determinants of mortality. Antiplatelet versus anticoagulation therapy was the sole determinant of vascular recurrence. Anticoagulation was associated with decreased risk of death (HR 0.47; 95% CI, 0.31 to 0.72, $p=0.001$) and recurrent thromboembolism (HR 0.31; 95% CI, 0.16 to 0.62, $p=0.002$). These results suggest that the benefits of anticoagulation for secondary stroke prevention in AF patients extend to elderly.

A retrospective cohort analysis¹³⁵ evaluated persons discharged on warfarin after an AF admission using data from Medicare's National Stroke Project. It examined antiplatelet therapy among warfarin users and the impact on major bleeding rates. Prediction of concurrent antiplatelet use and hospitalization with a major acute bleed within 90 days after discharge from the index AF admission was assessed. A total of 10,093 warfarin patients met inclusion criteria with a mean age of 77 years; 19.4 percent received antiplatelet therapy. Antiplatelet use was less common among women, older persons, and persons with cancer, terminal diagnoses, dementia, and bleeding history. Persons with coronary disease were more likely to receive an antiplatelet agent. Antiplatelets increased major bleeding rates from 1.3 percent to 1.9 percent ($P=0.052$). In the multivariate analysis, factors associated with bleeding events included age (OR, 1.03; 95% CI, 1.002 to 1.05), anemia (OR, 2.52; 95% CI, 1.64 to 3.88), a history of bleeding (OR, 2.40; 95% CI, 1.71 to 3.38), and concurrent antiplatelet therapy (OR, 1.53; 95% CI, 1.05 to 2.22).

A substudy¹⁶² of the BAFTA trial¹³¹ evaluated 665 patients aged 75 or over with AF based in the community who were randomized within the BAFTA trial and were not taking warfarin throughout or for part of the study period. A total of 54 (8%) patients had an ischemic stroke, four (0.6%) had a systemic embolism, and 13 (2%) had a TIA. Based on this single trial

population, current risk stratification schemes in older people with AF have only limited ability to predict the risk of stroke.

Another study¹⁴⁹ examined the effectiveness of oral anticoagulation on risk of stroke of any nature (fatal and nonfatal ischemic and/or hemorrhagic stroke) in patients with nonvalvular AF or flutter living in the County of North Jutland, Denmark. This study used the Hospital Discharge Registry covering the county (490,000 inhabitants) from 1991 to 1998 to identify 2,699 men and 2,425 women with AF or flutter, aged 60–89 years. The risk of stroke associated with use of oral anticoagulation compared with no use was estimated, after adjustment for age, diabetes and underlying cardiovascular diseases. A total of 838 of 2,699 men (31%) and 552 of 2,425 women (23%) with AF had one or more recorded prescriptions of oral anticoagulation. The incidence rates of stroke were 31 per 1000 person-years of followup in men, and 30 per 1000 person-years of followup in women. The adjusted relative risks of stroke during anticoagulation were 0.6 (95% CI, 0.4 to 1.0) in men, and 1.0 (95% CI, 0.7 to 1.6) in women compared with nonuse periods. The adjusted relative risks of stroke associated with use of oral anticoagulation compared with no use varied by age in men, but not in women. In men aged 60–74 years the adjusted relative risk associated with use of oral anticoagulation compared with no use was 0.5 (95% CI, 0.3 to 0.9), and in men aged 75–89 years the adjusted relative risk of stroke associated with oral anticoagulation compared with no use was 0.9 (95% CI, 0.4 to 1.8). The adjusted relative risk of stroke increased with age. In men and women, the risk of stroke amongst patients aged 80–89 years was increased by a factor of 2.0 and 2.9 relative to the stroke risk amongst patients aged 60–69 years.

The RE-LY trial²⁶ randomized 18,113 patients to receive dabigatran 110 or 150 mg twice a day or warfarin dose adjusted to an INR of 2.0–3.0 for a median followup of 2.0 years. A substudy of this trial¹⁶³ assessed the impact of age on the findings and found that there was a significant treatment-by-age interaction, such that dabigatran 110 mg twice a day compared with warfarin was associated with a lower risk of major bleeding in patients aged <75 years (1.89% vs. 3.04%; $p < 0.001$) and a similar risk in those aged ≥ 75 years (4.43% vs. 4.37%; $P = 0.89$; P for interaction < 0.001), whereas dabigatran 150 mg twice a day compared with warfarin was associated with a lower risk of major bleeding in those aged <75 years (2.12% vs. 3.04%; $p < 0.001$) and a trend toward higher risk of major bleeding in those aged ≥ 75 years (5.10% vs. 4.37%; $p = 0.07$; p for interaction < 0.001). The interaction with age was evident for extracranial bleeding, but not for intracranial bleeding, with the risk of the latter being consistently reduced with dabigatran compared with warfarin irrespective of age. Based on these results, patients with AF at risk for stroke, both doses of dabigatran compared with warfarin have lower risks of both intracranial and extracranial bleeding in patients aged <75 years. In those aged ≥ 75 years, intracranial bleeding risk is lower but extracranial bleeding risk is similar or higher with both doses of dabigatran compared with warfarin.

Patients With AF Undergoing Drug-Eluting Stent Implantation

One prospective cohort study¹⁴⁰ analyzed the outcomes in 622 AF patients who underwent drug-eluting stent (DES) implantation. Among them, 142 patients (TT group) continued triple antithrombotic therapy comprising aspirin, clopidogrel, and warfarin after discharge; 355 patients (DT group) had dual antiplatelet therapy; 125 patients (WS group) were discharged with warfarin and a single antiplatelet agent. Primary endpoint was defined as the occurrence of major adverse cardiac and cerebral events (MACCE) including death, MI, target vessel revascularization, stent thrombosis, or stroke at 12 months. The TT group had a significant

reduction in stroke and MACCE (8.8% vs. 20.1% vs. 14.9%, p=0.010) as compared with either the DT or WS group. Warfarin use (HR 0.49; 95% CI, 0.31 to 0.77; p=0.002) and baseline CHADS₂ score ≥2 (HR 2.09; 95% CI, 1.27 to 3.45; p=0.004) were independent predictors of MACCE. Importantly, the incidence of major bleeding was comparable among the three groups (2.9% vs. 1.8% vs. 2.5%; p=0.725), although the overall bleeding rate was increased in the TT group. Analyzing the events separately in two ways of comparison (all three therapies and therapies with warfarin versus therapy without warfarin), the only event that achieved statistical significance was stroke in the comparison of therapy with warfarin (DT and TT) versus dual antiplatelet therapy without warfarin (less stroke in warfarin group).

Patients With AF and Myocardial Infarction

One substudy of the RE-LY trial²⁶ evaluated the use of therapies for stroke prevention in AF patients with MI.¹⁶⁴ In this analysis, the relative effects of dabigatran versus warfarin on myocardial ischemic events were consistent in patients with or without a baseline history of MI or coronary artery disease. Patients with a baseline history of coronary artery disease (CAD) or previous MI are at risk for recurrent ischemic events. There were 1,886 (31%) CAD/MI patients in the dabigatran 110 mg group, 1,915 (31%) in the dabigatran 150 mg group, and 1,849 (31%) in the warfarin group. The relative effects of dabigatran compared with warfarin were highly consistent between patients with prior CAD/MI compared with those without (all probability values for interaction were nonsignificant).

Table 19 summarizes the strength of evidence for the various comparisons and outcomes of interest.

Table 19. Strength of evidence domains for preventing thromboembolic events

Outcome	Number of Studies (Subjects)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
ASA versus Warfarin						
Ischemic stroke	2 (99,061)	Observational/Moderate	Consistent	Direct	Precise	SOE=Moderate Two retrospective studies showing consistent reduction in stroke for patients on warfarin compared with ASA
Bleeding	2 (99,061)	Observational/Moderate	Consistent	Direct	Precise	SOE=Moderate Warfarin is associated with increased rates of severe bleeding
All-cause mortality	1 (601)	Observational/High	NA	Direct	Imprecise	SOE=Insufficient
Warfarin + ASA versus Warfarin						
Ischemic stroke	1 (69,264)	Observational/Moderate	NA	Direct	Precise	SOE=Moderate HR 1.27 (95% CI, 1.14 to 1.40) increase in warfarin + ASA arm

Outcome	Number of Studies (Subjects)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Bleeding	1 (69,264)	Observational/ Moderate	NA	Direct	Precise	SOE=Moderate HR 1.83 (95% CI, 1.72 to 1.96) increase in warfarin + ASA arm
Clopidogrel + ASA versus ASA						
Any stroke	2 (8,147)	RCT/Low	Inconsistent	Direct	Imprecise	One large RCT showing similar rates (HR 1.03 [95% CI, 0.49 to 2.13]), but another smaller study showed significant reduction in clopidogrel + ASA arm (HR 0.72 [95% CI, 0.62 to 0.83]); low strength of evidence of similar rates of stroke between treatment arms
Ischemic stroke	2 (8,147)	RCT/Low	Inconsistent	Direct	Imprecise	SOE=Low One large RCT showing similar rates (HR 0.96 [95% CI, 0.46 to 2.01]), but another smaller study showed significant reduction in clopidogrel + ASA arm (HR 0.68 [95% CI, 0.57 to 0.80]); low strength of evidence of similar rates of stroke between treatment arms
Systemic embolism	1 (7,554)	RCT/Low	NA	Direct	Imprecise	SOE=Moderate Similar between treatment groups (HR 0.96 [95% CI, 0.66 to 1.40])
Hemorrhagic stroke	2 (8,147)	RCT/Low	Consistent	Direct	Imprecise	SOE=Moderate Similar between treatment groups in both studies
Major bleeding	1 (7,554)	RCT/Low	NA	Direct	Precise	SOE=High Clopidogrel + ASA associated with higher rates (HR 1.57 [95% CI, 1.29 to 1.92])

