

Evidence-based Practice Center Systematic Review Protocol

Project Title: Stroke Prevention in Atrial Fibrillation

I. Background and Objectives for the Systematic Review

Epidemiology of Atrial Fibrillation

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 seen in clinical practice, accounting for approximately one-third of hospitalizations for cardiac rhythm disturbances. The estimated prevalence of AF is 0.4 percent to 1 percent in the general population,^{2,3} occurring in about 2.2 million people in the United States. The prevalence increases to about 6 percent in people age 65 or older and to 10 percent in people age 80 or older.⁴ Management of AF involves three distinct areas, namely, rate control, rhythm control, and prevention of thromboembolic events. This project will focus on the last area. A second comparative effectiveness review focusing on the treatment of AF through rate or rhythm control is being performed in parallel.

Atrial Fibrillation and Stroke

Although generally not as immediately life-threatening as ventricular arrhythmias, AF is associated with significant morbidity and mortality. Patients with AF have increased risk of embolic stroke, heart failure, and cognitive impairment; reduced quality of life; and higher overall mortality.⁵⁻⁷ 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 more likely to result in death.⁸⁻¹⁰ Consistent with the nature of these events, AF-related stroke constitutes a significant economic burden, costing Medicare approximately \$8 billion annually.¹¹

The rate of ischemic stroke among patients with nonvalvular AF averages 5 percent per year, 2 to 7 times that of the general population.⁸ The risk of stroke increases from 1.5 percent for patients with AF who are 50 to 59 years old to 23 percent for those who are 80 to 89 years old.⁹ 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 CHADS2 score.^{12,13} This score ranges from 0 to 6 (with increasing scores corresponding to increasing stroke risk) and is easy to calculate and apply in clinical practice.¹ The adjusted annual rates of stroke vary from 1.9 percent in patients with a 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 independent of or as a result of AF.

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Much of the focus of AF management has been on treatment strategies for stroke prevention. Antithrombotic and antiplatelet therapies are the mainstays used to prevent thromboembolic events in patients with AF. Oral antiplatelet agents and systemic anticoagulation have been shown to reduce the risk of stroke by two-thirds. Unfortunately, two critical issues regarding stroke prevention in AF remain: 1) despite existing evidence, only a minority of patients who have AF and are at risk for stroke receive optimal treatment for thromboembolic prevention,¹ and 2) patients with AF on stroke prophylaxis still have higher rates of stroke than patients who do not have AF, suggesting that gaps still exist in our understanding of risk stratification and treatment. With the advent of newer systemic anticoagulants for stroke prevention, medical decisionmaking for identifying high-risk patients and choosing the optimal treatment will become even more complex.

Current Evidence for Risk Stratification and Stroke Prevention

Risk Stratification

A number of studies have examined the appropriate populations and appropriate therapies for adequate 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.¹² However, because of the overlap with factors also associated with increased risk of bleeding, the CHADS2 score seems to be underused to appropriately guide the decision of antithrombotic therapy.

The current underutilization of risk assessments could be due to: perceived lack of convincing studies or evidence to support routine use, limited comparative studies on different risk tools, difficulty in applying assessments at the bedside, clinical inertia, inadequate provider education of existence and use of tools, et cetera. Independent assessments of the currently available risk-assessment tools for thromboembolic events and major bleeding episodes are required to highlight the relative strengths of individual 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 improves outcomes and providing a clinical guidance document could help improve the utility of their use in clinical practice.

Additionally, the use of imaging to assess thromboembolic risk has not been formally reviewed to date. Elucidating 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 preventing 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).¹⁴ In a meta-analysis of 29 randomized clinical trials (RCTs) including

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28,000 patients with nonvalvular AF, warfarin therapy led to a 64 percent reduction in stroke (95 percent confidence interval [95% CI], 49 to 74 percent) when compared to placebo. Even more importantly, warfarin therapy was associated with a 26 percent reduction in all-cause mortality (95% CI, 3 to 34 percent).¹⁵

