FINAL APPRAISAL DOCUMENT

RHYTHM CONTROL AND STROKE PREVENTION STRATEGIES FOR PATIENTS WITH ATRIAL FIBRILLATION

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CONTENTS

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EXECUTIVE SUMMARY

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia in the US population (Fuster, 2006). AF can be asymptomatic but it may also be associated with shortness of breath, difficulty with exercise, palpitations, general fatigue, dizziness, and confusion. Importantly, AF is the second-leading cause of stroke, after atherosclerosis (Heron, 2009); the risk of stroke among those with AF is estimated to be fivefold higher than in patients without this disorder (National Stroke Association, 2010).

AF may be episodic or chronic in nature. AF is classified as "paroxysmal" when episodes last 7 days or less and terminate spontaneously. "Persistent" AF occurs when episodes do not self-terminate and last longer than 7 days; this classification also includes a "long-standing" category, described as persistent AF for longer than one year. Finally, "permanent" AF describes a situation in which restoration of sinus rhythm is no longer considered possible.

In the symptomatic patient, the goals of treatment are twofold: (1) to reduce AF symptoms and its contribution to comorbidity; and (2) to prevent stroke. Attempts to reduce or eliminate AF symptoms can be accomplished via several strategies:

- Cardioversion to return the heart to normal sinus rhythm
- Medications to control heart rate and reduce AF symptoms
- Medications to restore and maintain normal sinus rhythm
- Catheter-based and surgical ablation techniques to interrupt the electrical pathways triggering AF

Management of all patients with AF also involves a stroke prevention component. This is most often accomplished using an oral antithrombotic medication such as warfarin or aspirin; other approaches, such as use of the direct thrombin inhibitor dabigatran or the LAA exclusion device known as the WATCHMAN®, are currently under consideration by the FDA as future alternatives for stroke prevention in AF.

Rate control with medications is often considered to be the most appropriate initial strategy for AF management, as it is well-accepted that slowing ventricular response both at rest and during activity will result in symptom improvement and likely reduce the risk of cardiovascular events (Dorian, 2010). Recent guidelines suggest that rate control medications be continued for long-term management in most AF patients, with the addition of rhythm control medications for patients who remain symptomatic despite adequate rate control, or for those with special considerations such as degree of symptoms, younger age, or higher activity levels (Camm, 2010). For patients such as these, the choice among rhythm control strategies becomes a paramount clinical concern, and given the number and variety of options, the comparative effectiveness of rhythm control strategies is a key question for clinical and policy decision-making. The typical entry criteria for the catheter ablation vs.

AAD RCTs in our review illustrate the type of patient for whom adequate control of symptoms is the major goal:

- Multiple episodes of AF within 3-6 months prior to study entry
- Prior failure of at least one AAD
- Reported intolerance of AF symptoms

Our review therefore emphasizes data relevant for those patients with moderately or highly symptomatic AF who require further alleviation of symptoms despite best attempts to achieve rate control, and who are therefore considering some form of rhythm control as an additional treatment approach.

This appraisal sought to evaluate the comparative clinical effectiveness and comparative value of alternative rhythm control and stroke prevention strategies for AF patients with moderate-to-severe symptoms, with a special focus on the following key comparisons:

1) Rhythm control with left atrial catheter ablation (LACA) vs. anti-arrhythmic drugs
2) Rhythm control with LACA vs. thorascopic, off-pump (TOP) surgical ablation
3) Rhythm control with amiodarone vs. dronedarone
4) Stroke prevention with warfarin/aspirin vs. dabigatran
5) Stroke prevention with warfarin/aspirin vs. left atrial appendage (LAA) exclusion devices

Evidence related to these comparisons was evaluated for patients with paroxysmal, persistent, or long-standing persistent AF. Data were sought in the published literature that might provide insights into different risks and benefits for identifiable patient subpopulations, including subpopulations based on clinical, racial, ethnic, and gender characteristics. In particular, guided at the outset of our review by input from our external Evidence Review Group, we sought to frame the available evidence as it relates to three "prototypical" AF patients, each of whom represents a category of patients for whom the selection of appropriate treatment raises important clinical and policy questions:

1) A 60 year-old otherwise healthy patient with paroxysmal AF
2) A 65 year-old patient with persistent AF and congestive heart failure
3) A 75 year-old patient with persistent AF, diabetes mellitus and hypertension

This appraisal includes evidence based on systematic review and synthesis of published peer-reviewed studies. Our review of evidence regarding catheter ablation was built upon the recently completed AHRQ systematic review. Our appraisal also includes the results of a new decision analytic model built specifically to support this effort.