Outcome	Number of Studies (Subjects)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Minor bleeding	1 (7,554)	RCT/Low	NA	Direct	Precise	SOE=High Clopidogrel + ASA associated with higher rates (HR 2.42 [95% CI, 2.03 to 2.89])
Intracranial bleeding	2 (8,147)	RCT/Low	Inconsistent	Direct	Imprecise	SOE=Low One large RCT showing higher rate with clopidogrel + ASA (HR 1.87 [95% CI, 1.19 to 2.94]), but other study showed other showed no difference (0.62)
Extracranial bleeding	2 (8,147)	RCT/Low	Inconsistent	Direct	Imprecise	SOE=Low One large RCT showing higher rate with clopidogrel + ASA (HR 1.51 [95% CI, 1.21 to 1.88]), but other study showed no difference (0.51)
All-cause mortality	2 (8,147)	RCT/Low	Consistent	Direct	Imprecise	SOE=Moderate Did not differ between arms in either study (in the 2 studies, HR 0.98 [95% CI, 0.89 to 1.08] and HR 1.12 [95% CI, 0.65 to 1.90])
Death from vascular causes	2 (8,147)	RCT/Low	Consistent	Direct	Imprecise	SOE=Moderate Did not differ between arms in either study (in the 2 studies, HR 1.00 [95% CI, 0.89 to 1.12] and HR 1.68 [95% CI, 0.83 to 3.42])
Myocardial infarction	2 (8,147)	RCT/Low	Consistent	Direct	Imprecise	SOE=Moderate Did not differ between arms in either study (in the 2 studies, HR 0.78 [95% CI, 0.59 to 1.03] and HR 1.43 [95% CI, 0.51 to 4.01])
Hospitalization	1 (593)	RCT/Low	NA	Direct	Imprecise	SOE=Insufficient

Outcome	Number of Studies (Subjects)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Clopidogrel versus Warfarin						
Ischemic stroke	1 (54,636)	Observational/ Moderate	NA	Direct	Precise	SOE=Moderate Increased risk with clopidogrel (HR 1.86 [95% CI, 1.52 to 2.27])
Bleeding	1 (54,636)	Observational/ Moderate	NA	Direct	Precise	SOE=Moderate Similar between groups (HR 1.06 [95% CI, 0.87 to 1.29])
Clopidogrel + ASA versus Warfarin						
Stroke or systemic embolism	2 (60,484)	RCT+ Observational/ Low	Consistent	Direct	Precise	SOE=High Clopidogrel + ASA increased risk (in the 2 studies HR 1.56 [95% CI, 1.17 to 2.10] and HR 1.72 [95% CI, 1.24 to 2.37])
Hemorrhagic stroke	1 (6,706)	RCT/Low	NA	Direct	Imprecise	SOE=Moderate Increased risk in warfarin group (HR 0.34 [95% CI, 0.12 to 0.93])
Major bleeding	2 (60,484)	RCT+ Observational/ Low	Inconsistent	Direct	Imprecise	SOE=Low Large RCT showed no difference (HR 1.10 [95% CI, 0.83 to 1.45]), retrospective study showed greater risk in clopidogrel + ASA arm (HR 1.66 [95% CI, 1.34 to 2.04]); low strength of evidence of similar rates of major bleeding between treatment arms
Minor bleeding	1 (6,706)	RCT/Low	NA	Direct	Precise	SOE=High Clopidogrel + ASA increased risk (HR 1.23 [95% CI, 1.09 to 1.39])
Intracranial bleeding	1 (6,706)	RCT/Low	NA	Direct	Imprecise	SOE=Insufficient
All-cause mortality	1 (6,706)	RCT/Low	NA	Direct	Precise	SOE=High No difference (HR 1.01 [95% CI, 0.81 to 1.26])

Outcome	Number of Studies (Subjects)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Death from vascular causes	1 (6,706)	RCT/Low	NA	Direct	Imprecise	SOE=Moderate No difference (HR 1.14 [95% CI, 0.88 to 1.48])
Myocardial infarction	1 (6,706)	RCT/Low	NA	Direct	Imprecise	SOE=Moderate MI occurred at rates of less than 1% per year in both groups and was not significantly different between treatments
Clopidogrel + Warfarin versus Warfarin						
Ischemic stroke	1 (52,349)	Observational/Moderate	NA	Direct	Imprecise	SOE=Low No difference between treatments (HR 0.70 [95% CI, 0.35 to 1.40])
Bleeding	1 (52,349)	Observational/Moderate	NA	Direct	Precise	SOE=Moderate Higher for patients on clopidogrel + warfarin (HR 3.08 [95% CI, 2.32 to 3.91])
Warfarin + ASA + Clopidogrel versus Warfarin						
Ischemic stroke	1 (52,180)	Observational/Moderate	NA	Direct	Imprecise	SOE=Low No difference between treatments (HR 1.45 [95% CI, 0.84 to 2.52])
Bleeding	1 (52,180)	Observational/Moderate	NA	Direct	Precise	SOE=Moderate Higher for patients on clopidogrel + warfarin (HR 3.70 [95% CI, 2.89 to 4.76])
Factor II Inhibitor (Dabigatran 150 mg) versus Warfarin						
Stroke or systemic embolism	1 (12,098)	RCT/Low	NA	Direct	Precise	SOE=High Dabigatran reduced risk (HR 0.66 [95% CI, 0.53 to 0.82])
Ischemic or uncertain stroke	1 (12,098)	RCT/Low	NA	Direct	Imprecise	SOE=Moderate Dabigatran reduced risk (HR 0.76 [95% CI, 0.60 to 0.98])
Hemorrhagic stroke	1 (12,098)	RCT/Low	NA	Direct	Precise	SOE=High Dabigatran reduced risk (HR 0.26 [95% CI, 0.14 to 0.49])

Outcome	Number of Studies (Subjects)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Major bleeding	1 (12,098)	RCT/Low	NA	Direct	Precise	SOE=High No difference (HR 0.93 [95% CI, 0.81 to 1.07])
Minor bleeding	1 (12,098)	RCT/Low	NA	Direct	Imprecise	SOE=Moderate Dabigatran reduced risk (HR 0.91 [95% CI, 0.85 to 0.97])
Intracranial bleeding	1 (12,098)	RCT/Low	NA	Direct	Precise	SOE=High Dabigatran reduced risk (HR 0.40 [95% CI, 0.27 to 0.60])
All-cause mortality	1 (12,098)	RCT/Low	NA	Direct	Imprecise	SOE=Moderate No difference (HR 0.88 [95% CI, 0.77 to 1.00])
Death from vascular causes	1 (12,098)	RCT/Low	NA	Direct	Imprecise	SOE=Moderate Dabigatran reduced risk (HR 0.85 [95% CI, 0.72 to 0.99])
Myocardial infarction	1 (12,098)	RCT/Low	NA	Direct	Imprecise	SOE=Moderate Dabigatran increased risk (HR 1.38 [95% CI, 1.00 to 1.91])
Hospitalization	1 (12,098)	RCT/Low	NA	Direct	Precise	SOE=High No difference (HR 0.97 [95% CI, 0.92 to 1.03])
Adverse events	1 (12,098)	RCT/Low	NA	Direct	Imprecise	SOE=Moderate Dyspepsia was more common with dabigatran (11.3% of patients with 150 mg compared with 5.8% with warfarin, p<0.001). No differences in liver function or other adverse events were seen between groups.
Factor II Inhibitor (Dabigatran 110 mg) versus Warfarin						
Stroke or systemic embolism	1 (12,037)	RCT/Low	NA	Direct	Precise	SOE=High No difference (HR 0.91 [95% CI, 0.74 to 1.11])
Ischemic or uncertain stroke	1 (12,037)	RCT/Low	NA	Direct	Imprecise	SOE=Moderate No difference (HR 1.11 [95% CI, 0.89 to 1.40])

Outcome	Number of Studies (Subjects)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Hemorrhagic stroke	1 (12,037)	RCT/Low	NA	Direct	Precise	SOE=High Dabigatran reduced risk (HR 0.31 [95% CI, 0.17 to 0.56])
Major bleeding	1 (12,037)	RCT/Low	NA	Direct	Precise	SOE=High Dabigatran reduced risk (HR 0.80 [95% CI, 0.69 to 0.93])
Minor bleeding	1 (12,037)	RCT/Low	NA	Direct	Precise	SOE=High Dabigatran reduced risk (HR 0.79 [95% CI, 0.74 to 0.84])
Intracranial bleeding	1 (12,037)	RCT/Low	NA	Direct	Precise	SOE=High Dabigatran reduced risk (HR 0.31; 95% CI, 0.20 to 0.47])
All-cause mortality	1 (12,037)	RCT/Low	NA	Direct	Imprecise	SOE=Moderate No difference (HR 0.91 [95% CI, 0.80 to 1.03])
Death from vascular causes	1 (12,037)	RCT/Low	NA	Direct	Imprecise	SOE=Moderate No difference (HR 0.90 [95% CI, 0.77 to 1.06])
Myocardial infarction	1 (12,037)	RCT/Low	NA	Direct	Imprecise	SOE=Moderate Dabigatran increased risk (HR 1.35 [95% CI, 0.98 to 1.87])
Hospitalization	1 (12,037)	RCT/Low	NA	Direct	Precise	SOE=High Dabigatran reduced risk (HR 0.92 [95% CI, 0.87 to 0.97])
Adverse events	1 (12,037)	RCT/Low	NA	Direct	Imprecise	SOE=Moderate Dyspepsia was more common with dabigatran (11.8% of patients with 110 mg compared with 5.8% with warfarin, p<0.001). No differences in liver function or other adverse events were seen between groups.

