Overview
Atrial fibrillation (AF) is the most common cardiac arrhythmia seen in clinical practice, affecting approximately 2.5 million persons in the U.S. AF is not only common but also carries significant risks of mortality and morbidity, raising the risk of stroke more than five-fold and contributing to an estimated 15-20% of strokes annually in the U.S. Even patients with AF who do not suffer a stroke often experience diminished quality of life and require frequent hospitalization.

This appraisal will evaluate the evidence on the comparative risks, benefits, and cost-effectiveness of management strategies for patients with 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

Descriptions of these management strategies as well as relevant guidelines, coverage policies, and ongoing research can be found in Appendices A-D of this document.

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

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?

**Catheter Ablation**

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

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?

**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?

**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 anti-arrhythmic 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?

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

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?
APPENDIX A

Medical Management of Atrial Fibrillation
Introduction
The medical management of atrial fibrillation (AF) includes two primary options: rate control or rhythm control. For patients who are placed on a rate-control strategy, restoration of sinus rhythm is not the goal; the objective is control of the ventricular response, most often through therapy with calcium channel blockers, beta blockers, or digitalis. In contrast, the goal of a rhythm control strategy is return to sinus rhythm and long-term suppression of AF itself. Restoring the normal heart rhythm can be attempted through either electrical cardioversion or antiarrhythmic drugs (AADs), with or without a concurrent rate-control approach. Although the effects of electrical cardioversion are more immediate, it does not work for many patients, and even when it works initially, many patients will have recurrent AF in the future.

AADs may be used to try to maintain sinus rhythm after electrical cardioversion, or they may be initiated independently. Amiodarone (Cordarone®, Pacerone®) is generally viewed as the most effective at maintaining rhythm in patients who have undergone cardioversion and is therefore the most commonly used AAD. It is also commonly used in patients with underlying structural heart disease, as the risk of proarrhythmia in patients with heart disease is much lower with amiodarone than with other AADs. Other common AADs include flecainide (Tambocor®), dofetilide (Tikosyn®), propafenone (Rythmol®), and ibutilide (Corvert®).

In addition, dronedarone (Multaq®), an amiodarone analogue developed by the same manufacturer, was recently approved by the FDA for use in patients with AF but who do not have severe heart failure. Findings from Phase III clinical trials indicated a 24% reduction in the rate of cardiovascular hospitalization or death from any cause as compared to placebo. Also, recently presented post-hoc analyses of trial data suggest that dronedarone may be associated with a one-third reduction in the risk of stroke in patients with AF, regardless of whether they were also receiving concomitant anticoagulation.

As with any medication, patients and their physicians must weigh the relative risks and benefits of each when deciding on a treatment approach. For example, amiodarone’s high effectiveness is counter-balanced to some extent by its potential to cause severe side effects, such as thyroid dysfunction, pulmonary fibrosis, liver toxicity, and gastrointestinal complications. Amiodarone also interacts with many drugs including insulin or diabetes medication, cholesterol-lowering medicines, and warfarin. In contrast, dronedarone does not appear to be associated with thyroid or pulmonary toxicity, and is simpler to dose. However, it does not appear to be as effective as amiodarone at restoring sinus rhythm. Other AADs may also be associated with serious side effects, including renal toxicity, hypotension, and development of a rare but dangerous ventricular arrhythmia, torsades de pointes.
Professional Organization and Agency Recommendations

- The American College of Cardiology, the American Heart Association, and the European Society of Cardiology (ACC/AHA/ESC, 2006)
  http://circ.ahajournals.org/cgi/reprint/CIRCULATIONAHA.106.177031v1
  The use of antiarrhythmic drugs is recommended for both pharmacological cardioversion of AF as well as maintenance of sinus rhythm; infrequent, well-tolerated instances of AF are considered a successful outcome of drug therapy. Direct-current cardioversion is most often recommended as part of a long-term strategy for AF management and only after patients are first controlled on AADs.