Alternative Treatment Options

I. Rhythm Control Strategies for Atrial Fibrillation

Antiarrhythmic Drugs

Antiarrhythmic drugs (AADs) may be used to try to maintain sinus rhythm after electrical cardioversion, or they may be initiated independently (Gopinathannair, 2009). It should be noted that AF recurrence is frequent even with the most effective AADs; in this context, success of rhythm control therapies is typically defined by reduction in the frequency and severity of symptoms, not by their elimination (Fuster, 2006).

There are many options among AADs, and the available drugs have differing levels and types of side effects (Reiffel, 2009). Among all AADs, amiodarone, although it is technically "off-label" for use in treating AF, is generally viewed as the most effective available drug at maintaining sinus rhythm. Amiodarone is frequently used in patients with underlying structural heart disease, as the risk of proarrhythmia (increased frequency and/or severity of atrial arrhythmias) in patients with heart disease is much lower with amiodarone than with other AADs (Zimetbaum, 2007). However, amiodarone's relative effectiveness is counter-balanced by its potential to cause severe side effects such as thyroid dysfunction and pulmonary fibrosis, particularly with long-term use. Because of these risks, for many patients with AF amiodarone is considered a second-line agent, used only if another AAD fails to control the rhythm adequately. Recently, a new non-iodinated amiodarone analogue, dronedarone, was approved by the FDA for use in patients with AF without severe heart failure (Stiles, 2009). The absence of iodine in dronedarone is thought to render the drug less toxic, but its comparative effectiveness vs. amiodarone and its optimal role in AF management is still controversial (Chan, 2009; Singh, 2010). Recently, reports have surfaced regarding incident cases of torsades de pointes and worsening CHF for patients on dronedarone, but their association with dronedarone use is still under investigation (FDA Adverse Event Reporting System, 2010).

Catheter Ablation

Among patients with atrial fibrillation, 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 (Crandall, 2009). The most common type of catheter ablation performed is pulmonary vein isolation (PVI) (Callahan, 2009). 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 (Crandall, 2009). Rare but serious complications can occur, including stroke during the procedure, cardiac tamponade, and atrioesophageal fistula from the energy source.

Proponents of catheter ablation argue that, by "curing" AF, the procedure provides permanent symptom relief and may produce electroanatomic remodeling of the atrial space, thereby reducing the risk of recurrence (Pappone, 2001). Others contend that the idea of a "cure" is oversold; recurrence of AF remains common after ablation, requiring

multiple repeat ablations in many patients. Moreover, there remain questions about whether ablation offers significant long-term improvements in quality of life compared to rate-control strategies; and, even after a successful ablation, current guidelines recommend continuation of antithrombotic therapy based on patients' underlying risks for stroke.

Surgical Ablation

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 greater consideration of surgical ablation as a potential treatment for AF among patients with no other indication for cardiac surgery.

There are three major types of surgical techniques used in the treatment of AF. Like catheter ablation, all approaches seek to interrupt abnormal electrical impulses that cause AF, but surgical techniques also involve excision or exclusion of the left atrial appendage (LAA), which is thought to be the location of 60-90% of the thrombi that cause AF-related strokes (Blackshear, 1996):

1. **"Cox-Maze III" –**Involves a full thoracotomy, cardiopulmonary bypass, and left and right atrial incisions, which are then sutured back together ("cut and sew" approach). This is a technically demanding procedure; as a result, only a limited number of centers worldwide perform it, and it is infrequently performed unless as an adjunct to other open-heart surgery.

2. **"Cox-Maze IV" –** Involves a smaller, "mini-thoracotomy" and cardiopulmonary bypass. Radiofrequency and/or cryothermal lesions are created rather than incisions. This procedure is considered simpler to perform and is associated with reduced operating-room time relative to Cox-Maze III (Melby, 2006b).

3. **Thorascopic "Off-Pump" (TOP) Approaches** – Performed on a "beating heart" – the heart is not arrested via bypass, and minimally-invasive techniques are used. Radiofrequency energy applied to the outside of the heart (epicardial ablation) is used for lesion creation. This approach has many variants, but typically involves pulmonary vein isolation at a minimum, as well as other potential ablation lines.