Outcome	Number of Studies (Subjects)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Xa Inhibitor (apixaban) versus ASA						
Stroke or systemic embolism	1 (5,599)	RCT/Low	NA	Direct	Precise	SOE=High Apixaban reduced risk (HR 0.45 [95% CI, 0.32 to 0.62])
Ischemic stroke	1 (5,599)	RCT/Low	NA	Direct	Precise	SOE=High Apixaban reduced risk (HR 0.37 [95% CI, 0.25 to 0.55])
Hemorrhagic stroke	1 (5,599)	RCT/Low	NA	Direct	Imprecise	SOE=Moderate No difference (HR 0.67 [95% CI, 0.24 to 1.88])
Major bleeding	1 (5,599)	RCT/Low	NA	Direct	Precise	SOE=High No difference (HR 1.13 [95% CI, 0.74 to 1.75])
Minor bleeding	1 (5,599)	RCT/Low	NA	Direct	Precise	SOE=High No difference (HR 1.24 [95% CI, 1.00 to 1.53])
Intracranial bleeding	1 (5,599)	RCT/Low	NA	Direct	Imprecise	SOE=Moderate No difference (HR 0.85 [95% CI, 0.38 to 1.90])
All-cause mortality	1 (5,599)	RCT/Low	NA	Direct	Imprecise	SOE=Moderate No difference (HR 0.79 [95% CI, 0.62 to 1.02])
Death from vascular causes	1 (5,599)	RCT/Low	NA	Direct	Imprecise	SOE=Moderate No difference (HR 0.87 [95% CI, 0.66 to 1.17])
Myocardial infarction	1 (5,599)	RCT/Low	NA	Direct	Imprecise	SOE=Moderate No difference (HR 0.86 [95% CI, 0.50 to 1.48])
Hospitalization	1 (5,599)	RCT/Low	NA	Direct	Precise	SOE=High Apixaban reduced risk (HR 0.79 [95% CI, 0.69 to 0.91])
Adverse events	1 (5,599)	RCT/Low	NA	Direct	Imprecise	SOE=Moderate No differences in liver function or other adverse events were seen between groups
Xa Inhibitor (apixaban) versus Warfarin						
Stroke or systemic embolism	1 (18,201)	RCT/Low	NA	Direct	Precise	SOE=High Apixaban reduced risk (HR 0.79 [95% CI, 0.66 to 0.95])

Outcome	Number of Studies (Subjects)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Ischemic stroke	1 (18,201)	RCT/Low	NA	Direct	Precise	SOE=High No difference (HR 0.92 [95% CI, 0.74 to 1.13])
Hemorrhagic stroke	1 (18,201)	RCT/Low	NA	Direct	Precise	SOE=High Apixaban reduced risk (HR 0.51 [95% CI, 0.35 to 0.75])
Systemic embolism	1 (18,201)	RCT/Low	NA	Direct	Imprecise	SOE=Moderate No difference (HR 0.87 [95% CI, 0.44 to 1.75])
Major bleeding	1 (18,201)	RCT/Low	NA	Direct	Precise	SOE=High Apixaban reduced risk (HR 0.69 [95% CI, 0.60 to 0.80])
All-cause mortality	1 (18,201)	RCT/Low	NA	Direct	Imprecise	SOE=Moderate Apixaban reduced risk (HR 0.89 [95% CI, 0.80 to 0.998])
Death from cardiovascular causes	1 (18,201)	RCT/Low	NA	Direct	Precise	SOE=High No difference (HR 0.89 [95% CI, 0.76 to 1.04])
Myocardial infarction	1 (18,201)	RCT/Low	NA	Direct	Imprecise	SOE=Moderate No difference (HR 0.88 [95% CI, 0.66 to 1.17])
Intracranial bleeding	1 (18,201)	RCT/Low	NA	Direct	Precise	SOE=High Apixaban reduced risk (HR 0.42 [95% CI, 0.30 to 0.58])
Adverse events	1 (18,201)	RCT/Low	NA	Direct	Imprecise	SOE=Moderate Adverse events occurred in almost equal proportions of patients in the apixaban group and the warfarin group (81.5% and 83.1%, respectively). Rates of abnormalities on liver function testing and liver-related serious adverse events were also similar in the two groups.

Outcome	Number of Studies (Subjects)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Xa Inhibitor (rivaroxaban) versus Warfarin						
Stroke or systemic embolism	1 (14,264)	RCT/Low	NA	Direct	Precise	SOE=High Rivaroxaban reduced risk (HR 0.79 [95% CI, 0.65 to 0.95])
Major bleeding	1 (14,264)	RCT/Low	NA	Direct	Precise	SOE=High No difference (HR 1.04 [95% CI, 0.90 to 1.20])
All-cause mortality	1 (14,264)	RCT/Low	NA	Direct	Precise	SOE=High No difference (HR 0.85 [95% CI, 0.70 to 1.02])
Myocardial infarction	1 (14,264)	RCT/Low	NA	Direct	Precise	SOE=High No difference (HR 0.81 [95% CI, 0.63 to 1.06])
Intracranial bleeding	1 (14,264)	RCT/Low	NA	Direct	Precise	SOE=High Rivaroxaban reduced risk (HR 0.67 [95% CI, 0.47 to 0.93])
Percutaneous LAA Closure versus Warfarin						
Ischemic stroke	1 (707)	RCT/Low	NA	Direct	Imprecise	SOE=Low 9 patients in the LAA group (1.3 events per 100 patient-years) and 6 patients in the warfarin group (1.6 events per 100 patient-years) had ischemic stroke, demonstrating no difference between arms
All strokes	1 (707)	RCT/Low	NA	Direct	Imprecise	SOE=Moderate No difference (RR 0.71 [95% CI, 0.35 to 1.64])
Major bleeding	1 (707)	RCT/Low	NA	Direct	Imprecise	SOE=Low Less frequent in the LAA group than in the warfarin group (3.5% vs. 4.1%)
All-cause mortality	1 (707)	RCT/Low	NA	Direct	Imprecise	SOE=Moderate No difference (RR 0.62 [95% CI, 0.34 to 1.24])
Adverse events	1 (707)	RCT/Low	NA	Direct	Imprecise	SOE=Moderate Higher rate in LAA group (RR 1.69 [95% CI, 1.01 to 3.19])

Abbreviations: ASA=aspirin; CI=confidence interval; HR=hazard ratio; LAA=left atrial appendage; NA=not applicable; RCT=randomized controlled trial; RR=relative risk; SOE=strength of evidence; TIA=transient ischemic attack

Key Question 4. Anticoagulation Strategies in Patients Undergoing Invasive Procedures

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

Key Points

- The included post-PCI studies were too small to be conclusive and reached different conclusions regarding the effectiveness of triple therapy compared with other combinations of therapies for both bleeding and ischemic outcomes.
- Studies of bridging strategies were hampered by the variety of procedures (RFA, other surgeries) and strategies assessed and provided inconclusive findings.
- Current evidence is insufficient to make any statements about the comparative safety and effectiveness of available strategies for anticoagulation in patients with nonvalvular AF who are undergoing invasive procedures (insufficient strength of evidence).

Description of Included Studies

A total of eight studies were included in our analysis (Appendix Table F-4),¹⁶⁵⁻¹⁷² of which five were prospective cohort studies^{165-168,171} and three were retrospective cohort studies.^{169,170,172} These studies assessed anticoagulation during or after ablation procedures,^{165,166,171,172} other operative procedures,¹⁶⁷ or after a percutaneous coronary intervention (PCI).¹⁶⁸⁻¹⁷⁰ The numbers of patients analyzed varied from 104–703, with six single-center^{165-169,172} and one multicenter study.¹⁷⁰ Studies were conducted in the United States,^{171,172} South America,¹⁶⁵ Asia,¹⁶⁶ and Europe¹⁶⁷⁻¹⁷⁰ between the years 1999 and 2009. Five of the studies were considered of good quality,^{166,168-171} two of fair quality,^{165,167} and one was rated as poor quality.¹⁷² The funding source was reported by only two studies, one of which was government funded,¹⁶⁶ and one sponsored by industry.¹⁶⁷

Subjects ranged in age from a mean of 55–78.6 years; a total of 2,621 subjects were enrolled. Five studies evaluated anticoagulation therapies around non-PCI procedures,^{165-167,171,172} while three studies evaluated oral anticoagulation after a PCI with stenting.¹⁶⁸⁻¹⁷⁰

Among studies looking at bridging therapies, two compared heparin with low molecular weight heparin (LMWH)^{165,166} (enoxaparin specified in one study¹⁶⁶), while two compared different doses of enoxaparin with concomitant warfarin therapy¹⁷¹ or as standalone bridging therapy.¹⁶⁷ Followup in these studies varied from 1 month¹⁶⁷ to 3–4 months¹⁷¹ to 12-16 months.^{165,172} Four of the studies assess anticoagulation strategies during or after radiofrequency ablation (RFA) procedures,^{165,166,171,172} while one assessed bridging anticoagulation during other operative procedures.¹⁶⁷

Of the three post-PCI studies, all compared warfarin plus antiplatelet therapy with antiplatelet therapy alone; however, the specific individual comparator arms were different in each study. In addition, a single study¹⁶⁸ also compared a strategy of LMWH with dual

antiplatelet therapy. The duration of followup in these studies was reported to be between 2 months and 5.7 years.

We analyze each of these groups separately below.

Detailed Synthesis

Overview

Our analysis was limited by the small number of included studies, the variability of the clinical context studied, and the variability of the anticoagulation strategies employed. For the purposes of this analysis, the studies are grouped according to indication studied, in particular according to whether they assessed anticoagulation post-PCI or bridging therapies. The main findings are summarized in Table 20.

Table 20. Summary of findings for KQ 4

Study	N	Comparators	Outcomes	Results
PCI				
Maegdefessel, 2008 ¹⁶⁸	159	Clopidogrel + ASA (n=103) Clopidogrel + ASA + LMWH (n=42) Clopidogrel + ASA + OAC (n=14)	Followup 1.4 years Major bleed MI Ischemic stroke CV mortality	Major bleeding: 2 vs. 0 vs. 0 events MI: 4 vs. 0 vs. 0 events Ischemic stroke: 9 vs. 4 vs. 0 CV death: 3 vs. 5 vs. 1
Manzano-Fernandez, 2008 ¹⁶⁹	104	Clopidogrel + ASA (n=53) Clopidogrel + ASA + OAC (n=51)	Followup 12 months Major bleed (early [within 48 hours] and late [after 48 hours] post-PCI) Composite outcome: CV mortality, MI, revascularization, stent thrombosis	Early major bleeding: 5.3% vs. 11.3% (p=0.33) Late major bleeding: 3.8% vs. 21.6% (p=0.006) HR: 7.1 (95% CI, 1.5 to 32.4) MACE rates: 21.0% vs. 25.5% (p=0.53)
Ruiz-Nodar, 2008 ¹⁷⁰	426	Antiplatelet agents only (n=184) OAC + antiplatelet therapy (n=242)	Composite: MACE (death, MI, TVR) Composite: MACE+ major bleeding, stroke Individual outcomes: Major bleeding Minor bleeding Death MI	MACE: 38.7% vs. 26.5% (p=0.01) MACE + major bleeding + stroke: 39.2% vs. 26.8%, p=0.014) Major bleeding: 9.0 vs. 14.9% p=0.19 Minor bleeding: 9.0% vs. 12.6% p=0.32 Death: 27.8% vs. 17.8% p=0.02 MI: 10.4% vs. 6.5% p=0.14

