Effective Health Care

Stroke Prevention in Atrial Fibrillation: Update of 2013 Review

Results of Topic Selection Process & Next Steps

The nominator, the American College of Cardiology/American Heart Association (ACC/AHA), is interested in an update to the 2013 AHRQ systematic review "Stroke Prevention in Atrial Fibrillation." They plan to use an updated systematic review to inform the update on their 2014 clinical practice guidelines on the management of patients with atrial fibrillation.

In December 2016, the Patient-Centered Outcomes Research Institute (PCORI) decided to fund an update of the 2013 AHRQ systematic review as part of their Evidence Synthesis Program. PCORI will be partnering with AHRQ on this update. This report will be updated through AHRQ's EPC Program.

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Topic Brief

Topic Name: Stroke Prevention in Atrial Fibrillation: Update of 2013 Review

Topic #: 0700

Nomination Date: August 2, 2016

Topic Brief Date: January 30, 2017

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

Summary of Key Findings:

- Appropriateness and importance: The topic is both appropriate and important.
- Duplication: A new review on this topic would be duplicative of an in-process product. PCORI has partnered with AHRQ to update the 2013 AHRQ systematic review "Stroke Prevention in Atrial Fibrillation" as part of their Evidence Synthesis Program.

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Introduction

Atrial fibrillation (AF) is a condition in which the heart's two upper chambers beat irregularly. Patients with AF often experience irregular and rapid heartbeat, heart palpitations, dizziness, sweating, chest pain or pressure, shortness of breath, and syncope.[1] AF is the most common cardiac arrhythmia in clinical practice, occurring in approximately 2.3 million people in the U.S.[2] The prevalence of AF is higher among older populations, occurring in 6% of patients 65 or older and 12% of those 85 or older.[3] Patients with AF are at a particularly high risk of stroke due to the formation of blood clots in the heart that can travel to the brain. AF patients have five times the risk of stroke and are more likely to be bedridden or die as a result of a stroke than those without AF.[4]

Various clinical and imaging tools have been utilized to identify which AF patients are at highest risk of stroke and other thromboembolic events. In 2014, the ACC/AHA recommended the $CHAD_2VASc$ tool for predicting thromboembolic risk[5], although other tools such as the ABC (age, biomarker, clinical history) stroke risk score have been developed more recently.[6] The use of bleeding risk tools, such as HAS-BLED, are more controversial due to limited evidence of benefits.[5] Additionally, the comparative effectiveness of various treatments for preventing stroke in AF patients is still debated. Pharmacological treatments for preventing stroke include anticoagulation therapy such as Warfarin (coumadin), vitamin K antagonists, novel oral anticoagulants; heparins; and antiplatelets. Nonpharmacological interventions include the surgical removal of the left atrial appendage and devices that prevent blood clots from entering the bloodstream from the heart.

Topic nomination *#700 Stroke Prevention in Atrial Fibrillation* was received on August 2, 2016. It was nominated by the American College of Cardiology/American Heart Association (ACC/AHA). The ACC/AHA is interested in an update of the 2013 AHRQ systematic review "Stroke Prevention in Atrial Fibrillation" to inform the update of their clinical practice guidelines. We reviewed the key questions from the original review and made minor updates based on feedback from both a clinical expert and the nominator. The questions for this nomination are:

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

Key Question 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?

Key Question 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?

Key Question 4: What are the comparative safety and effectiveness of available strategies for anticoagulation in patients with nonvalvular atrial fibrillation who are undergoing invasive procedures?

Key Question 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?

Key Question 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?

a) "Does the effectiveness of stopping and/or resuming anticoagulation therapy vary by the length of time anticoagulants are stopped?

To define the inclusion criteria for the key questions we specify the population, interventions, comparators, outcomes and timing (PICOTs) of interest. See Table 1.

