

Treatment Options for Atrial Fibrillation Overview, Key Questions & Model Description

This appraisal will evaluate the evidence on the comparative risks, benefits, and cost-effectiveness of management strategies for patients with atrial fibrillation (AF). We will include in the scope of the appraisal:

- Antiarrhythmic drug therapy to return the heart to sinus rhythm
- Radiofrequency catheter ablation to terminate AF and prevent further episodes
- Minimally-invasive surgical techniques to terminate AF and prevent further episodes
- Aspirin, warfarin, and dabigatran for anticoagulation to prevent strokes
- The WATCHMAN left atrial appendage occlusive device to prevent strokes

The key questions that will help frame the scope of this appraisal are outlined below, and a brief description of the proposed economic model follows along with questions to help frame the model scope.

Systematic Review

General

1. What are the most important questions about the clinical effectiveness of the management options for patients with AF whose answers would help patients, clinicians, and payers best judge the appropriate use of these strategies?
2. We will evaluate the existing evidence for all patients, but based on guidance from clinical experts and our initial review of the literature, we plan to highlight evidence on the following key subpopulations. Do these categories capture those for whom there is the greatest interest and/or controversy in determining appropriate treatment options?
 - Younger patients who have symptomatic, paroxysmal AF without structural heart disease
 - Patients in persistent AF with structural heart disease who are not suitable candidates for long-term anticoagulation therapy

- Patients in persistent AF with symptomatic left ventricular dysfunction for whom the question is whether return to sinus rhythm may improve cardiac function, quality of life, and length of life

ERG members expressed strong interest in understanding the evidence and outcomes for patients with long-standing persistent AF (e.g., 3-4 years), fatigue, and exertional dyspnea, which would essentially be in lieu of the third bullet above. While some in the group felt that there were few outstanding questions with regard to treatment of paroxysmal AF in younger patients, others felt that there was sufficient uncertainty, particularly for 1st-line treatment with more invasive treatment approaches. Finally, rather than a focus on patients in persistent AF (<12 months) who are not candidates for long-term anticoagulation, the ERG felt there would be more value in examining outcomes of persistent AF by well-accepted strata of stroke risk, such as CHADS₂ score.

Patient representatives to the ERG are interested in exploring whether AF- and treatment-related outcomes differ by patient characteristics, including sex, ethnicity, and type of AF. Others mentioned that these characteristics have not been shown to have an impact in most AF clinical trials, but that it may be worthwhile to explore variation in the burden AF places on individuals (e.g., time in AF, level of symptoms).

3. Key outcomes of focus in our review will include freedom from AF at 12 months as well as the impact of treatment on quality of life, AF recurrence, and long-term outcomes such as stroke and mortality. Are there other outcomes of critical importance, such as freedom from anticoagulation or others?

Outcomes of specific interest to patient representatives included freedom from anticoagulation, examination of stroke risk factors beyond those in the CHADS₂ framework (e.g., female, cardiovascular comorbidity), and side effects of both rate-control and rhythm-control medications.

The importance of quantifying AF burden was underscored. Input from ERG clinicians suggested that the typical “time to AF recurrence” curve data was of limited utility, and that “time in and out of AF” over a given time period would be a much more useful construct for both the literature synthesis and modeling effort.

Catheter Ablation

4. We plan to make techniques of pulmonary vein isolation (PVI) the focus of our review, and do not plan any further subgrouping by the presence of additional ablation sets. Is this approach appropriate?

ERG clinicians cautioned that there is no real standardization of PVI approaches between centers and even providers, and that this variability in practice and approach should be a consideration in the review.

5. We do not plan to discriminate by type of energy used for ablation (e.g., radiofrequency, cryothermal, etc.). Is this appropriate, or are there fundamental differences that should be considered?

ERG clinicians and patient representatives felt it important to stratify findings by energy source, data permitting, to determine whether this affects the outcomes of interest.

Surgical Ablation

6. Minimally-invasive surgical ablation will be the only surgical approach in the scope of the appraisal. Do you consider any of the evidence gleaned from the literature on the traditional Cox Maze procedure applicable to the minimally-invasive approach?