Study	N	Comparators	Outcomes	Results
Ablation				
Saad, 2011 ¹⁶⁵	140	Enoxaparin 1 mg/kg (n=55) Warfarin (n=49)	Followup 16 months Minor bleed Major bleed CV mortality All-cause mortality Systemic embolism	Minor bleeding: 4(5.7%) vs. 2 (2.8%) Major bleeding: 1 (1.4%) vs. 1 (1.4%) CV mortality: None All-cause mortality: None Systemic embolism: None
Kwak, 2010 ¹⁶⁶	104	Enoxaparin 1 mg/kg (n=70) Warfarin (n=70)	In-hospital: Major bleed Minor bleed Ischemic stroke	Major bleeding: 2 (3.6%) vs. 6 (12.2%) events (p=0.14) Minor bleeding: 8 (14.5%) vs. 3 (6.1%) p=0.28 Ischemic stroke: None
Wazni, 2007 ¹⁷¹	355	Enoxaparin 1 mg/kg twice daily Enoxaparin 0.5 mg/kg twice daily Warfarin (INR 2-3.5)	Followup 3 months: Ischemic stroke Minor bleeding Major bleeding	Ischemic stroke: 1 (1.0%) vs. 2 (2.0%) vs. 0 p=0.12 Minor bleeding: 23 (21.9%) vs. 19 (19.0%) vs. 8 (5.3%) p<0.001 Major bleeding: 9 (8.6%) vs. 0 vs. 0 p<0.001
Bunch, 2009 ¹⁷²	630	Aspirin (n=123) Warfarin (n=507)	Follow-up 12 months Death CVA/TIA	Death: 0 vs. 5 (1.0%), p=0.59 CVA: 0 vs. 4 (0.8%) p=0.24
Surgery (major and minor)				
Hammerstingl, 2009 ¹⁶⁷	703	Patients at low risk of thromboembolic events: Enoxaparin 1 mg/kg once a day (n=345) Patients at high risk of thromboembolic events: Enoxaparin 1 mg/kg twice day (n =358)	Follow-up 30 days: Composite outcome: stroke/TIA, arterial embolism Major bleed Minor bleed	Composite: No events Major bleeding: 1 (0.29%) vs. 2 (0.56%) Minor bleeding: 25 (7.25%) vs. 35 (9.78%)

Abbreviations: ASA=aspirin; CI=confidence interval; CV=cardiovascular; CVA=cerebrovascular accident; HR=hazard ratio; INR=international normalized ratio; KQ=Key Question; LMWH=low molecular weight heparin; MACE=major adverse cardiac event; MI=myocardial infarction; N=number of participants; OAC=oral anticoagulation; PCI=percutaneous coronary intervention; TIA=transient ischemic attack; TVR=target vessel revascularization

Post-PCI

Three studies assessed the incidence of major bleeding post-PCI, comparing warfarin plus antiplatelet therapy with antiplatelet therapy alone.¹⁶⁸⁻¹⁷⁰ All were cohort studies subject to the biases inherent in the clinical decision of anticoagulation strategy implemented at the discretion of the physician. The strategies compared differed across studies, making cross-study analysis difficult. One study compared therapy with aspirin and clopidogrel with “triple therapy,” defined separately as either aspirin, clopidogrel, and LMWH, or as aspirin, clopidogrel, and warfarin.¹⁶⁸ A second study compared triple therapy with dual antiplatelet therapy and warfarin with non-triple therapy;¹⁶⁹ however, non-triple therapy consisted of any two oral anticoagulant or antiplatelet agents in combination. Finally, the third study compared a strategy of antiplatelet agents alone with antiplatelet agents in conjunction with oral anticoagulation;¹⁷⁰ however, the

antiplatelet agents used were not consistent. Given the known association of both bleeding and protection against thromboembolic events with each of the agents considered, it was deemed inappropriate to combine any of these treatment strategies.

In general, these studies enrolled an older patient population (mean age 69–71) with a high proportion of patients with diabetes (33–54%), hypertension (82–91%), and hyperlipidemia (>50%), reflecting the demographics of a patient population with AF and coronary disease. The median CHADS₂ score was 2, with an IQR of 2–3, indicating that a vast majority of patients had a CHADS₂ score of at least 2.

Major Bleeding

One study¹⁶⁹ reported major bleeding within 48 hours of PCI, showing that there was no significant difference in the occurrence of early major bleeding between the two treatment arms (5.8% for triple therapy vs. 11.3% for dual therapy, $p=0.33$). In the same study, triple therapy was associated with a higher rate of major bleeding (21.6% for triple therapy vs. 3.8% for dual therapy, $p=0.006$) during the first 6 months of followup.

At followup at 1.4 years, one study¹⁶⁸ reported two major bleeding events in the dual antiplatelet therapy group and none in the triple therapy arms. The third study¹⁷⁰ reported a nonsignificant increase of major (14.9% vs. 9.0%, $p=0.19$) and minor (12.6% vs. 9.0%) bleeding among patients discharged on triple therapy compared with those on dual antiplatelet therapy.

Myocardial Infarction

Two studies compared the effect of triple therapy versus dual antiplatelet therapy on myocardial infarction among patients with AF undergoing PCI.^{168,170} One of these studies¹⁶⁸ reported four myocardial infarction events in the dual antiplatelet therapy group and none in the triple therapy arms. The second study¹⁷⁰ reported a nonsignificant increase in the rate of myocardial infarction events (10.4% vs. 6.5%) among patients discharged on dual antiplatelet therapy compared with those on triple therapy.

Mortality

Two studies compared the effect of triple therapy versus dual antiplatelet therapy on mortality among patients with AF undergoing PCI.^{168,170} One study¹⁶⁸ reported three cardiovascular deaths in the dual antiplatelet therapy group, five cardiovascular deaths among patients receiving triple therapy with LMWH, and one cardiovascular death among patients receiving triple therapy with oral anticoagulant. The second study¹⁷⁰ reported a statistically significant higher rate of all-cause mortality among patients discharged on dual antiplatelet therapy compared with those on triple therapy (10.4% vs. 6.5%; HR 3.43; 95% CI, 1.61 to 7.54; $p=0.002$).

Composite Outcomes

Two studies compared the effect of triple therapy versus dual antiplatelet therapy on the composite outcome of death, myocardial infarction, and revascularization and stent thrombosis among patients with AF undergoing PCI.^{169,170} One study¹⁶⁹ found no significant difference in the rate of the composite endpoint between the two treatment arms (25.5% triple therapy vs. 21.0% dual therapy, $p=0.53$). The second study¹⁷⁰ reported a statistically significant higher rate of the composite of death, myocardial infarction, and target vessel revascularization among patients discharged on dual antiplatelet therapy compared with those on triple therapy (38.7% vs.

26.5%; HR 4.9; 95% CI, 2.17 to 11.1; p=0.01). Similarly, a significant increase in the secondary safety endpoint (any major adverse cardiovascular event, major bleeding, and/or stroke) was observed among patients treated with dual therapy compared with triple therapy (39.2% vs. 26.8%, p=0.014)

Studies of Bridging Therapy

A total of five studies assessed bridging therapies during cardiac and non-cardiac procedures. Three studies compared a bridging strategy involving LMWH with a strategy not employing LMWH; however, the surgical procedures (RFA,^{165,166} minor and major surgery¹⁶⁷) varied, as did the comparator arms.

Two trials compared a strategy of “bridging” peri-RFA with enoxaparin versus continuous oral anticoagulation.^{165,166} The only demographic data available for both studies were on the age of the population, which appears to have differed significantly across the two studies (mean age 73–76 years in one study¹⁶⁵ and 55–56 years in the other¹⁶⁶) and sex (~83% male in one study,¹⁶⁵ 74% male in the other¹⁶⁶). Other risk factors for thromboembolism and bleeding were inconsistently reported between the two studies.

Major and Minor Bleeding

Major and minor bleeding events were reported by four of the five studies. In one study,¹⁶⁵ one patient experienced a major bleeding complication (1.4%) in the LMWH group versus none in the oral anticoagulation group at 16 ± 8 months followup. In the same study, minor bleeding complications occurred at a higher rate in the LMWH group compared with the oral anticoagulation group (5.7% vs. 2.8%). Similarly, in another study¹⁷¹ patients in the LMWH group exhibited higher rates of major bleeding than those in the oral anticoagulation group (9 vs. 0 patients, p < 0.001). In another study,¹⁶⁶ the in-hospital bleeding complication rate was not statistically different in the oral anticoagulation group compared with the LMWH group (18.4% vs. 18.2%, p=1.000), and the major bleeding rate was higher in the oral anticoagulation group (12.2%) than in the LMWH group (3.6%) but did not reach statistical significance (p=0.1444). In the study that assessed bridging anticoagulation during other operative procedures, only three major bleeding events were reported in the entire cohort (n=703).¹⁶⁷

Myocardial Infarction

Myocardial infarction events were not reported as an outcome in any of the included studies.

Mortality

There were no deaths reported in one report.¹⁶⁵ Two reports failed to comment on death explicitly, although one indicated no post-discharge thrombotic or bleeding complications.¹⁶⁶ One study reported five deaths in patients treated with warfarin post-RFA compared with none in those treated with aspirin; however, there was no attempt to correct for pre-procedural differences in these patients, and the difference was not statistically significant (p=0.59).¹⁷²

Other Thromboembolic Outcomes

In three studies,¹⁶⁵⁻¹⁶⁷ none of the patients experienced ischemic stroke, peripheral embolism, or other thromboembolic complications during followup. In one study,¹⁷¹ one patient in the LMWH full-dose group and two patients in the LMWH lower dose group developed ischemic stroke, but no patient developed ischemic stroke in the oral anticoagulation group (p=0.12). In

the study by Bunch et al, there were four CVA/TIA events in patients treated with warfarin compared with aspirin; however, there were multiple baseline differences for which no statistical modeling/correction was attempted.¹⁷²

Table 21 summarizes the strength of evidence for the various comparisons and outcomes of interest.

Table 21. Strength of evidence domains for anticoagulation strategies in patients undergoing invasive procedures

Outcome	Number of Studies (Subjects)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
PCI/Stenting						
Major bleeding	2 (263)	Observational/ Moderate	Inconsistent	Direct	Imprecise	SOE=Insufficient
Myocardial Infarction	2 (585)	Observational/ Moderate	Inconsistent	Direct	Imprecise	SOE=Insufficient
Mortality	2 (585)	Observational/ Moderate	Inconsistent	Direct	Imprecise	SOE=Insufficient
Bridging Therapies						
Major and minor bleeding	4 (1828)	Observational/ High	Inconsistent	Direct	Imprecise	SOE=Insufficient
Mortality	3 (874)	Observational/ High	Inconsistent	Direct	Imprecise	SOE=Insufficient
Other thromboembolic outcomes	5 (1932)	Observational/ High	Inconsistent	Direct	Imprecise	SOE=Insufficient

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

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

KQ 5. What are the comparative safety and effectiveness of available strategies for switching between warfarin and other novel oral anticoagulants, in patients with nonvalvular AF?