All surgical approaches carry small risks of serious complications, including stroke, tamponade, coronary artery injury, phrenic nerve paralysis, and esophageal perforation (Lee, 2009a), in addition to traditional surgical risks (e.g., myocardial infarction [MI], infection). In addition, as with catheter ablation, temporary recurrence of AF in the 3-6 months post-surgery is common, and many patients receive AADs during this period to aid in the return to sinus rhythm.

Proponents of surgical ablation describe several advantages over catheter-based ablation techniques, including removal of the LAA and use of bipolar energy. On the other hand, it is argued that effective management of AF can be accomplished through less invasive

means for many patients, and the additional risks posed by surgery may outweigh any potential clinical benefits offered by surgery.

The field of surgical ablation continues to evolve rapidly, and there are widely varying techniques used by different surgeons and surgical centers. Until recently, surgical ablation was performed by a relatively small number of centers given the complexity of the Cox-Maze procedures, and most patients referred for surgery were seeking an alternative after one or more failed catheter ablation attempts. As expertise and less-invasive TOP approaches have spread, however, there has been growing interest in the possibility of using surgical ablation as a primary treatment for highly symptomatic patients with AF for whom rate control is not an option and who have failed or are not suitable candidates for AAD therapy. Therefore, while evidence on all forms of surgical ablation is presented in this review, we emphasize evidence on TOP approaches as potential alternatives to catheter ablation or AAD therapy among patients who are not undergoing concurrent cardiac surgery for other indications.

II. Prevention of Stroke

Standard Care

Clinical guidelines link the choice of anti-thrombotic therapy to the patient's stroke risk. A well-accepted framework for measuring stroke risk in AF is the $CHADS_2$ score (Gage, 2001), based on the presence of the following risk factors:

- Congestive heart failure
- Hypertension
- Age ≥75 years
- Diabetes mellitus
- Prior stroke/transient ischemic attack (TIA)

Risk is scored on a 0-6 scale using one point for each of the first four risk factors, and two points for prior stroke/TIA. Guideline recommendations call for the long-term use of aspirin (75-325 mg daily) for patients at lower stroke risk ($CHADS_2$ scores of 0 or 1). For all other patients, long-term use of anticoagulants is recommended. Warfarin, which has been shown to be highly effective in preventing stroke in a variety of populations with AF, is the most common anticoagulant used in the US for this purpose, as well as for other conditions such as deep vein thrombosis and pulmonary embolism (Go, 2001).

While warfarin's effectiveness has been well-documented, its use is also associated with significant risks (Hylek, 2009). Frequent monitoring by blood test must be performed to ensure that the level of anticoagulant effect as measured by the international normalized ratio (INR) is neither too low nor too high. If the INR is too low, the patient is at increased risk for thrombotic stroke; if the INR is too high, there is an increased risk of major bleeding, including into the brain (hemorrhagic stroke). Warfarin treatment is also complicated by interactions with other drugs, alcohol, and certain foods. Due to these

concerns, dosing and management of patients on warfarin is a highly individualized, often intensive effort that persists for the duration of treatment.

Dabigatran Extexilate

Dabigatran extexilate is an orally administered direct-acting thrombin inhibitor (Kalus, 2009). It has been approved by the European Medicines Agency for use in the prevention of venous thromboembolism following total hip and total knee surgery. Dabigatran differs substantially from warfarin in that it offers once-daily fixed dosing without requirement for laboratory monitoring. Dabigatran is also not significantly affected by interactions with food and has a shorter half life than warfarin (Hylek, 2009). On September 20, 2010, the FDA's cardiovascular and renal drugs advisory committee voted unanimously to recommend dabigatran's approval (Drahl, 2010).