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 when compared with patients already on warfarin.^{16,17} 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.^{18,19} One out of three Medicare patients with AF who is eligible for anticoagulation therapy is not prescribed warfarin. In the Get With The Guidelines registry, only 65 percent of eligible patients with heart failure and AF were prescribed warfarin at discharge.^{20,21} Unfortunately, use of warfarin in the Get With The Guidelines quality-improvement program did not improve over time, and if warfarin was not prescribed at discharge after a stroke related to AF, then its initiation in eligible patients was low in the ambulatory setting. Thus, a large number of patients with AF who could benefit from warfarin are 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 their use. For example, left atrial appendage (LAA) occlusive devices are an alternative treatment strategy used to prevent blood clot formation in patients with AF. For patients with AF who are elderly (at high risk for falls), have a history of bleeding, are pregnant, and/or are not compliant with treatment (which can be a significant issue for those on warfarin), LAA occlusion may be a better stroke prevention strategy. 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 VKA for stroke prophylaxis in AF. Since 2007, three large trials comparing novel anticoagulants to VKA have been completed, with a combined sample size of ~50,000 subjects:

- Re-LY, with approximately 18,000 subjects and the new direct factor II (thrombin) dabigatran (Connolly et al. *N Engl J Med* 2009;361(12):1139-51²²)
- ROCKET AF, with approximately 14,000 subjects and the new direct factor X inhibitor rivaroxaban (presented to the American Heart Association in 2010 and due to be published early 2011; rationale and design already published [ROCKET AF Study Investigators. *Am Heart J* 2010;159(3):340-7²³])
- ARISTOTLE, with approximately 14,000 subjects and the new direct factor X inhibitor apixaban (Lopes et al. *Am Heart J* 2010;159(3):331-9²⁴)

The evolution of the newer anticoagulation agents investigated in the large trials listed above—as well as the risks and benefits of the newer agents when compared to LAA occlusion devices and older antiplatelet and anticoagulation strategies—makes stroke prevention in patients with AF an area of further clinical uncertainty that supports both the importance and

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appropriateness of further evidence development and the systematic review of existing evidence. Furthermore, these new therapies highlight the need to reconsider their comparative effectiveness and safety 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, strategies for switching patients from warfarin to the new generation of direct thrombin inhibitors, and considerations for restarting anticoagulation therapy in patients after a hemorrhagic event. For example, in patients with AF undergoing surgery or percutaneous procedures, the duration of holding anticoagulant therapy is not well defined. Also, synthesis of the evidence for the safety and timing of restarting patients on VKA or antithrombin inhibitors after a hemorrhagic stroke remain lacking. These are complex and common scenarios, and there has yet to be a guidance document on the available literature for these important clinical decisions. A review of the current available data can help shed light on areas that require further clinical investigation or provide clinicians with adequate evidence to incorporate into their clinical practice.

II. The Key Questions

The draft Key Questions (KQs) developed during Topic Refinement were available for public comment from September 27, 2011, to October 25, 2011. The comments received led to the inclusion of additional subgroups of interest, additional outcomes, and clarification that we will be exploring the comparative safety and effectiveness of all novel anticoagulants in KQ 5. There were no other significant changes to our KQs or proposed methods.

Specifically our key questions are:

KQ 1: 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 available clinical and imaging tools for predicting thromboembolic risk?

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?

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?

KQ 4: What are the comparative safety and effectiveness of available strategies for anticoagulation in patients with nonvalvular AF 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 AF?

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?

PICOTS (Populations, Interventions, Comparators, Outcomes, Timing, and Settings)

• Populations:

- Adults (age ≥ 18 years) with nonvalvular AF (includes atrial flutter):
 - Including paroxysmal AF (recurrent episodes that self-terminate in less than 7 days), persistent AF (recurrent episodes that last more than 7 days), and permanent AF (an ongoing long-term episode)
 - Excluding patients with known reversible causes of AF (including but not limited to postoperative AF, hyperthyroidism)
 - Including patients with prior AF who experience acute coronary syndrome
- Subpopulations, 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

• Interventions:

- Clinical and imaging tools for assessment/evaluation of thromboembolic risk:
 - Clinical:
 - CHADS2 score
 - CHADS2-VASc score
 - Imaging:
 - Transthoracic echo
 - Transesophageal echo
 - Computed tomography scans
 - Cardiac magnetic resonance imaging
- Clinical tools and individual risk factors for assessment/evaluation of intracerebral hemorrhage bleeding risk:

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- Patient age
- Prior stroke
- Type of AF (paroxysmal, persistent, or permanent)
- International normalized ratio (INR)
- Dementia/cognitive impairment
- Falls risk
- HAS-BLED score
- Anticoagulation therapy (all oral anticoagulants):
 - Warfarin (Coumadin[®])
 - Vitamin K antagonists
 - Dabigatran (Pradaxa[®])
 - Rivaroxaban (Xarelto[®])
 - Apixaban (Eliquis[®])
 - Edoxaban (DU-176b)
- Procedural interventions:
 - Surgical procedures (surgical resection/removal of LAA)
 - Minimally invasive procedures (Atriclip[™] device)
 - Transcatheter procedures (WATCHMAN[®] device, AMPLATZER[®] cardiac plug, and PLAATO[®] device)
- Antiplatelet therapy:
 - Clopidogrel (Plavix[®])
 - Aspirin
 - Aspirin + dipyridamole (Aggrenox[®])
 - Dipyridamole (Persantine[®])
 - Combinations of antiplatelet drugs
- Anticoagulation bridging therapies:
 - U.S. Food and Drug Administration (FDA)-approved low-molecular-weight heparins (e.g., bemparin, certoparin, dalteparin, enoxaparin, nadroparin, parnaparin, reviparin, tinzaparin)
 - Intravenous heparin
 - Dabigatran (off-label usage)
- **Comparators:**
 - **KQ 1:** Other clinical or imaging tools listed for assessing thromboembolic risk
 - **KQ 2:** Other clinical tools listed for assessing bleeding risk
 - **KQ 3:** Other anticoagulation therapies, antiplatelet therapies, or procedural interventions for preventing thromboembolic events
 - **KQ 4:** Other anticoagulation therapies
 - **KQ 5:** Other anticoagulation bridging strategies

- **KQ 6:** Other strategies for resuming anticoagulation therapy following a hemorrhagic event

- **Patient-centered outcome measures for each question:**
 - Assessment of thromboembolic outcomes:
 - Cerebrovascular infarction
 - TIA
 - Systemic embolism (note: excludes pulmonary embolism and deep vein thrombosis)

 - Prevention of bleeding outcomes:
 - 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:
 - 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:
 - Diagnostic accuracy efficacy
 - Diagnostic thinking efficacy
 - Therapeutic efficacy
 - Patient outcome efficacy