- The National Collaborating Centre for Chronic Conditions (NCC-CC, 2006)
  http://guidance.nice.org.uk/CG36
  o Amiodarone and Class 1C AADs are both appropriate for pharmacological cardioversion.
  o For maintaining sinus rhythm among patients with paroxysmal AF, no drug therapy or “as needed” therapy is appropriate for those with infrequent episodes and few symptoms. Class 1C agents or amiodarone are appropriate if initial beta blocker therapy has failed.
  o Among patients with persistent AF, AAD therapy is not required among patients who have undergone successful ablation and cardioversion. Class 1C agents, amiodarone, or solatol can be administered if beta blocker therapy fails to control symptoms.

Recent Technology Assessments

- Dronedarone
  o The Cochrane Collaboration
    http://www.cochrane.org/reviews/en/ab005049.html
    Dronedarone appears to reduce atrial fibrillation recurrence by approximately 40%. Dronedarone is not associated with a significant impact on all-cause mortality when compared to placebo care, but is associated with increased stoppage of use due to adverse effects.

  o National Institute for Health and Clinical Excellence (NICE):
    Technology assessment in progress, due June 2010.

Coverage Policies

- Dronedarone
  o Humana: Use of dronedarone requires prior approval. Humana considers dronedarone to be medically necessary when the following criteria are met:
    1. The patient must have a diagnosis of either atrial flutter or AF;
2. The patient has documented contraindications, intolerance, adverse reactions, or is non-responsive to amiodarone;
3. The patient’s last amiodarone dose was at least seven days prior to administration of dronedarone, or the patient has neither Class IV heart failure nor Class II or III failure with a recent decompensation that requires hospitalization or referral to a specialized heart failure clinic.

- Aetna: The physician must obtain a medical exception in order for the medication to be eligible for coverage.

### Ongoing Research (from [www.clinicaltrials.gov](http://www.clinicaltrials.gov))

<table>
<thead>
<tr>
<th>Trial Sponsor /Title</th>
<th>Design</th>
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<th>Populations</th>
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<th>Comments</th>
</tr>
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</table>
| Cardiome Pharma, NCT00668759/A Phase III Superiority Study of Vernakalant vs Amiodarone in Subjects With Recent Onset Atrial Fibrillation | RCT    | Proportion of subjects with conversion of atrial fibrillation to sinus rhythm within 90 minutes after the start of infusion. | • N = 240
• 18 Years to 85 Years | Vernakalant Injection vs. Amiodarone Injection | Study Completion Date: October 2009 |
| Astellas Pharma Inc/Cardiome Pharma, NCT00115791/Study to Determine the Response and Effectiveness of RSD1235 in Subjects With Atrial Fibrillation or Atrial Flutter | RCT    | Occurrences of hypotension, ventricular arrhythmias and death; successful conversion to sinus rhythm for at least one minute | • N = 470
• 18 Years to 85 Years | Vernakalant vs. Placebo | Estimated Study Completion Date: May 2011 |
APPENDIX B

Catheter Ablation for Atrial Fibrillation
**Introduction**

Among patients with atrial fibrillation (AF), catheter ablation is a common technique used to restore normal heart rhythm. During catheter ablation, abnormal tissue in the atrial space is destroyed to interrupt faulty electrical signals and restore normal sinus rhythm. Ablation is most frequently accomplished using radiofrequency (RF) energy, which also cauterizes the lesions created. Cryothermal approaches also may be used to freeze tissue.

The most common type of catheter ablation performed is pulmonary vein isolation (PVI). The pulmonary vein is a common source of abnormal electrical activity that can trigger AF; the goal of PVI is therefore to create lesions that will interrupt all electrical communication between the pulmonary vein and the atria. Other sites of ablation may include the vein of Marshall and the superior vena cava, although these are most frequently ablated as an adjunct to PVI rather than a substitute. For patients with persistent or chronic AF, so-called “linear ablation” may be employed, in which pulmonary vein lesions are anchored to other ablation sites or the mitral valve in an attempt to create an unfavorable environment for sustained AF.

Catheter ablation is performed in an electrophysiology (EP) lab. In most cases the location of catheter insertion will be either the neck or groin area. One or more diagnostic catheters will be inserted into the blood vessel and are moved toward the heart. The physician will follow the catheter’s progress via a special monitor connected to a fluoroscopic camera. The diagnostic catheters will be used to study the arrhythmia. Through the use of these catheters, the physician can get a better understanding of the arrhythmia and determine how best to treat it. Once the physician determines the location of the abnormal tissue, it can be ablated.

