Prior Key Questions from the 2013 Systematic Review on Stroke Prevention in Atrial Fibrillation

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?

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?

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?

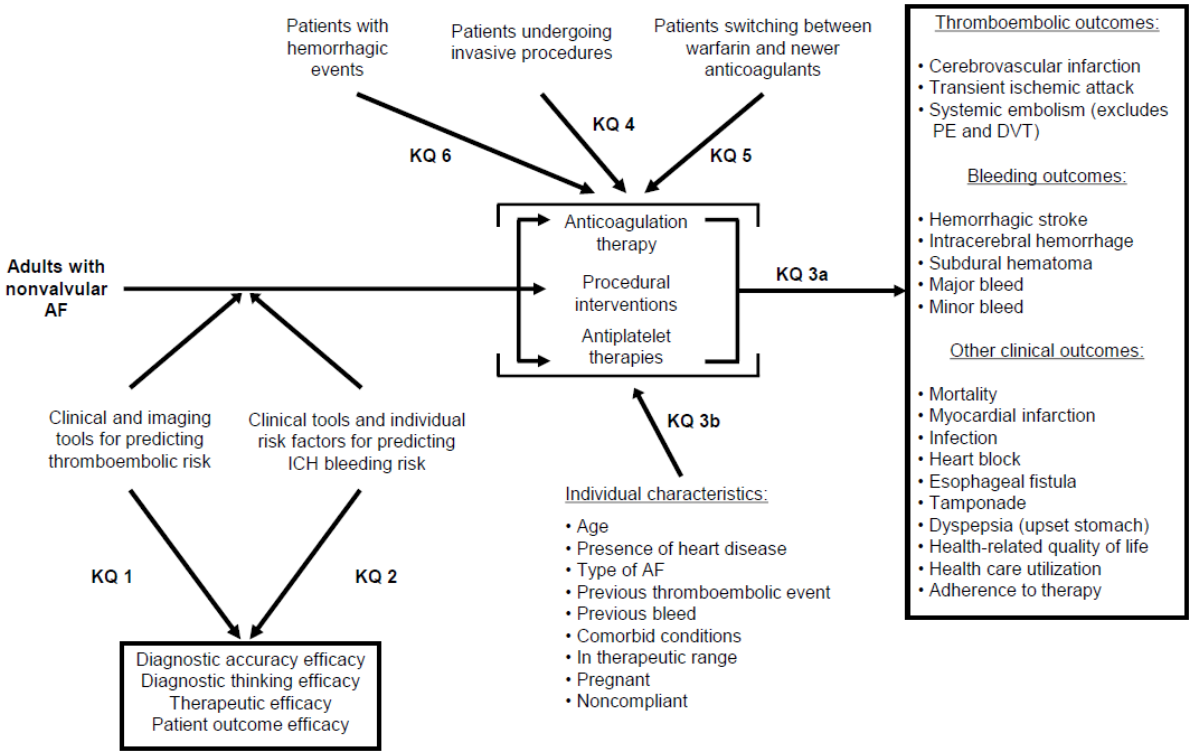
4. What are the comparative safety and effectiveness of available strategies for anticoagulation in patients with nonvalvular atrial fibrillation who are undergoing invasive procedures?

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 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?

Prior Analytic Framework

Figure A. Analytic framework



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

Summary of Comments Related to Stroke Prevention in Atrial Fibrillation from Previous Stakeholder Workshop (December 7, 2016)

- Clear interest in focusing on how the benefits and harms of various anticoagulants may be different for specific subpopulations (e.g., older adults and specifically older women)
    - Within this, need to understand falls risk as well as need for/impact of variable dosing

- Interest in understanding how adherence (or lack thereof) to newer anticoagulants (NOACs) may influence ultimate benefit (given lack of monitoring compared to warfarin)

- Does the risk of falls/bleeding impact treatment decisions in stroke prevention? That is, is it being used as a justification not to anticoagulate in atrial fibrillation?