- **Timing:**

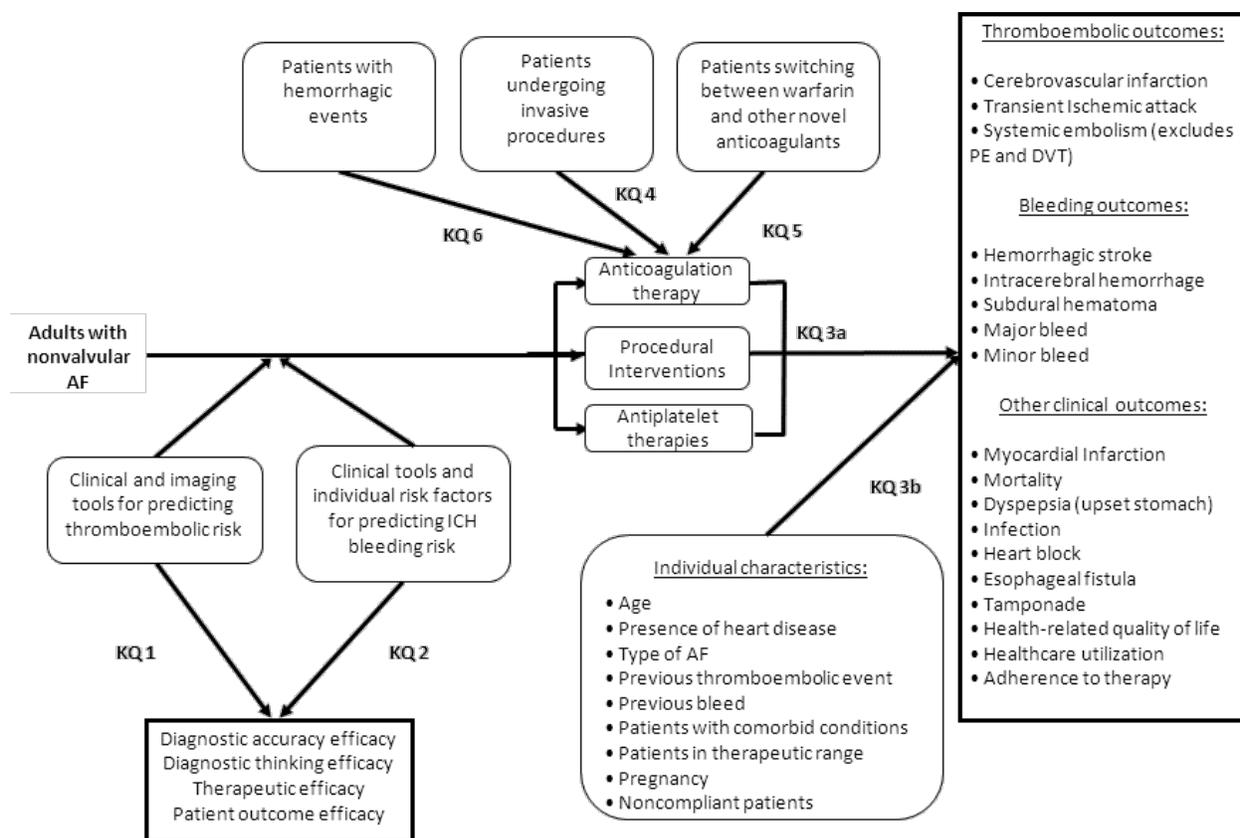
Not applicable

- **Settings:**

All settings

III. Analytic Framework

Figure. Provisional analytic framework for the prevention of stroke in patients with atrial fibrillation



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

IV. Methods

In developing this comprehensive review, we will apply the rules of evidence and evaluation of strength of evidence recommended by the Agency for Healthcare Research and Quality (AHRQ) in its *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (hereafter referred to as the *Methods Guide*).²⁵ We will solicit feedback about conduct of the work (such as development of search strategies and identifying outcomes of key importance) from the Task Order Officer and the Technical Expert Panel. We will follow the methodology recommended to the Evidence-based Practice Centers for literature search strategies,

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inclusion/exclusion of studies in our review, abstract screening, data abstraction and management, assessment of methodological quality of individual studies, data synthesis, and grading of evidence for each KQ.

A. Criteria for Inclusion/Exclusion of Studies in the Review

We will apply the inclusion and exclusion criteria described in the Table below to studies identified by our literature search.

Table. 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 (vs. 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 AF, hyperthyroidism) • All subjects are <18 years of age, or some subjects are <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 ▪ CHADS2-VASc score ○ Imaging: <ul style="list-style-type: none"> ▪ Transthoracic echo ▪ Transesophageal echo ▪ Computed tomography scans ▪ Cardiac magnetic resonance imaging • 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, and permanent) ○ International normalized ratio (INR) ○ Dementia/cognitive impairment ○ Risk of falls 	None

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PICOTS Element	Inclusion Criteria	Exclusion Criteria
	<ul style="list-style-type: none"> ○ HAS-BLED score ● Anticoagulation therapy (all oral anticoagulants): <ul style="list-style-type: none"> ○ Warfarin (Coumadin[®]) ○ Vitamin K antagonists ○ Dabigatran (Pradaxa[®]) ○ Rivaroxaban (Xarelto[®]) ○ Apixaban (Eliquis[®]) ○ Edoxaban (DU-176b) ● Procedural interventions: <ul style="list-style-type: none"> ○ Surgical procedures (surgical resection/removal of LAA) ○ Minimallyinvasive procedures (AtriClip™ device) ○ Transcatheter procedures (WATCHMAN[®] device, AMPLATZER[®] cardiac plug, and PLAATO[®] device) ● Antiplatelet therapy: <ul style="list-style-type: none"> ○ Clopidogrel (Plavix[®]) ○ Aspirin ○ Aspirin + dipyridamole (Aggrenox[®]) ○ Dipyridamole (Persantine[®]) ○ Combinations of antiplatelet drugs ● 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) ○ Intravenous 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 ● KQ 4: Other anticoagulation therapies ● KQ 5: Other anticoagulation bridging strategies ● KQ 6: Other strategies for resuming anticoagulation therapy after a hemorrhagic event 	None
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 ○ 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) 	Study does not include any outcomes of interest

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PICOTS Element	Inclusion Criteria	Exclusion Criteria
	<ul style="list-style-type: none"> ○ 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 	
Timing	<ul style="list-style-type: none"> ● Timing of followup will not be limited^a 	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 only ● Relevant systematic reviews, meta-analyses, or methods articles (used for background only) 	<ul style="list-style-type: none"> ● Given the high volume of literature available in English-language publications, non-English-language articles will be excluded^b

^a For all included studies, we will indicate the total number of patients enrolled and the longest length (weeks or months) of followup if relevant.