A catheter ablation procedure can take between 2-6 hours to complete, depending upon the level of complexity. The patient must lie flat and remain still for several hours. Care must be taken to avoid bending or lifting the legs, to allow the vessels an opportunity to heal properly afterwards. Sometimes the patient is allowed to go home on the day of the procedure; otherwise the patient will be required to stay in the hospital overnight. Some patients experience swelling, bruising, and bleeding where the catheters were inserted. Serious complications that can occur include stroke, abnormally slow heart rate (bradycardia), fluid buildup and cardiac pressure (cardiac tamponade), and formation of blood clots or air pockets in the bloodstream (emboli). Death is very rare during these procedures. Catheter ablation can be used as both a second-line (following a failed trial of drug therapy) and first-line treatment for AF.
Professional Organization and Agency Recommendations

  
The Task Force considers the following indications to be appropriate for catheter ablation:
  
  o Symptomatic AF refractory or intolerant to at least one Class 1 or Class 3 antiarrhythmic medication; or
  o Selected symptomatic patients with heart failure and/or reduced ejection fraction.

  In rare clinical situations, it may be appropriate to perform catheter ablation as first-line therapy. Catheter ablation should not be performed in patients with left atrial thrombus.

- The American College of Cardiology, the American Heart Association, and the European Society of Cardiology (ACC/AHA/ESC, 2006) [http://circ.ahajournals.org/cgi/reprint/CIRCULATIONAHA.106.177031v1](http://circ.ahajournals.org/cgi/reprint/CIRCULATIONAHA.106.177031v1)
  
  ACC/AHA/ESC recognizes catheter ablation as a practical alternative in those with symptomatic AF with little or no left atrium enlargement. However, catheter ablation should not be attempted in those who have not undergone previous medical management for ventricular rate control.

  
  Atrioventricular junction (AVJ) catheter ablation is an option in those who have drug-resistant AF, especially those who have no existing cardiac co-morbidities.

Recent Technology Assessments

  
  Patients who receive RF ablation as a second-line therapy are more likely to have maintained sinus rhythm than those who were treated with medical therapy alone at 12 months post-procedure. Existing levels of evidence are insufficient to evaluate the effectiveness of RF ablation as a first-line treatment, as well as its impact on severity of congestive heart failure, stroke, and quality of life.

- Health Technology Assessment NIHR HTA Programme (2008) [http://www.hta.ac.uk/fullmono/mon1234.pdf](http://www.hta.ac.uk/fullmono/mon1234.pdf)
  
  RF catheter ablation (RFCA) is a relatively safe and efficacious procedure for the treatment of both AF and atrial flutter. There is some data to suggest that

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RFCA is a better treatment option than AADs in patients with refractory paroxysmal AF in terms of freedom from arrhythmia at 12 months. There is uncertainty regarding the long-term effects of RFCA.

  The evidence on the safety and efficacy of percutaneous RF ablation is adequate to support the use of this procedure in a select group of patients. This group of patients includes symptomatic patients with AF refractory to anti-arrhythmic drugs or where medical therapy is contraindicated because of co-morbidities or drug intolerance.

  There is insufficient evidence from available controlled trials to allow a conclusion to be formed. PVI as a treatment for atrial fibrillation does not meet the TEC criteria.

Coverage Policies

- Centers for Medicare and Medicaid Services (CMS): Medicare does not currently have a national coverage determination for the use of catheter ablation in the treatment of atrial fibrillation. A meeting of the Medicare Evidence Development and Coverage Advisory Committee (MedCAC) meeting was held in October 2009 to discuss this topic. The evidence was judged to be adequate to evaluate catheter ablation for AF recurrence and symptom relief; there was also consensus that 2nd-line therapy with ablation improves health outcomes relative to standard care. However, a lack of evidence regarding catheter ablation’s impact on long-term outcomes, as well as its effects among Medicare beneficiaries was noted; it was suggested that a “coverage with evidence development” policy may be appropriate.