Key Points

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

Description of Included Studies

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

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

Detailed Synthesis

The RE-LY study protocol¹⁷³ advised providers to stop warfarin on the day of randomization and begin the assigned drug (dabigatran) when the INR fell below 2.0 (if randomized to dabigatran) or below 3.0 (if randomized to warfarin).

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

- “Discontinue warfarin and start Xarelto[®] [rivaroxaban] as soon as the INR is below 3.0 to avoid periods of inadequate anticoagulation.”¹⁷⁴
- “Discontinue warfarin and start Pradaxa[®] [dabigatran] when the INR is below 2.0.”¹⁷⁵

These statements do not reference any published evidence.

Finally, although we did not identify any relevant studies within the published literature, our search of ClinicalTrials.gov identified four clinical trials (two ongoing, two recently completed) that may provide data regarding optimal switching strategies between warfarin and other novel oral anticoagulants for patients with AF. These are described briefly in Table 22.

Table 22. Ongoing and recently completed trials relevant to KQ 5

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

Key Question 6. Stroke Prevention After a Hemorrhagic Event

KQ 6. What are the comparative safety and effectiveness of available strategies for resuming anticoagulation therapy or performing a procedural intervention as a stroke prevention strategy following a hemorrhagic event (stroke, major bleed, or minor bleed) in patients with nonvalvular AF?

Key Points

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

Description of Included Studies

There is no evidence to report that answers this question.

Detailed Synthesis

Although we did not identify any relevant studies within the published literature, future substudy analyses likely to be reported from three major RCTs (RE-LY,²⁶ ROCKET-AF,^{27,139} and ARISTOLE¹²¹) may provide data regarding optimal anticoagulation management strategies for patients with AF who have had prior bleeding events.

Discussion

Key Findings and Strength of Evidence

In this comparative effectiveness review (CER), we reviewed 74 unique studies represented by 96 publications and involving over 700,000 patients that evaluated stroke and bleeding prediction tools and stroke prevention strategies in patients with nonvalvular atrial fibrillation (AF). The current evidence base was greatest for the comparative safety and effectiveness of stroke prevention therapies and tools for predicting thromboembolic and bleeding risk; however, the evidence was very limited or nonexistent regarding AF patients undergoing invasive procedures, switching among anticoagulant therapies, and starting or restarting anticoagulant therapy in patients with previous major bleeding events.

KQ 1. Predicting Thromboembolic Risk

Our review included 31 studies comparing the diagnostic accuracy and impact on clinical decisionmaking of available clinical and imaging tools for predicting thromboembolic risk. The clinical tools assessed for this question included the CHADS₂ score (Congestive heart failure, Hypertension, Age ≥ 75 , Diabetes mellitus, prior Stroke/transient ischemic attack [2 points]), CHA₂DS₂-VASc score (Congestive heart failure/left ventricular ejection fraction $\leq 40\%$, Hypertension, Age ≥ 75 [2 points], Diabetes mellitus, prior Stroke/transient ischemic attack/thromboembolism [2 points], Vascular disease, Age 65–74, Sex category female), Framingham risk score, and imaging tools, as well as international normalized ratio (INR) monitoring for patients treated with warfarin. The reviewed studies had varying categorical arrangements of risk scores with patients receiving antiplatelet therapy and/or anticoagulant therapy or not, making direct comparisons across studies examining these tools difficult. The CHADS₂ and CHA₂DS₂-VASc continuous scores had the best prediction abilities given available evidence. Imaging risk tools found conflicting results when the presence of left atrial thrombus was assessed, and only one advanced imaging study utilizing magnetic resonance angiography (MRA)/magnetic resonance imaging (MRI) was reviewed.

Table 23 summarizes the strength of evidence for the predictive abilities of the included tools. This summary table represents only those studies that evaluated the predictive abilities of the tools using a c-statistic. Details about the specific components of these ratings (risk of bias, consistency, directness, and precision) are available in the Results section.

Table 23. Summary of strength of evidence and c-statistic estimate for KQ 1 (predicting thromboembolic risk)

Tool	Number of Studies (Patients)	Strength of Evidence and Effect Estimate ^a
CHADS ₂ (Categorical)	6 (210,033)	SOE=Insufficient
CHADS ₂ (Continuous)	7 (209,464)	SOE=Low Modest risk prediction (c-statistic=0.71; 95% CI, 0.65 to 0.77)
CHA ₂ DS ₂ -VASc (Categorical)	4 (161,373)	SOE=Insufficient
CHA ₂ DS ₂ -VASc (Continuous)	4 (201,620)	SOE=Low Modest risk prediction (c-statistic=0.71; 95% CI, 0.64 to 0.79)
Framingham (Categorical)	4 (88,962)	SOE=Moderate Limited risk prediction (c-statistic=0.62; 95% CI, 0.61 to 0.74)
Framingham (Continuous)	2 (80,928)	SOE=Insufficient
Imaging	0	SOE=Insufficient
INR	0	SOE=Insufficient

^aAll strength of evidence ratings of “Insufficient” are shaded in grey.

Abbreviations: CI=confidence interval; 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; INR=international normalized ratio; SOE=strength of evidence

KQ 2. Predicting Bleeding Events

Fifteen studies were included in our analyses comparing the diagnostic accuracy and impact on clinical decisionmaking of clinical tools and associated risk factors for predicting bleeding events. Six different bleeding risk scores were evaluated in these studies, all based on clinical parameters, including ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation), Bleeding Risk Index, CHADS₂, CHA₂DS₂-VASc, HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly [> 65 years], Drugs/alcohol concomitantly), and HEMORR₂HAGES (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).

Among the bleeding risk tools, HAS-BLED was the most predictive score in general. There was not sufficient evidence to make recommendations regarding CHADS₂ and CHA₂DS₂-VASc predictive accuracy for bleeding events, but the limited studies suggest that there is an increase in bleeding risk with increasing CHADS₂ score.

Table 24 summarizes the strength of evidence for the predictive abilities of the included tools. This summary table represents only those studies that evaluated the predictive abilities of the tools using a c-statistic. Details about the specific components of these ratings (risk of bias, consistency, directness, and precision) are available in the Results section.

Table 24. Summary of strength of evidence and c-statistic estimate for KQ 2 (predicting bleeding risk)

Tool	Number of Studies (Patients)	Strength of Evidence and Effect Estimate ^a
Summary c-statistic		
ATRIA	1 (3,063)	SOE=Insufficient
Bleeding Risk Score	3 (14,183)	SOE=Moderate Limited risk prediction (c-statistic ranging from 0.56 to 0.65)
HAS-BLED	3 (129,369)	SOE=Moderate Modest risk prediction (c-statistic ranging from 0.66 to 0.80)
HEMORR ₂ HAGES	5 (135,233)	SOE=Moderate Limited risk prediction (c-statistic=0.68; 95% CI, 0.61 to 0.74)
CHADS ₂	6 (155,220)	SOE=Insufficient
CHA ₂ DS ₂ -VASc	1 (132,372)	SOE=Insufficient
Comparative Predictive Abilities		
Major bleeding rates among patients with AF on warfarin	5 (142,346)	SOE=Low HAS-BLED tool appears to have the highest predictive accuracy
Major bleeding rates among patients with AF off of antithrombotic therapy	3 (14,576)	SOE=Low HAS-BLED tool appears to have the highest predictive accuracy
Major bleeding rates among patients with AF on aspirin alone	2 (7,247)	SOE=Low HAS-BLED tool appears to have the highest predictive accuracy

^aAll strength of evidence ratings of “Insufficient” are shaded in light grey.

Abbreviations: AF=atrial fibrillation; ATRIA=Anticoagulation and Risk Factors in Atrial Fibrillation; 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; HAS-BLED=Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (> 65 years), Drugs/alcohol concomitantly; HEMORR₂HAGES=Hepatic or renal disease, Ethanol abuse, Malignancy, Older (age >75 years), Reduced platelet count or function, Re-bleeding risk (2 points), Hypertension (uncontrolled), Anemia, Genetic factors, Excessive fall risk, Stroke; KQ=Key Question; SOE=strength of evidence

KQ 3. Interventions for Preventing Thromboembolic Events

Our review included 36 studies comparing the safety and effectiveness of specific anticoagulation therapies, antiplatelet therapies, and procedural interventions for preventing thromboembolic events. Among these studies, several new agents were evaluated including Factor II inhibitors (dabigatran) and novel Xa inhibitors (apixaban, edoxaban, rivaroxaban, idraparinux). Although the number of studies for any specific comparison of interest was limited, the included RCTs were often very large, of good quality, and considered definitive in the field. These trials were, however, limited by comparing novel therapies with warfarin or aspirin and have not involved head-to-head comparison among the newer agents.

In comparative effectiveness analyses, warfarin was found to be superior to aspirin for stroke prevention, and the combination of aspirin and clopidogrel was found to be superior to aspirin alone in patients with warfarin contraindications. Triple therapy with aspirin, clopidogrel, and warfarin did not provide any additional protection beyond warfarin alone, but increased bleeding events significantly. Percutaneous left atrial appendage (LAA) closure is non-inferior to warfarin, while novel antithrombotics (apixaban, rivaroxaban, dabigatran) were non-inferior or superior to warfarin for stroke prevention.

Table 25 summarizes the strength of evidence for the various comparisons and outcomes of interest. Details about the specific components of these ratings (risk of bias, consistency, directness, and precision) are available in the Results section.