Table 1. Key Questions and PICOTs

Key Question	1. In patients with nonvalvular atrial fibrillation, what are the comparative diagnostic accuracy and impact on clinical decision-making (diagnostic thinking, therapeutic, and patient outcome efficacy) of available clinical and imaging tools for predicting thromboembolic risk?	2. In patients with nonvalvular atrial fibrillation, what are the comparative diagnostic accuracy and impact on clinical decision-making (diagnostic thinking, therapeutic, and patient outcome efficacy) of clinical tools and associated risk factors for predicting bleeding events?	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 (eg, age, presence of heart disease, type of atrial fibrillation, previous thromboembolic event, previous bleed, recent ACS without PCI/stenting, comorbid conditions [especially ESRD], in therapeutic range, pregnant, or noncompliant)?	4. What are the comparative safety and effectiveness of available strategies for anticoagulation in patients with nonvalvular atrial fibrillation who are undergoing invasive procedures?	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?	6. What are the comparative safety and effectiveness of available strategies for stopping anticoagulation therapy, resuming anticoagulation therapy or performing a procedural intervention as a stroke prevention strategy following a hemorrhagic event (stroke, major bleed, or minor bleed) or following multiple falls in patients with nonvalvular atrial fibrillation? a) Does the effectiveness of stopping and/or resuming anticoagulation therapy vary by the length of time anticoagulants are stopped?
Population	Patients with nonvalvular atrial fibrillation	Patients with nonvalvular atrial fibrillation	Patients with nonvalvular atrial fibrillation	Patients with nonvalvular atrial fibrillation	Patients with nonvalvular atrial fibrillation	Patients with nonvalvular atrial fibrillation
Intervention	Clinical tools 1. $CHADS_2$ score 2. $CHADS_2$-VASc score 3. Framingham risk score 4. ABC (age, biomarker, clinical history) stroke risk score Individual risk factors • International Normalized Ratio (INR) level • Duration and frequency (ie,	Clinical tools: • HAS-BLED score • $CHADS_2$ score • $CHA2S_2$-VASc score • Framingham risk score • $HEMORR_2HAGES$ score • ATRIA score • Bleeding Risk Index (BRI) Individual risk factors • Patient age • Prior stroke • Type of AF	Anticoagulation therapy (all oral anticoagulants): • Warfarin (Coumadin) • Vitamin K antagonists (VKAs) • Dabigatran (Pradaxa) • Rivaroxaban (Xarelto) • Apixaban (Eliquis) • Edoxaban (DU-176b) Antiplatelet therapy: • Clopidogrel (Plavix) • Aspirin (ASA) • ASA + dipyridamole (Aggrenox)	Anticoagulation therapy (all oral anticoagulants): • Warfarin (Coumadin) • Vitamin K antagonists (VKAs) • Dabigatran (Pradaxa) • Rivaroxaban (Xarelto) • Apixaban (Eliquis) • Edoxaban (DU-176b) Anticoagulation bridging therapies: • FDA-approved low molecular weight heparins (e.g., bemiparin,	Anticoagulation bridging therapies: • FDA-approved low molecular weight heparins (e.g., bemiparin, certoparin, dalteparin, enoxaparin, nadroparin, parnaparin, reviparin, tinzaparin) • IV heparin • Dabigatran (off-label usage)	Anticoagulation therapy (all oral anticoagulants): • Warfarin (Coumadin) • Vitamin K antagonists (VKAs) • Dabigatran (Pradaxa) • Rivaroxaban (Xarelto) • Apixaban (Eliquis) • Edoxaban (DU-176b) Procedural interventions: • Surgical procedures (surgical