- CIGNA: CIGNA considers transcatheter ablation of the pulmonary veins a medically necessary alternative to long-term antiarrhythmic drug therapy for atrial fibrillation treatment for individuals who are (a) symptomatic for recurrent paroxysmal or persistent atrial fibrillation; and (b) have little or no left atrial enlargement present.

- Aetna: Cardiac catheter ablation procedures are considered medically necessary by Aetna for members with drug-resistant or drug-intolerant atrial tachycardia, atrial flutter, or either of these symptoms associated with paroxysmal atrial fibrillation; or, members with any of these conditions who do not want to undergo long-term drug therapy.
Wellpoint/Anthem: Transcatheter radiofrequency ablation of arrhythmogenic foci in the pulmonary veins is considered medically necessary when the patient meets both of the following criteria:
  - Is symptomatic; AND
  - Is resistant or has intolerance to one or more antiarrhythmic drugs, or has a contraindication to the appropriate therapy

Ongoing Research (from www.clinicaltrials.gov)

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<thead>
<tr>
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<th>Population</th>
<th>Variables</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Population Health Research Institute, NCT00392054/ The RAAFT Study | RCT | Time to 1st recurrence of electrocardiographically documented symptomatic atrial fibrillation lasting >30 seconds during follow-up | Pulmonary Vein Isolation vs. Anti-Arrhythmic Drugs per ACC/AHA 2006 Guidelines for the Management of Patients with AF | • N = 400
  • Age >18 years old | Estimated Study Completion Date: December 2009 |
| Mayo Clinic, NCT00911508/ Ablation Versus Anti-Arrhythmic (AA) Drug Therapy for AF - Pivotal Trial (CABANA) | RCT | Reducing total mortality in patients with untreated or incompletely treated AF | Pharmacologic Therapy Rate and/or Rhythm Control vs. NAVI-STAR Thermo-cool (Left Atrial Catheter Ablation) | • N = 3000
  • 18 Years to 90 Years | Estimated Study Completion Date: September 2015 |
APPENDIX C

Surgical Ablation for Atrial Fibrillation
Introduction
Surgical ablation techniques have evolved over the past 20 years and serve as a viable option for rhythm control among patients with atrial fibrillation (AF). Surgical ablation has historically been reserved for patients who are considering surgery for other cardiovascular conditions (e.g., valve replacement); however, the advent of minimally-invasive surgical techniques has led to their use for AF ablation alone in some patients.

There are 2 major types of surgical techniques used in the treatment of AF:

1. **Cox-Maze** – This is the traditional, open surgical approach to treatment of AF. The surgeon creates multiple left and right atrial incisions, which are then sutured back together. This creates lesions of scar tissue, which interrupt re-entrant circuits, preventing abnormal electrical activity from circulating through the heart and restoring normal sinus rhythm. The Cox-Maze procedure also includes excising the left atrial appendage for stroke prevention.

2. **Mini-Maze** – This procedure was first performed in 2003 and has been performed in over 750 patients worldwide. The mini-Maze features a minimally-invasive approach, using devices that are inserted into incisions made between the ribs. Use of a thoroscope (a video telescope) helps surgeons guide the energy source to the atria. Radiofrequency energy, similar to that used in catheter ablation, is used to create lesions that disrupt irregular electrical pathways. Mini-maze includes bilateral pulmonary vein isolation and allows for excision of the left atrial appendage. The procedure has typically been used to treat patients who have chronic atrial fibrillation and are non-responsive to pharmacological treatment, but has also been used as a first-line approach in some instances.

Depending on whether a traditional or minimally-invasive approach is used, the ablation procedure will either be “on-pump” (i.e., use of a cardiopulmonary bypass system to maintain heart and lung function) or “off pump”. In either case, an inpatient stay in the hospital is required; the length of stay will vary depending on any other cardiac surgical procedures performed. All approaches to surgical ablation carry risks of serious complications, including coronary artery injury, phrenic nerve paralysis, and esophageal perforation. In addition, temporary recurrence of atrial fibrillation in the 3-6 months post-surgery is common, and many patients receive anti-arrhythmic drugs to aid in the return to sinus rhythm.
Professional Organization and Agency Recommendations

- Institute for Clinical Systems Improvement (ICSI, 2008) http://www.icsi.org/atrial_fibrillation__guideline_/atrial_fibrillation__guideline_38782.html
  ICSI recommends surgical ablation as an option for patients for whom antiarrhythmic treatment has failed and the patient requires further treatment.