Table 25. Summary of strength of evidence and effect estimate for KQ 3 (interventions for preventing thromboembolic events)

Outcome	Number of Studies (Subjects)	SOE and Magnitude of Effect ^a (95% CI)
ASA versus Warfarin		
Ischemic stroke	2 (99,061)	SOE=Moderate Two retrospective studies showing consistent reduction in stroke for patients on warfarin compared to ASA
Bleeding	2 (99,061)	SOE=Moderate Warfarin is associated with increased rates of severe bleeding
All-cause mortality	1 (601)	SOE=Insufficient
Warfarin + ASA versus Warfarin		
Ischemic stroke	1 (69,264)	SOE=Moderate HR 1.27 (95% CI, 1.14 to 1.40) increase in warfarin + ASA arm
Bleeding	1 (69,264)	SOE=Moderate HR 1.83 (95% CI, 1.72 to 1.96) increase in warfarin + ASA arm
Clopidogrel + ASA versus ASA		
Any stroke	2 (8,147)	SOE=Low One large RCT showing similar rates (HR 1.03 [95% CI, 0.49 to 2.13]), but another smaller study showed significant reduction in clopidogrel + ASA arm (HR 0.72 [95% CI, 0.62 to 0.83]); low strength of evidence of similar rates of stroke between treatment arms
Ischemic stroke	2 (8,147)	SOE=Low One large RCT showing similar rates (HR 0.96 [95% CI, 0.46 to 2.01]), but another smaller study showed significant reduction in clopidogrel + ASA arm (HR 0.68 [95% CI, 0.57 to 0.80]); low strength of evidence of similar rates of stroke between treatment arms
Hemorrhagic stroke	2 (8,147)	SOE=Moderate Similar between treatment groups in both studies
Major bleeding	1 (7,554)	SOE=High Clopidogrel + ASA associated with higher rates (HR 1.57 [95% CI, 1.29 to 1.92])
Intracranial bleeding	2 (8,147)	SOE=Low One large RCT showing higher rate with clopidogrel + ASA (HR 1.87 [95% CI, 1.19 to 2.94]), but other study showed other showed no difference (0.62)
Extracranial bleeding	2 (8,147)	SOE=Low One large RCT showing higher rate with clopidogrel + ASA (HR 1.51 [95% CI, 1.21 to 1.88]), but other study showed other showed no difference (0.51)
All-cause mortality	2 (8,147)	SOE=Moderate Did not differ between arms in either study (in the 2 studies, HR 0.98 [95% CI, 0.89 to 1.08] and HR 1.12 [95% CI, 0.65 to 1.90])
Death from vascular causes	2 (8,147)	SOE=Moderate Did not differ between arms in either study (in the 2 studies, HR 1.00 [95% CI, 0.89 to 1.12] and HR 1.68 [95% CI, 0.83 to 3.42])
Myocardial infarction	2 (8,147)	SOE=Moderate Did not differ between arms in either study (in the 2 studies, HR 0.78 [95% CI, 0.59 to 1.03] and HR 1.43 [95% CI, 0.51 to 4.01])
Clopidogrel versus 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 groups (HR 1.06 [95% CI, 0.87 to 1.29])

Outcome	Number of Studies (Subjects)	SOE and Magnitude of Effect ^a (95% CI)
Clopidogrel + ASA versus Warfarin		
Stroke or systemic embolism	2 (60,484)	SOE=High Clopidogrel + ASA increased risk (in the 2 studies, HR 1.56 [95% CI, 1.17 to 2.10] and HR 1.72 [95% CI, 1.24 to 2.37])
Hemorrhagic stroke	1 (6,706)	SOE=Moderate Increased risk in warfarin group (HR 0.34 [95% CI, 0.12 to 0.93])
Major bleeding	2 (60,484)	SOE=Low Large RCT showed no difference (HR 1.10 [95% CI, 0.83 to 1.45]), retrospective study showed greater risk in clopidogrel + ASA arm (HR 1.66 [95% CI, 1.34 to 2.04]); low strength of evidence of similar rates of major bleeding between treatment arms
Intracranial bleeding	1 (6,706)	SOE=Insufficient
All-cause mortality	1 (6,706)	SOE=High No difference (HR 1.01 [95% 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 MI occurred at rates of less than 1% per year in both groups and was not significantly different between treatments
Clopidogrel + Warfarin versus Warfarin		
Ischemic stroke	1 (52,349)	SOE=Low No difference between treatments (HR 0.70 [95% 0.35 to 1.40])
Bleeding	1 (52,349)	SOE=Moderate Higher for patients on clopidogrel + warfarin (HR 3.08 [95% CI, 2.32 to 3.91])
Warfarin + ASA + Clopidogrel versus Warfarin		
Ischemic stroke	1 (52,180)	SOE=Low No difference between treatments (HR 1.45 [95% CI, 0.84 to 2.52])
Bleeding	1 (52,180)	SOE=Moderate Higher for patients on clopidogrel + warfarin (HR 3.70 [95% CI, 2.89 to 4.76])
Factor II Inhibitor (Dabigatran 150 mg) versus Warfarin		
Stroke or systemic embolism	1 (12,098)	SOE=High Dabigatran reduced risk (HR 0.66 [95% CI, 0.53 to 0.82])
Ischemic or uncertain stroke	1 (12,098)	SOE=Moderate Dabigatran reduced risk (HR 0.76 [95% CI, 0.60 to 0.98])
Hemorrhagic stroke	1 (12,098)	SOE=High Dabigatran reduced risk (HR 0.26 [95% CI, 0.14 to 0.49])
Major bleeding	1 (12,098)	SOE=High No difference (HR 0.93 [95% CI, 0.81 to 1.07])
Intracranial bleeding	1 (12,098)	SOE=High Dabigatran reduced risk (HR 0.40 [95% CI, 0.27 to 0.60])
All-cause mortality	1 (12,098)	SOE=Moderate No difference (HR 0.88 [95% CI, 0.77 to 1.00])
Death from vascular causes	1 (12,098)	SOE=Moderate Dabigatran reduced risk (HR 0.85 [95% CI, 0.72 to 0.99])
Myocardial infarction	1 (12,098)	SOE=Moderate Dabigatran increased risk (HR 1.38 [95% CI, 1.00 to 1.91])
Adverse events	1 (12,098)	SOE=Moderate Dyspepsia was more common with dabigatran (11.3% of patients with 150 mg compared with 5.8% with warfarin, p<0.001). No differences in liver function or other adverse events were seen between groups.

Outcome	Number of Studies (Subjects)	SOE and Magnitude of Effect ^a (95% CI)
Factor II Inhibitor (Dabigatran 110 mg) versus Warfarin		
Stroke or systemic embolism	1 (12,037)	SOE=High No difference (HR 0.91 [95% CI, 0.74 to 1.11])
Ischemic or uncertain stroke	1 (12,037)	SOE=Moderate No difference (HR 1.11 [95% CI, 0.89 to 1.40])
Hemorrhagic stroke	1 (12,037)	SOE=High Dabigatran reduced risk (HR 0.31 [95% CI, 0.17 to 0.56])
Major bleeding	1 (12,037)	SOE=High Dabigatran reduced risk (HR 0.80 [95% CI, 0.69 to 0.93])
Intracranial bleeding	1 (12,037)	SOE=High Dabigatran reduced risk (HR 0.31; 95% CI, 0.20 to 0.47))
All-cause mortality	1 (12,037)	SOE=Moderate No difference (HR 0.91 [95% CI, 0.80 to 1.03])
Death from vascular causes	1 (12,037)	SOE=Moderate No difference (HR 0.90 [95% CI, 0.77 to 1.06])
Myocardial infarction	1 (12,037)	SOE=Moderate Dabigatran increased risk (HR 1.35 [95% CI, 0.98 to 1.87])
Adverse events	1 (12,037)	SOE=Moderate Dyspepsia was more common with dabigatran (11.8% of patients with 110 mg compared with 5.8% with warfarin, p<0.001). No differences in liver function or other adverse events were seen between groups.
Xa Inhibitor (apixaban) versus 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 No difference (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])
Intracranial bleeding	1 (5,599)	SOE=Moderate No difference (HR 0.85 [95% CI, 0.38 to 1.90])
All-cause mortality	1 (5,599)	SOE=Moderate No difference (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])
Adverse events	1 (5,599)	SOE=Moderate No differences in liver function or other adverse events were seen between groups
Xa Inhibitor (apixaban) versus Warfarin		
Stroke or systemic embolism	1 (18,201)	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])
Major bleeding	1 (18,201)	SOE=High Apixaban reduced risk (HR 0.69 [95% CI, 0.60 to 0.80])
All-cause mortality	1 (18,201)	SOE=Moderate Apixaban reduced risk (HR 0.89 [95% CI, 0.80 to 0.998])

Outcome	Number of Studies (Subjects)	SOE and Magnitude of Effect^a (95% CI)
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])
Intracranial bleeding	1 (18,201)	SOE=High Apixaban reduced risk (HR 0.42 [95% CI, 0.30 to 0.58])
Adverse events	1 (18,201)	SOE=Moderate Adverse events occurred in almost equal proportions of patients in the apixaban group and the warfarin group (81.5% and 83.1%, respectively). Rates of abnormalities on liver function testing and liver-related serious adverse events were also similar in the two groups.
Xa Inhibitor (rivaroxaban) versus Warfarin		
Stroke or systemic embolism	1 (14,264)	SOE=High Rivaroxaban reduced risk (HR 0.79 [95% CI, 0.65 to 0.95])
Major bleeding	1 (14,264)	SOE=High No difference (HR 1.04 [95% CI, 0.90 to 1.20])
All-cause mortality	1 (14,264)	SOE=High No difference (HR 0.85 [95% CI, 0.70 to 1.02])
Myocardial infarction	1 (14,264)	SOE=High No difference (HR 0.81 [95% CI, 0.63 to 1.06])
Intracranial bleeding	1 (14,264)	SOE=High Rivaroxaban reduced risk (HR 0.67 [95% CI, 0.47 to 0.93])
Percutaneous LAA Closure versus Warfarin		
Ischemic stroke	1 (707)	SOE=Low 9 patients in the LAA group (1.3 events per 100 patient-years) and 6 patients in the warfarin group (1.6 events per 100 patient-years) had ischemic stroke.
All strokes	1 (707)	SOE=Moderate No difference (RR 0.71 [95% CI, 0.35 to 1.64])
Major bleeding	1 (707)	SOE=Low Less frequent in the LAA group than in the warfarin group (3.5% vs. 4.1%)
All-cause mortality	1 (707)	SOE=Moderate No difference (RR 0.62 [95% CI, 0.34 to 1.24])
Adverse events	1 (707)	SOE=Moderate Higher rate in LAA group (RR 1.69 [95% CI, 1.01 to 3.19])

^aAll strength of evidence ratings of “Insufficient” are shaded in light grey.