Left Atrial Appendage Exclusion

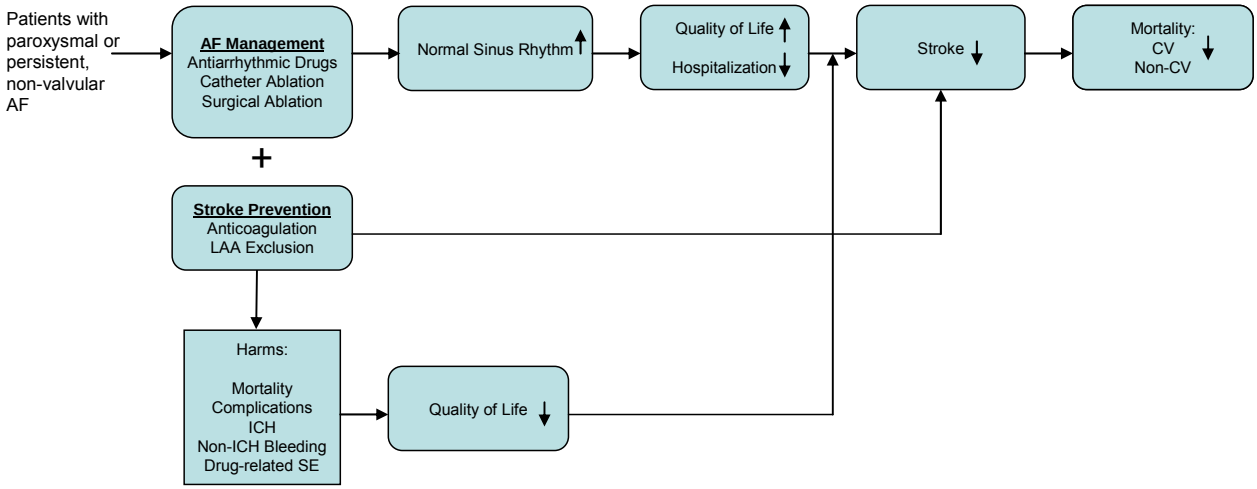
An alternative to surgical excision of the left atrial appendage is device-based exclusion. In the United States, the FDA recently gave 510 (k) clearance to the AtriClip® Gillinov-Cosgrove device for use during surgical ablation procedures. Findings from clinical testing suggest a high rate of confirmed LAA exclusion with no related safety events; stroke rates were not measured in this study, however, and no comparison group was included (AtriCure, 2010).

Another device that has been submitted for FDA approval is the WATCHMAN, an expandable nitinol (a nickel–titanium alloy) cage covered with a porous fabric (Fountain, 2006). When implanted in the left atrial appendage, it acts as a filter to block the formation of clots. In April 2009, based on the result of a randomized clinical trial, the FDA circulatory systems device advisory panel voted for approval of the WATCHMAN. However, several safeguards were recommended, including implantation of the WATCHMAN only in centers with adequate surgical backup and extensive follow-up of patients in current trials (O'Riordan, 2010). In March 2010, the FDA requested that the manufacturer design and conduct a confirmatory study on the WATCHMAN's safety and effectiveness (Atritech, 2010); the manufacturer expects to begin the study later this year, which will likely delay final regulatory approval by an additional year or more.

Analytic Framework

The analytic framework for this review is shown in the Figure on the following page. Note that the figure is intended to convey the conceptual links involved in evaluating outcomes of these management options, and are not intended to depict a clinical pathway that all patients would transit through. This framework also does not represent the clinical pathways as they were constructed for the decision analytic model (see Section 8).

Analytic Framework: Strategies to Restore Normal Sinus Rhythm in Atrial Fibrillation



AF: Atrial fibrillation; CV: Cardiovascular; LAA: Left atrial appendage; ICH: Intracranial hemorrhage; SE: Side effects

There are little to no data directly demonstrating the impact of AF management strategies on ischemic stroke or cardiovascular and overall patient mortality, so judgments about the effectiveness of these interventions must rest almost exclusively upon surrogate endpoints as well as evaluation of treatment-associated risks. In contrast, evidence on stroke prevention strategies contains direct measures of ischemic stroke rates as well as specific harms (i.e., intracranial hemorrhage, other major bleeding).

There is considerable debate about how much credence to place in comparisons across studies of surrogate outcome measures for the treatment of AF. Study measurements of normal sinus rhythm or "freedom from AF" are typically constructed as point-in-time measurements and may not capture previous or subsequent episodes of AF recurrence. Some studies focus on symptomatic AF alone while others include asymptomatic AF; measurement of AF itself can vary widely, from single in-office electrocardiograms, to longer Holter examinations; and, in addition, may also incorporate patient-reported episodes of AF. It has been noted that the more diligently AF is sought, the more is found, and so comparisons across studies using different methods is fraught with the risk that differences in AF recurrence may be nothing but measurement artifact (Henry, 2010).