  The Task Force considers the following indications to be appropriate for surgical ablation:
  - Symptomatic atrial fibrillation in patients who are undergoing other cardiac surgery;
  - Select asymptomatic atrial fibrillation in patients in whom surgical ablation can be performed with minimal risk; or
  - Stand-alone atrial fibrillation surgery as an option for AF patients who either prefer surgery, have failed one or more catheter ablation attempts, or are not candidates for catheter ablation.

  Arrhythmia surgery is recommended for patients who are undergoing concomitant cardiac surgery. No other evidence currently exists to identify specific patients for referral for arrhythmia surgery other than those who have previously failed antiarrhythmic treatment.

Recent Technology Assessments

  Patients who have drug-resistant atrial fibrillation who undergo concomitant heart surgery, while a small minority of AF patients, may benefit greatly from surgical ablation in addition to surgery vs. heart surgery alone.
• National Institute for Health and Clinical Excellence (NICE, 2005)
  Current evidence on the use of the Cox Maze procedure appears to be
  sufficient to support its use when performed in conjunction with other
  cardiac surgery and if appropriate arrangements are in place for consent,
  audit, and clinical governance.

  Other organizations with technology assessments in progress on surgical
  ablation include the Cochrane Collaboration and the Canadian Agency for Drugs
  and Technologies in Health (CADTH).

Coverage Policies
• Centers for Medicare and Medicaid Services (CMS): Medicare has not
  made a national coverage determination for the use of surgical ablation in the
  treatment of atrial fibrillation. Representative local coverage determinations
  consider both the Cox-Maze and mini-Maze reasonable and necessary in
  patients with any of the following indications:
  o Resistance to or intolerance of drug therapy
  o Atrial fibrillation or flutter for >6 months with an enlarged left atrium
  o High risk for thromboembolism

• CIGNA: The Maze procedure is considered medically necessary in patients
  who have medically refractory symptomatic atrial fibrillation of any type for
  whom rhythm control is considered essential. CIGNA does not cover
  minimally-invasive, off-pump Maze procedures. They are considered
  experimental and investigational.

• Aetna: Both the Cox-Maze and mini-Maze procedures are considered
  medically necessary for the following situations:
  o The patient is suffering hemodynamic consequences of chronic atrial
    fibrillation.
  o The patient cannot tolerate the side effects of drug therapy.
  o The patient is at high risk for thromboembolism due to either of the
    following:
    a. Experienced a previous episode of venous thromboembolism, yet other
       causes have been ruled out; or
    b. Long-standing atrial fibrillation has been documented in
       patients with mitral valve disease

• Wellpoint/Anthem: Both the Cox-Maze and mini-Maze procedures are
  considered medically necessary for drug-resistant atrial fibrillation or flutter.
  They are also considered medically necessary for those with highly
  symptomatic atrial fibrillation who require other surgery for valvular,
  ischemic, or congenital heart disease.
• Blue Cross Blue Shield of Massachusetts: The Cox-Maze procedure is covered, with or without concomitant cardiac surgery, when it is used for the treatment of drug-resistant atrial fibrillation or flutter. Minimally invasive, off-pump procedures are not covered as they are considered investigational.