^b It is the opinion of the investigators that the resources required to translate non-English-language articles would not be justified by the low potential likelihood of identifying relevant data unavailable from English-language sources. We will monitor the number of articles excluded at the abstract stage for English language and determine whether this exclusion criterion should be revisited if the proportion of non-English language articles is greater than 10%.

Abbreviations: AF = atrial fibrillation; CHADS2 = congestive heart failure, hypertension, age >75, diabetes, stroke/TIA; CHADS2-VASc = congestive heart failure/left ventricular ejection fraction ≤40%, hypertension, age ≥75, diabetes, stroke/TIA/thromboembolism, vascular disease, age 65–74, female; FDA = U.S. Food and Drug Administration; HAS-BLED = hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly (>65), drugs/alcohol concomitantly; INR = international normalized ratio; KQ = key question; LAA = left atrial appendage; PICOTS = Populations, Interventions, Comparators, Outcomes, Timing, and Settings; RCT = randomized controlled trial; TIA = transient ischemic attack;

B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies To Answer the Key Questions

To identify relevant published literature, we will search PubMed[®], EMBASE[®], and the Cochrane Database of Systematic Reviews, limiting the search to studies conducted in adults from January 1, 2000, to the present. We believe that the evidence published from 2000 on will represent the current standard of care for patients with AF and relevant comorbidities. Where possible, we will use existing validated search filters (such as the Clinical Queries Filters in PubMed). An experienced search librarian will guide all searches. We will supplement the electronic searches with a manual search of citations from a set of key primary and review articles. The reference list for identified pivotal articles will be manually hand-searched and cross-referenced against our database, and additional relevant manuscripts will be retrieved. All citations will be imported into an electronic bibliographical database (EndNote[®] Version X4; Thomson Reuters, Philadelphia, PA).

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

We will use several approaches to identify relevant gray literature, including requests to drug and device manufacturers for scientific information packets and a search of U.S. Food and Drug Administration (FDA) device registration studies and new drug applications. We will also search study registries and conference abstracts for relevant articles from completed studies. Gray literature databases will include ClinicalTrials.gov; metaRegister of Controlled Trials; ClinicalStudyResults.org; the World Health Organization (WHO) International Clinical Trials Registry Platform search portal; and ProQuest COS Conference Papers Index.

For citations retrieved from PubMed, EMBASE, and the Cochrane Database of Systematic Reviews, two reviewers using prespecified inclusion/exclusion criteria will review titles and abstracts for potential relevance to the research questions. Articles included by either reviewer will undergo full-text screening. At the full-text screening stage, two independent reviewers must agree on a final inclusion/exclusion decision. Articles meeting eligibility criteria (see Table above) will be included for data abstraction. All results will be tracked using the DistillerSR data synthesis software program (Evidence Partners Inc., Manotick, ON, Canada).

C. Data Abstraction and Data Management

The research team will create data abstraction forms for the KQs that will be programmed in the DistillerSR software. Based on their clinical and methodological expertise, a pair of researchers will be assigned to abstract data from each of the eligible articles. One researcher will abstract the data, and the second will over-read the article and the accompanying abstraction to check for accuracy and completeness. Disagreements will be resolved by consensus or by obtaining a third reviewer's opinion if consensus cannot be reached. Guidance documents will be drafted and provided to the researchers to aid both reproducibility and standardization of data collection.

We will design the data abstraction forms for this project 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 will pay 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., RCT vs. observational) that may be related to outcomes. In addition, we will describe comparators carefully, as treatment standards may have changed during the period covered by the review. The safety outcomes will be framed to help identify adverse events, including those from drug therapies and those resulting from procedural complications. Data needed to assess quality and applicability, as described in the *Methods Guide*,²⁵ will also be abstracted. Before they are used, data abstraction form templates will be pilot-tested with a sample of included articles to ensure that all relevant data elements are captured and that there is consistency/reproducibility between abstractors. Forms will be revised as necessary before full abstraction of all included articles.