	burden) of atrial fibrillation Imaging tools 1. Transthoracic echo (TTE) 2. Transesophageal echo (TEE) 3. CT scans 4. Cardiac MRIs	(paroxysmal, persistent, permanent) • International normalized ratio (INR) level • Dementia/cognitive impairment • Falls risk • Presence of heart disease • Duration and frequency (ie, burden) of atrial fibrillation	• Dipyridamole (Persantine) • Combinations of antiplatelets Procedural interventions: • Surgical procedures (surgical resection/removal of left atrial appendage [LAA], stapling, suturing) • Minimally invasive procedures (Atriclip device, LARIAT) • Transcatheter procedures (WATCHMAN device, AMPLATZER cardiac plug, PLAATO device)	certoparin, dalteparin, enoxaparin, nadroparin, parnaparin, reviparin, tinzaparin) • IV heparin • Dabigatran (off-label usage)		resection/removal of left atrial appendage [LAA], stapling, suturing) • Minimally invasive procedures (Atriclip device, LARIAT) • Transcatheter procedures (WATCHMAN device, AMPLATZER cardiac plug, PLAATO device)
Comparator	Other clinical or imaging tools listed for assessing thromboembolic risk	Other clinical tools listed for assessing bleeding risk	Other anticoagulation therapies, antiplatelet therapies, or procedural interventions for preventing thromboembolic events	Other anticoagulation therapies	Other anticoagulation bridging strategies	Other strategies for stopping/resuming anticoagulation therapy or completing a procedural intervention following a hemorrhagic event
Outcome	Clinical and imaging tool efficacy for predicting thromboembolic risk: • Diagnostic accuracy efficacy • Diagnostic thinking efficacy • Therapeutic efficacy • Cost-effectiveness • Patient outcome efficacy (see below) Patient outcomes • Cerebrovascular infarction • Transient ischemic attack (TIA) • Systemic embolism (note: excludes pulmonary embolism and deep vein	Clinical and imaging tool efficacy for predicting bleeding events: • Diagnostic accuracy efficacy • Diagnostic thinking efficacy • Therapeutic efficacy • Cost-effectiveness • Patient outcome efficacy (see below) Patient outcomes • Hemorrhagic stroke • Intracranial hemorrhage (intracerebral hemorrhage, subdural hematoma) • Extracranial bleeding • Major bleed (stratified by type and location)	Thromboembolic outcomes: • Cerebrovascular infarction • Transient ischemic attack (TIA) • Systemic embolism (note: excludes pulmonary embolism and deep vein thrombosis) Bleeding outcomes: • Hemorrhagic stroke • Intracranial hemorrhage (intracerebral hemorrhage, subdural hematoma) • Extracranial bleeding • Major bleed (stratified by type and location)	Thromboembolic outcomes: • Cerebrovascular infarction • Transient ischemic attack (TIA) • Systemic embolism (note: excludes pulmonary embolism and deep vein thrombosis) Bleeding outcomes: • Hemorrhagic stroke • Intracranial hemorrhage (intracerebral hemorrhage, subdural hematoma) • Extracranial bleeding • Major bleed (stratified by type and location)	Thromboembolic outcomes: • Cerebrovascular infarction • Transient ischemic attack (TIA) • Systemic embolism (note: excludes pulmonary embolism and deep vein thrombosis) Bleeding outcomes: • Hemorrhagic stroke • Intracranial hemorrhage (intracerebral hemorrhage, subdural hematoma) • Extracranial bleeding • Major bleed (stratified by type and location)	Thromboembolic outcomes: • Cerebrovascular infarction • Transient ischemic attack (TIA) • Systemic embolism (note: excludes pulmonary embolism and deep vein thrombosis) Bleeding outcomes: • Hemorrhagic stroke • Intracranial hemorrhage (intracerebral hemorrhage, subdural hematoma) • Extracranial bleeding • Major bleed (stratified by type and location)

	thrombosis)	• Minor bleed (stratified by type and location)	• Minor bleed (stratified by type and location) Other clinical outcomes: • Mortality • Myocardial infarction • 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	• Minor bleed (stratified by type and location) Other clinical outcomes: • Mortality • Myocardial infarction • 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	• Minor bleed (stratified by type and location) Other clinical outcomes: • Mortality • Myocardial infarction • 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	• Minor bleed (stratified by type and location) Other clinical outcomes: • Mortality • Myocardial infarction • 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
Timing	Any time	Any time	Any time	While undergoing invasive procedures	Any time	Following a hemorrhagic event

Methods

To assess topic nomination *#700 Stroke Prevention in Atrial Fibrillation* for priority for a systematic review or other AHRQ EHC report, we used a modified process based on established criteria. Our assessment is hierarchical in nature, with the findings of our assessment determining the need for further evaluation. Details related to our assessment are provided in Appendix A.

1. " Determine the *appropriateness* of the nominated topic for inclusion in the EHC program.
2. " Establish the overall *importance* of a potential topic as representing a health or " healthcare issue in the United States. "
3. " Determine the *desirability of new evidence review* by examining whether a new " systematic review or other AHRQ product would be duplicative. "
4. " Assess the *potential impact* a new systematic review or other AHRQ product.
5. " Assess whether the *current state of the evidence* allows for a systematic review or other AHRQ product (feasibility).
6. " Determine the *potential value* of a new systematic review or other AHRQ product.