Ongoing Research (from www.clinicaltrials.gov)

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<th>Comments</th>
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<td>National Heart, Lung, and Blood Institute (NHLBI)</td>
<td>RCT</td>
<td>Freedom from atrial fibrillation</td>
<td>Mitral valve surgery with ligation/excision of left atrial appendage vs. Mitral valve surgery with ligation/excision of left atrial appendage with ablation</td>
<td>• N = 260 • 18 Years and older</td>
<td>Estimated Study Completion Date: September 2013</td>
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<tr>
<td>National Institute of Neurological Disorders and Stroke (NINDS)</td>
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<tr>
<td>Canadian Institutes of Health Research (CIHR), NCT00903370/ Surgical Ablation Versus No Surgical Ablation for Patients With Atrial Fibrillation Undergoing Mitral Valve Surgery</td>
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<tr>
<td>Virginia Commonwealth University</td>
<td>Prospective Cohort Study</td>
<td>Minimally invasive surgical treatment for control of atrial fibrillation</td>
<td>Minimally Invasive Maze Procedure</td>
<td>• N = 5000 • 18 Years and older</td>
<td>Study Completion Date: September 2009</td>
</tr>
</tbody>
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APPENDIX D

Stroke Prevention in Atrial Fibrillation
Introduction
Atrial fibrillation (AF) is a powerful risk factor for stroke; it is estimated that patients with AF have a five-fold increased risk of stroke relative to those without this condition. Because of this, anticoagulation is often performed along with primary AF treatment to reduce the risk of blood clot formation that can lead to stroke. One such anticoagulant medication, warfarin (Coumadin®), has been shown to be effective in stroke prevention when used on a long-term basis among patients with AF. Warfarin is the most common oral anticoagulant in the US, and is used by approximately 2 million patients annually for a variety of conditions including venous thromboembolism (VTE), pulmonary embolism, and AF.

While warfarin’s effectiveness has been well-documented, its use is also associated with significant risks. Warfarin dosing varies by individual, and must be closely monitored to ensure that the blood clots within an appropriate timeframe, as measured by the international normalized ratio (INR). If the INR is too low, the patient is at increased risk for stroke; if the INR is too high, there is an increased risk of major bleeding. Patients must also discuss what other medications are being taken, since warfarin has interactions with many other drugs that may either interfere with its metabolism or increase the risk of side effects. Warfarin also interacts with alcohol, tobacco, and certain foods. Because of the complex nature of long-term use, there is interest in alternative means of stroke prevention among patients with AF. Several new strategies have been tested and are currently under consideration by the FDA; these strategies are summarized below.

Dabigatran
Dabigatran etexilate is an orally administered direct-acting thrombin inhibitor. It has been approved by the European Medicines Agency for use in the prevention of VTE following total hip and total knee surgery. Dabigatran differs substantially from warfarin in that it offers once-daily fixed oral dosing and there are no requirements for laboratory monitoring. Dabigatran is also not significantly affected by interactions with food and has a shorter half life than warfarin. In the Phase III RE-LY trial, the 150 mg dose of dabigatran was associated with significantly lower rates of hemorrhagic and non-hemorrhagic stroke as compared to warfarin; the rate of major bleeding was similar. However, dabigatran was associated with higher rates of certain adverse events relative to warfarin, including myocardial infarction and gastrointestinal side effects.

WATCHMAN® left atrial appendage (LAA) system
Between 60% and 90% of stroke-causing emboli originate in the LAA. Occlusion of the LAA may be achieved either through surgery or through the catheter-based implantation of an occlusive device. The WATCHMAN is an expandable nitinol (a nickel–titanium alloy) cage covered with a porous fabric. When implanted in the LAA, it blocks the formation of clots. In a Phase III clinical trial comparing the WATCHMAN to warfarin, a 32% reduction in the risk of stroke, cardiovascular or unexplained death, or systemic embolism was observed with the device; however,
the risk of immediate safety events (primarily pericardial effusion and other procedural complications) was twofold higher in the device group. In April 2009, the FDA circulatory systems device panel voted for approval of the WATCHMAN.

**Professional Organization and Agency Recommendations**

- American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (ACCP, 2008)  
  [http://chestjournal.chestpubs.org/content/133/6_supp...](http://chestjournal.chestpubs.org/content/133/6_supp/546S.full.pdf+html)
  - In all patients with AF, the ACCP recommends long-term treatment for stroke prevention.
  - Patients with 2 or more risk factors for stroke should receive warfarin or another vitamin K antagonist; those with 1 risk factor should receive aspirin or warfarin.