- Contextual interest in litigation ads related to NOACs and how this may affect care

- Need to consider additional outcomes not covered in the last review—particularly quality of life and cognitive function

- Need to include new interventions not available at time of last review, e.g., edoxaban, left atrial occlusion devices

- Note that the bleeding risk tool has inadequacies that should be considered and addressed with the new review

- Note need to consider more types of evidence than just RCTs

PCORI's Proposed Updated Key Questions: For Discussion

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?**
    a. Clinical tools include:
        i. CHADS2 score
        ii. CHADS2-VASc score
        iii. Framingham risk score
        iv. ABC stroke risk score
    b. Individual risk factors include:
        i. INR level
        ii. Duration and frequency of atrial fibrillation
    c. Imaging tools include:
        i. Transthoracic echo
        ii. Transesophageal echo
        iii. CT scans
        iv. Cardiac MRIs

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?**
    a. Clinical tools include:
        i. HAS-BLED score
        ii. CHADS2 score
        iii. CHADS2-VASc score
        iv. Framingham risk score
        v. HEMORR2HAGES score
        vi. ATRIA score
        vii. Bleeding Risk Index
    b. Individual risk factors include:
        i. Age
        ii. Prior stroke
        iii. Type of atrial fibrillation
        iv. INR level
        v. Cognitive impairment
        vi. Falls risk
        vii. Presence of heart disease
        viii. Duration and frequency of atrial fibrillation

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, to include (but are not limited to):
        i. Age
        ii. Presence of heart disease
        iii. Type of atrial fibrillation
        iv. Comorbid conditions (such as end-stage renal disease)
        v. When in therapeutic range
        vi. When non-adherent to medication
        vii. Previous thromboembolic event
        viii. Previous bleed
        ix. Recent acute coronary syndrome with or without PCI/stenting
        x. Recent PCI/stenting outside of an acute coronary syndrome
        xi. Recent stenting for peripheral vascular disease
        xii. Pregnant
    c. Interventions to be studied will include (but are not limited to):
        i. Anticoagulation therapy:
            1. Warfarin
            2. Vitamin K antagonists
            3. Dabigatran
            4. Rivaroxaban
            5. Apixaban
            6. **Edoxaban**
        ii. Antiplatelet therapy:
            1. Clopidogrel
            2. Aspirin
            3. Dipyridamole
            4. Combinations of antiplatelets
        iii. Procedures:
            1. Surgeries (e.g., **left atrial appendage occlusion,** resection/removal)
            2. Minimally invasive (e.g., Atriclip, LARIAT)
            3. Transcatheter (WATCHMAN, AMPLATZER, PLAATO)

Proposed Outcomes and Included Study Designs: For Discussion

Outcomes for Key Question #3:

- Thromboembolic outcomes:
    - Cerebrovascular infarction
    - Transient ischemic attack
    - Systemic embolism (excludes PE and DVT)
- Bleeding outcomes:
    - Hemorrhagic stroke
    - Intracranial hemorrhage
    - Extracranial hemorrhage
    - Major 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
    - **Health-related quality of life**
    - Functional capacity
    - Health services utilization
    - Long-term adherence to therapy
    - **Cognitive function**

Study designs for all questions:

- RCTS, prospective and retrospective observational studies, or registries

Questions to Guide the Scoping Discussion

PCORI will be conducting a **targeted update** of the prior systematic review. One emphasis for PCORI's new Evidence Synthesis Program is on achieving the relatively rapid deployment of rigorous, relevant, and actionable comparative effectiveness research, placed in context, for a wide variety of stakeholders. For this reason we are seeking your assistance in identifying the current **highest priority areas** from the prior comprehensive review to refine and focus the scope for this update.

1. **PCORI is proposing to focus the update on the first three key questions, based on the comments we heard during the first stakeholder workshop regarding priority areas in stroke prevention in atrial fibrillation.** This would allow the Evidence-based Practice Center to dig deep into the evidence on clinical risk prediction tools regarding thromboembolic and bleeding risk, and, most importantly, for studies of multiple designs that have emerged on newer interventions for stroke prevention since the prior review. It would also allow for a greater focus on how subpopulations of interest (such as older women, or those who are less adherent with treatment) might see a different balance of benefits and harms with various interventions. **We are interested in your feedback on this proposed approach to the update.**

2. **You will notice that we have provided specifics regarding the clinical tools, risk factors, patient subpopulations, treatment interventions, outcomes, and study designs we propose the Evidence-based Practice Center focus on** (note that these lists are not exhaustive, as the EPC will include other information they find in studies that meet the minimum inclusion criteria for their report, but this is intended to give them a good guide as to a set of priorities). We first want to acknowledge and thank AHRQ's EPC Program Scientific Resource Center at the Portland VA Research Foundation for doing the lion's share of this background work for us on this list. **We'd like your input on the list. Is anything critical missing?**

3. **Do you have any other comments for us on behalf of your organization?**

Thank you again on behalf of PCORI for your time and your assistance!