Abbreviations: ASA=aspirin; CI=confidence interval; HR hazard ratio; LAA=left atrial appendage; RCT=randomized controlled trial; RR=relative risk; SOE=strength of evidence

KQ 4. Anticoagulation Strategies in Patients Undergoing Invasive Procedures

We identified eight studies that assessed the comparative safety and effectiveness of available strategies for anticoagulation in patients with nonvalvular AF who are undergoing invasive procedures. These studies differed in design and invasive procedure, and they encompassed a wide variety of anticoagulation strategies, making synthesis of the findings difficult. Across the outcomes, the studies were often inconsistent, but given the variability described immediately above, the reasons for these inconsistencies are uncertain. As Table 26 below demonstrates, we had insufficient evidence to draw conclusions about any of the outcomes of interest in this KQ. Details about the specific components of these ratings (risk of bias, consistency, directness, and precision) are available in the Results section.

Table 26. Summary of strength of evidence and effect estimate for KQ 4 (anticoagulation therapies for patients undergoing invasive procedures)

Outcome	Number of Studies (Patients)	Strength of Evidence and Effect Estimate ^a
PCI/Stenting		
Major bleeding	2 (263)	SOE=Insufficient
Myocardial infarction	2 (585)	SOE=Insufficient
Mortality	2 (585)	SOE=Insufficient
Bridging Therapies		
Major and minor bleeding	4 (1,828)	SOE=Insufficient
Mortality	3 (874)	SOE=Insufficient
Other thromboembolic outcomes	5 (1,932)	SOE=Insufficient

^aAll strength of evidence ratings of “Insufficient” are shaded in light grey.

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

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

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

KQ 6. Stroke Prevention After a Hemorrhagic Event

We did not identify any relevant studies to assess the comparative safety and effectiveness of available strategies for resuming anticoagulation therapy or performing a procedural intervention as a stroke prevention strategy following a hemorrhagic event (stroke, major bleed, or minor bleed) in patients with nonvalvular AF. Although an important clinical question needing future research, the current evidence was insufficient to support any findings concerning this KQ.

Findings in Relationship to What is Already Known

At the time the current U.S. guidelines for management of AF were developed (developed in 2006 and then the topic of a focused update in 2011) 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 (namely dabigatran, rivaroxaban, and apixaban), but the guidelines have not yet been updated to reflect this new evidence. Our systematic review provides a timely review of the evidence both in stroke prediction and prevention in the new era of oral anticoagulants and potential stroke prevention therapies.

The need to ensure adequate benefit given the known bleeding risks of warfarin has led to the development of risk scores for thromboembolism and bleeding in patients with AF to help inform therapeutic decisions. Risk scores for prediction of these events have been touted as a way of guiding antithrombotic therapy in patients with AF. In the current CER, we found that of the available risk scores, the CHADS₂ and CHA₂DS₂VASc scores are the most commonly studied. A bleeding score, HAS-BLED, has recently been developed and was also reviewed. Although the CHADS₂, CHA₂DS₂VASc, and HAS-BLED scores aid in estimating the risk of stroke and bleeding in patients with AF and help guide decisions regarding the use of warfarin,

the value of these scores in guiding decisionmaking in patients with AF receiving other agents is still emerging but is currently limited to randomized controlled trials (RCTs). Therefore, it is important to demonstrate that the efficacy and safety of new anticoagulants, such as dabigatran, rivaroxaban and apixaban, are consistent across a broader patient profile with different risk of stroke and bleeding which was limited in our review of the currently available literature. Recent clinical trials have suggested that the benefits of the new agents when compared to warfarin are consistent and preserved across the full spectrum of patient risk groups, regardless of which scoring system (CHADS₂, CHA₂DS₂VASc, or HAS-BLED) is used. In general, it also seems that the benefits of the new agents compared with warfarin are consistent in most key subgroups of patients. However, further improvement in the tools and methods for risk stratification of both stroke and bleeding seems important to better individualize treatment with novel oral anticoagulants in patients with AF.

With more available treatments, our review suggests that not only do risk algorithms need to be updated, but physician decisionmaking about when to use which agent does as well. When anticoagulating a patient with an acute coronary syndrome, for example, physicians have an extensive array of effective parenteral and oral agents from which to choose. However, until very recently, there was only one established oral anticoagulant available for stroke prophylaxis in patients with AF. This single-agent agent—warfarin—while effective when compared with placebo or antiplatelet agents such as aspirin, is associated with significant limitations from both the health system and patient perspectives. Historically, this fundamental lack of choices in oral anticoagulation in AF was particularly challenging, given the significant heterogeneity present in the increasingly elderly AF population. In the setting of multiple limitations of current treatment with warfarin or other vitamin K antagonists (VKAs), several new oral anticoagulants have been developed for stroke prevention in nonvalvular AF. Trials of dabigatran, rivaroxaban, and apixaban have demonstrated favorable efficacy and safety results compared with warfarin, but direct comparisons of their efficacy and safety are not possible because these medications have not been compared with one another. In addition, the trials used different dosing strategies, were performed in different health systems, used varying event definitions, and recruited populations at varying risk for stroke and bleeding. Thus, it is not possible to affirm here which medication is better, and cross-trial comparisons may not be reliable. The newer oral anticoagulants do, however, have different attributes and important advantages over warfarin and offer, after many years without options, new alternatives for the treatment of patients with nonvalvular AF who are at risk for stroke. 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 some of them have been demonstrated in large RCTs to be more effective than warfarin (apixaban and higher dose dabigatran)
- In addition to these stroke prevention benefits, these new oral anticoagulants appear to be safer than warfarin in that:
 - All of them caused less intracranial bleeding than warfarin.
 - Some of them (apixaban or dabigatran [lower dose]) caused less major bleeding, including gastrointestinal bleeding, than warfarin.
- Apixaban was more effective than aspirin in stroke prevention for patients not suitable for oral anticoagulation. In addition, apixaban was better tolerated than and as safe as aspirin.

- All the new oral anticoagulants were better tolerated than warfarin, and rates of study drug discontinuation were lower with the new agents when compared with warfarin.
- Recent evidence showed that for the first time a new oral anticoagulant agent (apixaban) reduced all-cause mortality in patients with AF.

Despite all the potential advantages of the new drugs demonstrated in the clinical trials when compared to warfarin, the new drugs still do not have a well-validated and studied immediate antidote. It is, however, important to note that the shorter half-life of these drugs is a key feature that helps in the management of bleeding episodes in patients receiving these drugs.

Applicability

Efficacy of interventions as determined in RCTs does not always translate to usual practice, where patient characteristics, provider clinical training, and available resources may differ from trial conditions. Additionally, the availability and/or specific features of interventions studied in our review may differ from those available to patients within the United States.

Studies were conducted wholly or partly in continental Europe (47%), the United States or Canada (31%), Asia (19%), the UK (15%), South or Central America (7%), Australia or New Zealand (7%), Africa (4%), and unspecified or other locations (7%). Table 27 illustrates the specific issues with the applicability of our included evidence base by KQ.

Table 27. Potential issues with applicability of included studies

Issues	Key Question						
	KQ 1 N=31	KQ 2 N=15	KQ 3 N=36	KQ 4 N=8	KQ 5 N=0	KQ 6 N=0	Total N=78
Population (P)							
Narrow eligibility criteria and exclusion of those with comorbidities	0	0	1	0	0	0	1
Large differences between demographics of study population and community patients	2	0	2	0	0	0	4
Narrow or unrepresentative severity, stage of illness, or comorbidities	0	0	0	0	0	0	0
Run-in period with high exclusion rate for nonadherence or side effects	0	0	1	0	0	0	1
Event rates much higher or lower than observed in population-based studies	0	0	1	0	0	0	1
Intervention (I)							
Doses or schedules not reflected in current practice	0	0	1	0	0	0	1
Monitoring practices or visit frequency not used in typical practice	1	2	0	0	0	0	3
Older versions of an intervention no longer in common use	2	1	1	0	0	0	4
Cointerventions that are likely to modify effectiveness of therapy	0	0	1	0	0	0	1
Highly selected intervention team or level of training/proficiency not widely available	0	1	0	0	0	0	1

Issues	Key Question						
	KQ 1 N=31	KQ 2 N=15	KQ 3 N=36	KQ 4 N=8	KQ 5 N=0	KQ 6 N=0	Total N=78
Comparator (C)							
Inadequate comparison therapy	0	0	2	0	0	0	2
Use of substandard alternative therapy	0	0	0	0	0	0	0
Outcomes (O)							
Composite outcomes that mix outcomes of different significance	1	1	2	0	0	0	4
Short-term or surrogate outcomes	1	0	5	0	0	0	6
Setting (S)							
Standards of care differ markedly from setting of interest	0	0	0	0	0	0	0
Specialty population or level of care differs from that seen in community	0	0	0	0	0	0	0

Abbreviation: KQ=Key Question

In general, concerns about study applicability were not a major factor for this project's body of evidence. As demonstrated in Table 27, the main issues related to applicability of the evidence base included concerns about short-term outcomes (8% of studies), concerns about large differences between demographics of study populations and community patients (5% of studies) concerns about composite outcomes that mix outcomes of different significance (5% of studies), and concerns about use of older versions of an intervention no longer in common use (5% of studies).

Implications for Clinical and Policy Decisionmaking

Stroke prevention in patients with nonvalvular AF in contemporary clinical practice is complex and challenging, but critically important given the morbidity and mortality associated with stroke events. The use of common antiplatelet agents such as aspirin and traditional anticoagulants can significantly reduce the risk of stroke in patients with AF, however, bleeding risks increase with these agents, potentially attenuating their effects. Newer anticoagulants promise improved efficacy with reduction in bleeding events and more predictable pharmacokinetics. However, the long-term effects of these newer agents in broad populations have not been established, and early observational data suggest that their bleeding risks may have been underestimated in clinical trials. Therefore, clinicians are constantly struggling to find the right balance between efficacy and risk in the use of these therapies in this patient population.

Despite the availability and validation of numerous risk tools for both stroke and bleeding risk in patients with nonvalvular AF, evidence has shown that the routine use of these tools is low, and patients are paradoxically treated (e.g., low-risk patients with anticoagulants and high-risk patients with antiplatelet or no therapy). At the time the current U.S. guidelines for management of AF were developed (developed in 2006 and then the topic of a focused update in 2011) 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, but the guidelines have not yet been updated to reflect this new evidence. Furthermore, there have not been any comparative effectiveness studies examining these new agents head-to-head, and with more agents soon to be approved in the United States, the task of

stroke prevention for busy clinicians is no longer simply risk stratification and deciding between aspirin versus warfarin, but much more complex. Clinicians will have to understand the risk and benefits, indications, side effects, and monitoring of new anticoagulants, further complicating treatment decisions in patients with AF.