- The American College of Cardiology, the American Heart Association, and the European Society of Cardiology (ACC/AHA/ESC, 2006)  
  [http://circ.ahajournals.org/cgi/reprint/CIRCULATIONAHA.106.177031v1](http://circ.ahajournals.org/cgi/reprint/CIRCULATIONAHA.106.177031v1)
  - Antithrombotic therapy is recommended for all patients with AF. The exceptions to the recommendation include those with lone AF and those with contraindications.
  - For those with more than one moderate risk factor for stroke, anticoagulation with warfarin or another vitamin K antagonist is recommended.
  - Aspirin (81-325 mg daily) is a recommended alternative to vitamin K antagonists in low-risk patients (for stroke) or those who have contraindications to oral coagulation.

- The National Collaborating Centre for Chronic Conditions (NCC-CC, 2006)  
  - Paroxysmal AF: The decision to initiate antithrombotic therapy should be based on appropriate risk stratification.
  - Persistent AF: Following successful cardioversion, patients should be maintained on warfarin for a minimum of 3 weeks, longer if there is a high risk of AF recurrence.
  - Permanent AF: Long-term warfarin therapy (or aspirin in patients in whom warfarin is contraindicated) should be given after consideration of the long-term risks and benefits.

**Recent Technology Assessments**

- **Dabigatran:** There are currently no technology assessments of dabigatran use in the prevention of stroke in patients with AF. The following technology assessments have been completed for the use of dabigatran in the prevention of VTE:
Canadian Agency for Drugs and Technologies in Health (CADTH), Canadian Expert Drug Advisory Committee (CEDAC, 2009) http://www.cadth.ca/media/cdr/complete/cdr_complete_Pradax_January-28-2009.pdf
The Committee recommends that dabigatran not be listed as an option in the prevention of venous thromboembolism, based on the comparison of dabigatran extelixate to enoxaparin. Dabigatran at a dosage of 220 mg administered daily was associated with a significantly increased incidence of venous thromboembolism in the REMOBILIZE study.

NICE has recommended that dabigatran serve as an option for the primary prevention of venous thromboembolism in adults who have undergone hip or knee replacement surgery.

- **WATCHMAN**: There are currently no technology assessments that evaluate the use of the WATCHMAN in the prevention of stroke in patients with non-valvular atrial fibrillation. However, the following assessment has been performed to appraise left atrial appendage occlusion:

The current evidence on the safety and efficacy of percutaneous occlusion of the left atrial appendage (LAA) for atrial fibrillation does not appear to be adequate without having special arrangements for consent and for audit or research be arranged.

**Coverage Policies**
There are generally no coverage limitations on the use of aspirin or warfarin for anticoagulation (other than clinical indications and contraindications). Dabigatran and the WATCHMAN are not yet FDA-approved, and have therefore not yet been addressed by public and private payers.
### Ongoing Research (from www.clinicaltrials.gov)

- **Dabigatran**

<table>
<thead>
<tr>
<th>Trial Sponsor / Title</th>
<th>Design</th>
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| Boehringer Ingelheim Pharmaceuticals, NCT00808067/RELY-ABLE Long Term Multi-center Extension of Dabigatran Treatment in Patients With Atrial Fibrillation Who Completed RE-LY Trial | RCT    | Safety (lack of major bleeding events);                                         | • 18 Years and older  
+ N = 6200                   | Dabigatran etexilate vs. warfarin                                     | Active but not recruiting; estimated primary completion date is July 2011 |

- **WATCHMAN**

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| Atritech, NCT00851578/ASA Plavix Feasibility Study With WATCHMAN Left Atrial Appendage Closure Technology | Feasibility study | Characterize the performance of the WATCHMAN LAA Closure device in atrial fibrillation patients contraindicated to warfarin treatment | • N = 150  
+ 18 Years and older                  | WATCHMAN only                             | Estimated study completion date: February 2012 |
| Atritech, NCT00129545/WATCHMAN Left Atrial Appendage System for Embolic PROTECTION in Patients With Atrial Fibrillation | RCT    | Incidence of stroke, systemic embolism, and cardiovascular death                  | • N = 1550  
+ 18 Years and older                  | WATCHMAN device vs. warfarin therapy       | Estimated study completion date: October 2014 |