This question was not addressed on the call due to time constraints and scheduling conflicts with surgeon representatives. In subsequent follow-up, however, surgeons expressed a desire to include traditional "cut and sew" Cox Maze surgery in the scope of the review, as they believe the published literature suggests greater effectiveness than minimally-invasive approaches. However, because the target populations of interest in this review represent patients requiring primary treatment for AF, and because Cox Maze is typically used only in patients requiring open heart surgery, the review will focus on minimally-invasive surgery.

Economic Model Description

A state transition (Markov) model of atrial fibrillation management and outcomes will be created. The clinical course of patients will be modeled from the onset of treatment of atrial fibrillation; health states of interest will include normal sinus rhythm or recurrent atrial fibrillation, complications and/or side effects of treatment, stroke, and death. Patient populations will match those of focus in the systematic review, including younger, otherwise healthy patients with symptomatic, paroxysmal AF; patients in persistent AF with structural heart disease; and patients in persistent AF with symptomatic left ventricular dysfunction.

Management options to be evaluated in the model will include medical management using new or currently available antiarrhythmic drugs for rhythm or rate control, catheter ablation, and minimally-invasive surgical ablation. A variety of stroke prevention strategies will also be considered in conjunction with primary AF treatment, including anticoagulation of varying duration with aspirin, warfarin, or dabigatran, as well as use of the WATCHMAN occlusive device.

The management alternatives will be represented graphically in a decision tree and a cost-effectiveness (cost-utility) analysis will be conducted. The cost-effectiveness of each intervention will be evaluated compared to the current standard of care. The analysis will take a societal perspective and follow the recommendations of the Panel on Cost-Effectiveness in Health and Medicine and other organizations. Other

perspectives, such as that of the 3rd-party payer, will be examined in sensitivity analyses.

Outcomes of interest will include side effects and complications of treatment, AF recurrence, stroke, and death. The impact of AF and treatment on patient quality of life also will be examined. Costs will primarily include those of treatment, follow-up and monitoring, complications and side effects, and patient time. A variety of summary measures also will be calculated, including life expectancy and quality-adjusted life expectancy, total services utilized and total costs, and cost per life year and quality-adjusted life year gained.

The systematic review and meta-analysis of published studies will provide important parameters for the probabilities of outcomes of each intervention. Information on clinical epidemiology of atrial fibrillation will be obtained from the literature, and mortality data will be obtained from US vital statistics and life tables. Information on costs will be obtained using Medicare payment rates as well as acquisition costs of drugs and devices from manufacturers. Uncertainty in parameter estimates will be explored using a variety of deterministic and probabilistic sensitivity analyses.

Model Questions

1. In our economic modeling we base “costs” on third-party payments, using Medicare national average reimbursement as the base case. On a case-by-case basis we decide whether to include other costs. For this appraisal, should we include patient costs for time in treatment?

Input from ERG clinicians and patients suggested that patient costs were important to consider, not only for time in treatment but also for productivity loss due to AF symptoms. Other suggested components included the impact of anxiety/worry and caregiver burden, although economic experts on the ERG urged caution in maintaining consistent methodology with previous ICER appraisals. For example, ICER has previously considered the impact of anxiety/worry, but as an impact on quality of life, not on cost.

2. Should anticoagulation be considered a standard approach post-catheter ablation? Post-surgical ablation?

Rather than a binary decision on use of anticoagulation after certain interventions, ERG clinicians suggested that the model explore multiple anticoagulation strategies that vary in terms of both agent used and duration of therapy. This was felt to be particularly important for certain populations such as those with left atrial appendage exclusion via surgery or occlusive device.

3. We have received information suggesting reduced charges for repeat catheter ablations relative to the initial procedure, and are investigating this. Are there other billing and/or payment idiosyncrasies we should be aware of?
4. Amiodarone is perceived as a highly effective antiarrhythmic drug and the drug of choice for patients with structural heart disease, although there are toxicity concerns. Dronedarone is also of interest given its relatively benign side-effect profile. Are there other AADs that should be considered for the model, based on the populations of interest?

Clinical input from the ERG suggested that we consider antiarrhythmic therapy alternatively with amiodarone and dronedarone in the model. In addition, less toxic agents such as dofetilide were felt to be a reasonable consideration for younger patients without other major stroke risk factors.