D. Assessment of Methodological Quality of Individual Studies

We will assess methodological quality, or risk of bias, for each individual study by using the assessment instruments detailed in AHRQ's *Methods Guide*.²⁵ Briefly, we will rate each study as being of good, fair, or poor quality based on its adherence to well-accepted standard methodologies (e.g., QUADAS-2²⁶ for studies of diagnostic accuracy, the Downs and Black methodological quality assessment checklist²⁷ for intervention studies, and Cochrane's Risk of Bias tool for RCTs). For all studies, the overall study quality will be assessed as follows:

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

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

E. Data Synthesis

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

We will then determine the feasibility of completing a quantitative synthesis (i.e., meta-analysis). Feasibility depends 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. When a meta-analysis is appropriate, we will use random-effects models to synthesize the available evidence quantitatively. We will test for heterogeneity by 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 will also perform fixed-effect meta-analyses. We will present summary estimates, standard errors, and confidence intervals. We anticipate that intervention effects may be heterogeneous. We hypothesize that the methodological quality of individual studies, study type, the characteristics of the comparator, and patients' underlying clinical presentation or prior history of stroke or bleed will be associated

with the intervention effects. If there are sufficient studies, we will perform subgroup analyses and/or meta-regression analyses to examine these hypotheses.

F. Grading the Evidence for Each Key Question

We will grade the strength of evidence for each outcome assessed; thus, the strength of evidence for two separate outcomes in a given study may be graded differently. The strength of evidence will be assessed by using the approach described in AHRQ's *Methods Guide*.^{25,28} In brief, the approach requires assessment of four domains: risk of bias, consistency, directness, and precision. Additional domains to be used when appropriate are: coherence, dose-response association, impact of plausible residual confounders, strength of association (magnitude of effect), and publication bias. These domains will be considered qualitatively, and a summary rating of "high," "moderate," or "low" strength of evidence will be assigned for each outcome after discussion between two reviewers. In some cases, high, moderate, or low ratings will be impossible or imprudent to make, for example, when no evidence is available or when evidence on the outcome is too weak, sparse, or inconsistent to permit any conclusion. In these situations, a grade of "insufficient" will be assigned. This four-level rating scale is defined as follows:

- **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.

G. Assessing Applicability

We will assess applicability across our key questions using the method described in AHRQ's *Methods Guide*.^{25,29} 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 will use a checklist to guide the assessment of applicability. We will use 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 will summarize issues of applicability qualitatively.

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VI. Definition of Terms

AF	atrial fibrillation
AHRQ	Agency for Healthcare Research and Quality
CHADS2	congestive heart failure, hypertension, age > 75, diabetes, stroke/TIA
CHADS2-VASc	congestive heart failure/left ventricular ejection fraction ≤ 40%, hypertension, age ≥ 75, diabetes, stroke/TIA/thromboembolism, vascular disease, age 65-74, female
CI	confidence interval
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 INR, elderly (>65), drugs/alcohol concomitantly
INR	international normalized ratio
KQ	key question
LAA	left atrial appendage
PICOTS	Populations, Interventions, Comparators, Outcomes, Timing, Settings
QUADAS	quality assessment of diagnostic accuracy studies
RCT	randomized controlled trial
TIA	transient ischemic attack
VKA	vitamin K antagonist
WHO	World Health Organization

VII. Summary of Protocol Amendments

None

VIII. Review of Key Questions

For all EPC reviews, key questions were reviewed and refined as needed by the EPC with input from Key Informants and the Technical Expert Panel (TEP) to assure that the questions are specific and explicit about what information is being reviewed. In addition, for Comparative Effectiveness reviews, the key questions were posted for public comment and finalized by the EPC after review of the comments.

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IX. Key Informants

Key Informants are the end-users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform health care decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high-priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

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

X. Technical Experts

Technical Experts comprise a multidisciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes as well as identifying particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design and/or methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor contribute to the writing of the report and have not reviewed the report, except as given the opportunity to do so through the public review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. Peer reviewers do not participate in writing or editing of the final report or other products. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for CERs and Technical briefs, be published 3 months after the publication of the Evidence report.

Potential Reviewers must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than \$10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

XII. EPC team disclosures:

None of the EPC team members has any affiliations or financial involvement that conflicts with the material presented in this document.

XIII. Role of the Funder:

This project was funded under Contract No. 290-07-10066-I from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The Task Order Officer reviewed contract deliverables for adherence to contract requirements, including the objectivity and independence of the research process and the methodological quality of the report. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.