Appropriateness and Importance

We assessed the nomination for appropriateness and importance (see Appendix A).

Desirability of New Review/Duplication

We searched for high-quality, completed or in-process evidence reviews pertaining to the key questions of the nomination. Table 2 includes the citations for the reviews that were determined to address the key questions.

Compilation of Findings

We constructed a table outlining the selection criteria as they pertain to this nomination (see Appendix A).

Results

Appropriateness and Importance

This is an appropriate and important topic. AF is the most common cardiac arrhythmia in clinical practice, occurring in approximately 2.3 million people in the U.S.[2] The prevalence of AF is higher among older populations, occurring in 6% of patients 65 or older and 12% of patients 85 or older.[3] AF patients have five times the risk of stroke and are more likely to be bedridden or die as a result of a stroke than those without AF.[4]

Desirability of New Review/Duplication

A new evidence review examining would be duplicative of an in-process product. See Table 2, Duplication column for the systematic review citation that was determined to address the key questions.

Table 2. Key questions with the identified corresponding evidence reviews and original research

Key Question	Duplication (Completed or In-Process Evidence Reviews)
KQ 1-6: Comparative accuracy of clinical and imaging tools; comparative effectiveness of treatments	Total number of in-process systematic reviews – 1 • PCORI: 1[7]

Abbreviations: AF= Atrial Fibrillation; KQ=Key Question; PCORI=Patient-Centered Outcomes Research Institute

Summary of Findings

- Appropriateness and importance: The topic is both appropriate and important.
- Duplication: A new review on this topic would be duplicative of an in-process product. PCORI has chosen to partner with AHRQ to update the 2013 AHRQ systematic review "Stroke Prevention in Atrial Fibrillation" as part of their Evidence Synthesis Program.

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Appendices

Appendix A: Selection Criteria Summary

Appendix A. Selection Criteria Summary (

Selection Criteria	Supporting Data
1. Appropriateness	
1a. Does the nomination represent a health care drug, intervention, device, technology, or health care system/setting available (or soon to be available) in the U.S.?	Yes, this topic represents health care drugs and interventions that are available in the U.S.
1b. Is the nomination a request for a systematic review?	Yes, this topic is a request for a systematic review.
1c. Is the focus on effectiveness or comparative effectiveness?	The focus of this review is on comparative effectiveness.
1d. Is the nomination focus supported by a logic model or biologic plausibility? Is it consistent or coherent with what is known about the topic?	Yes, it is biologically plausible. Yes, it is consistent with what is known about the topic.
2. Importance	
2a. Represents a significant disease burden; large proportion of the population	Yes, this topic represents a significant burden. AF is the most common cardiac arrhythmia in clinical practice, occurring in approximately 2.3 million people in the U.S.[2] The prevalence of AF increases with age, occurring in 6% of those 65 or older and 12% of those 85 or older.[3]
2b. Is of high public interest; affects health care decision making, outcomes, or costs for a large proportion of the US population or for a vulnerable population	Yes, this topic affects heath care decisions for a large population.
2c. Represents important uncertainty for decision makers	Yes, this topic represents important uncertainty for decision makers.
2d. Incorporates issues around both clinical benefits and potential clinical	Yes, this nomination addresses both benefits and potential harms of clinical and imaging tools, pharmacological treatments, and non-pharmacological treatments for preventing stroke in AF.
2e. Represents high costs due to common use, high unit costs, or high associated costs to consumers, to patients, to health care systems, or to payers	Patients with AF have five times the risk of stroke and are more likely to be bedridden or die as a result of a stroke than those without AF.[4]
3. Desirability of a New Evidence Review/Duplication	
3. Would not be redundant (i.e., the proposed topic is not already covered by available or soon-to-be available high-quality systematic review by AHRQ or others)	A new review produced by the AHRQ EHC program would be redundant. In December 2016, the Patient-Centered Outcomes Research Institute (PCORI) decided to update the 2013 AHRQ systematic review as part of their Evidence Synthesis Program.[7]

Abbreviations: AF=Atrial Fibrillation; AHRQ=Agency for Healthcare Research and Quality; EHC=Effective Health Care