The current review underscores that further efforts are needed to continue to refine risk prediction tools, particularly in the context of newly available anticoagulants. 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, possibly in the form of physician decision support tools, will be important for clinical decisionmaking. Finally, many gaps have been identified in the current evidence for increasingly common clinical scenarios for patients on therapies for stroke prevention. Increased evidence and recommendations are needed for patients undergoing invasive procedures, switching among anticoagulant therapies, and starting or restarting anticoagulant therapy in patients with previous major bleeding events.

As new drugs are introduced, determining their relative risks and benefits in the overall scheme for stroke prevention in AF is critically important in order to minimize the use of less efficacious, less safe, and more expensive therapies. Although the results of the current review are largely consistent with existing guidelines, they do help identify gaps in the evidence base and areas of needed future research, particularly as newer agents are rapidly entering into broader clinical practice.

Limitations of the Evidence Base and the Comparative Effectiveness Review Process

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

Our review methods also had limitations. Our study was limited to English-language publications. It was the opinion of the investigators and the Technical Expert Panel (TEP) that the resources required to translate non-English articles would not be justified by the low potential likelihood of identifying relevant data unavailable from English-language sources. We also limited our analysis to studies published since 2000. Given the rapidly changing treatment alternatives for stroke prevention for patients with AF it was the opinion of the investigators and the TEP that this recent literature was the most relevant to today's clinical and policy uncertainties. Finally, as a comparative effectiveness study, for KQ3 we restricted our analysis to studies that compared two active therapies for AF stroke prevention and did not include placebo (only)-controlled trials. Inclusion of such placebo-controlled trials may have allowed additional quantitative analyses to be performed used mixed treatment meta-analyses. We did not perform meta-analysis using indirect comparisons of treatment given the heterogeneity of study designs, therapies, populations, and concomitant therapies in the included studies.

Research Gaps

In our analyses, we have identified research gaps for all the Key Questions (KQs) examined, including research gaps in the areas of risk stratification for thromboembolic and bleeding risk, comparative effectiveness and safety of different anticoagulation strategies, as well as the comparative effectiveness and safety of changing anticoagulation treatments for different reasons. We used the framework recommended by Robinson et al. to identify gaps in evidence and describe why these gaps exist.¹⁷⁶ This approach considers PICOTS (Populations, Interventions, Comparators, Outcomes, Timings, and Settings of interest) to identify gaps and classifies gaps as due to (a) insufficient or imprecise information; (b) biased information; (c) inconsistency or unknown consistency; and (d) not the right information. Results are described for each KQ below.

KQs 1–2: Predicting Thromboembolic and Bleeding Risk

While there are several scores available in clinical practice to predict stroke and bleeding in patients with AF, the major limitation of these scores is the overlap of clinical factors that goes 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 standard deviation of transformed international normalized ratio (SDT_{INR}) and time in therapeutic range (TTR) are needed to establish which variable has better predictive accuracy for major bleeding.

Also of note, although not addressed in this review, in an era of personalized medicine, it will 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.

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

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

1. In patients with nonvalvular AF, what are the comparative diagnostic accuracy and impact on clinical decisionmaking of clinical tools with modest or better predictive value for predicting the overall clinical risk of patients combining both their risk of stroke and their risk of bleeding?
2. In patients with nonvalvular AF, what are the comparative diagnostic accuracy and impact on clinical decisionmaking of imaging tools with modest or better predictive value for predicting the overall clinical risk of patients combining both their risk of stroke and their risk of bleeding?

3. What are the benefits, harms, and costs of incorporating genomics, proteomics, and metabolomics into risk scores for the prediction of thromboembolic and/or bleeding risk?
4. What is the most effective way to prospectively use thromboembolic and/or bleeding risk scores with evidence of modest or better predictive value in clinical practice?
Specifically, how can we increase dissemination of point-of-care tools to improve risk assessment and treatment choices for clinicians?

KQ 3: Interventions for Preventing Thromboembolic Events

Although recent years have been exciting in stroke prevention and development of new agents as alternatives to warfarin, there are several evidence gaps that remain and should inform future research needs. Given the risks associated with AF, the growing number of patients with AF, and the costs and risks associated with stroke prevention for AF, our review highlights that a better understanding of comparative safety and effectiveness of newer anticoagulant therapies is of paramount importance. There is 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. 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 other comorbidities that also require the use of other antithrombotic agents. There are many antithrombotic agents 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 area with new antiplatelet (prasugrel and ticagrelor) and new anticoagulant agents (dabigatran, rivaroxaban, apixaban).

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

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

1. What are the comparative safety and effectiveness of specific anticoagulation therapies, antiplatelet therapies, and procedural interventions for preventing thromboembolic events?
 - a. For the above evidence gap, we suggest focusing specifically on the comparative effectiveness of Factor II inhibitors, Xa inhibitors, and other novel anticoagulants and procedural interventions.
2. What are the comparative safety and effectiveness of specific anticoagulation therapies, antiplatelet therapies, and procedural interventions for preventing thromboembolic events specific to patients who have recently undergone rate or rhythm control procedures for treating their AF?

- a. For the above evidence gap, we suggest focusing on methods of determining the comparative effectiveness and safety of available stroke prevention therapies, and strategies for determining longer term therapy given successful AF treatment.

KQ 4: Anticoagulation Strategies in Patients Undergoing Invasive Procedures

Our review identified limited studies assessing the optimal strategy for anticoagulation either peri-radiofrequency ablation (RFA) or in the setting of other operative procedures. In addition, the few studies available suggest that ischemic event rates are likely to be extremely low; thus, trials powered adequately to assess the impact of different strategies, especially on ischemic events, would have to be large. Nonetheless, given the number of these procedures performed per year as well as the apparent uncertainty about optimal treatment of these patients, 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 numbers of treatment strategies available, initial research might be focused on comparing on continued anticoagulant therapy versus bridging therapies versus interruption of therapy (i.e., stopping anticoagulant therapy pre-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 required of an RCT to address this question, would be explore whether study designs other than RCTs would possible help decrease the evidence gap in this area.

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

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

Due to the increasing popularity of the new Xa agents, RCTs are needed to establish evidence to guide providers in managing patients with AF who are currently on warfarin and being switched to the newer Xa agents. Trials that include directions for managing patients who may be at different risk levels (as defined by CHADS₂ or Framingham risk scores), including type of AF, sex, age, and other co-existing risk factors. Additionally, evidence needs to be published in peer-reviewed journals on how to manage patients being switched off of the newer Xa agents and onto warfarin.

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

Conclusions

Patients with nonvalvular AF are at high risk for suffering from thromboembolic events. Given the morbidity and mortality related to stroke, the main goal of AF management is stroke prevention. There are currently two mainstays of stroke prevention therapy in patients with AF: antiplatelet agents and anticoagulants. However, the choice of therapy depends on the relative risk for thromboembolic events in individual patients, as stroke prevention therapy carries the

risk of minor and major bleeding events which must be weighed against the stroke prevention benefit of these therapies. As a result, accurate risk prediction tools for both stroke events and bleeding events on therapy are critical in the clinical decisionmaking for AF management.

In this CER, we examined the literature for quantitative assessment of the numerous clinical and imaging stroke risk prediction tools and bleeding risk prediction tools. We also investigated the comparative effectiveness of antiplatelet agents, anticoagulation agents, and procedures for stroke prevention. Finally, we evaluated the evidence for the modern clinical dilemmas of anticoagulation strategies in patients undergoing invasive procedures, switching between warfarin and novel anticoagulants, and stroke prevention after a hemorrhagic stroke.

Overall, we found that CHADS₂ and CHA₂DS₂-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 initial early promise of reducing stroke and bleeding events when compared with warfarin, and apixiban in particular 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.

Our CER highlights clear opportunities for future evidence generation in the gaps of care of AF patients and stroke prevention. Additional research on improving the tools and comparative effectiveness of newer agents, as well as strategies for starting on continuing therapy in high risk patients, is warranted.

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Abbreviations

AF	atrial fibrillation
AHRQ	Agency for Healthcare Research and Quality
ASA	aspirin
ATRIA	Anticoagulation and Risk Factors in Atrial Fibrillation
BRI	Bleeding Risk Index
CDSR	Cochrane Database of Systematic Reviews
CER	Comparative Effectiveness Review
CHADS ₂	Congestive heart failure, Hypertension, Age ≥ 75 , Diabetes mellitus, prior Stroke/transient ischemic attack (2 points)
CHA ₂ DS ₂ -VASc	Congestive heart failure/left ventricular ejection fraction $\leq 40\%$, Hypertension, Age ≥ 75 (2 points), Diabetes mellitus, prior Stroke/transient ischemic attack/thromboembolism (2 points), Vascular disease, Age 65–74, Sex category female
CI	confidence interval
CT	computed tomography
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 ₂ HAGES	Hepatic or renal disease, Ethanol abuse, Malignancy, Older (age > 75 years), Reduced platelet count or function, Re-bleeding risk (2 points), Hypertension (uncontrolled), Anemia, Genetic factors, Excessive fall risk, Stroke
HR	hazard ratio
ICH	intracranial hemorrhage
ICTRP	International Clinical Trials Registry Platform
INR	international normalized ratio
IV	intravenous
KQ	Key Question
LAA	left atrial appendage
LMWH	low molecular weight heparin
MRA	magnetic resonance angiography
MRI	magnetic resonance imaging
OR	odds ratio
PCI	percutaneous coronary intervention
PICOTS	Populations, Interventions, Comparators, Outcomes, Timings, and Settings of interest
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QUADAS-2	QUality Assessment tool for Diagnostic Accuracy Studies-2
RCT	randomized controlled trial

RFA	radiofrequency ablation
RR	relative risk
SDT _{INR}	standard deviation of transformed international normalized ratio
SE	standard error
TIA	transient ischemic attack
TEE	transesophageal echocardiography
TEP	Technical Expert Panel
TTE	transthoracic echo
TTR	time in therapeutic range
VKA	vitamin K antagonist
WHO	World Health Organization