Moreover, it must be acknowledged that measures of AF by themselves cannot tell us the degree to which AF episodes, particularly short ones, impact quality of life or other outcomes of interest to patients. Some patients have both symptomatic and asymptomatic episodes of AF, and even patients who have recurrent symptomatic AF following treatment may nevertheless be satisfied and have increased quality of life because the incidence of symptomatic episodes may be far lower than was experienced previously.

For all these reasons, clinical and policy decision-makers should be aware that evidence on the outcomes of treatment for AF is almost exclusively limited to surrogate outcomes that are difficult to compare and that can be over-interpreted; it is thus very important to maintain respect for the tenuous links between the components of the analytic framework for the evaluation of AF treatment options.

Evidence on Comparative Clinical Effectiveness

Data Quality

A total of 124 studies met all entry criteria for review. The most abundant data identified were for catheter ablation (79 studies), followed by AADs (33) and thorascopic, off-pump (TOP) surgical ablation (12). Of the 79 catheter ablation studies, 12 were from a previous AHRQ review of catheter ablation (Ip, 2009) and 67 were newly-abstracted as part of this appraisal. Single RCTs were identified examining dabigatran (Connolly, 2009b) and devices for LAA exclusion (the WATCHMAN; Holmes, 2009). While nearly 40% of the studies identified for this review were RCTs, these varied substantially in study quality, as fewer than half were rated as "good" quality studies. Evidence for TOP surgical ablation was particularly scant; no RCTs were identified, and the remaining case series and cohort studies varied significantly in technical approach, outcome measurement, and level of reporting detail. Study populations also differed substantially; as shown in Table ES1 on the following page, patients in the catheter ablation and TOP surgical ablation studies tended to be younger, more likely to be male, and more likely to have paroxysmal AF than patients receiving AADs.

In addition to the study differences by intervention noted previously, other more subtle differences in candidate populations for each treatment may also complicate comparisons. For example, while the general policy construct that positions TOP surgical ablation and catheter ablation as competing for the same set of patients may be reasonable, many surgical patients in the included case series had already failed multiple previous catheter ablation attempts. Previous catheter ablation was a protocol *requirement* in one TOP surgical ablation study (Castella, 2010); in the others, the proportion with failed prior catheter ablation ranged from 5-42% (mean: 24%).

Identification of studies of the impact on treatment in various key subgroups was also attempted, including by type of AF, age, sex, race/ethnicity, and the presence of key comorbidities such as CHF. With the exception of catheter ablation RCTs that focused on primarily paroxysmal vs. mixed forms of AF, there were few data with which to differentiate treatment effects by individual patient clinical characteristics.

Table ES1. Patient characteristics in atrial fibrillation studies, by type of intervention.

	Estimate (unweighted average across studies)		
Intervention	**% Paroxysmal AF**	**% Male**	**Age (y)**
Catheter Ablation	66.0	76.3	57.0
TOP Surgical Ablation	52.9	70.4	58.9
AADs	30.0	64.2	65.0

AF: Atrial fibrillation; TOP: Thorascopic, off-pump surgical ablation; AADs: Antiarrhythmic drugs

Clinical Benefits: AADs vs. Catheter Ablation vs. TOP Surgical Ablation

Mortality and Stroke

Given the short-term time frames for nearly all studies, data on the impact of different management options for AF rhythm control on cardiovascular mortality or overall mortality are extremely limited. While findings from a large cohort study comparing outcomes for patients receiving catheter ablation vs. AADs (Pappone, 2003) suggests a 50% lower rate of mortality for catheter ablation vs. AADs over a median time span of 2.5 years, this study is vulnerable to significant selection bias and no such difference in mortality has been observed in RCTs. The small body of evidence on TOP surgical ablation includes too few deaths to be useful in judging potential differences in short or long-term mortality compared to AADs or catheter ablation.

Data with which to compare the impact of AADs, catheter ablation, and TOP surgical ablation on the rate of stroke are extremely limited by the short follow-up times available. Data on long-term stroke rates with catheter ablation were available only from cohort studies and case series; annual rates ranged from 0-5%. As with mortality, stroke was infrequently reported in surgical series, and only as a peri-operative event.

Freedom from AF Recurrence

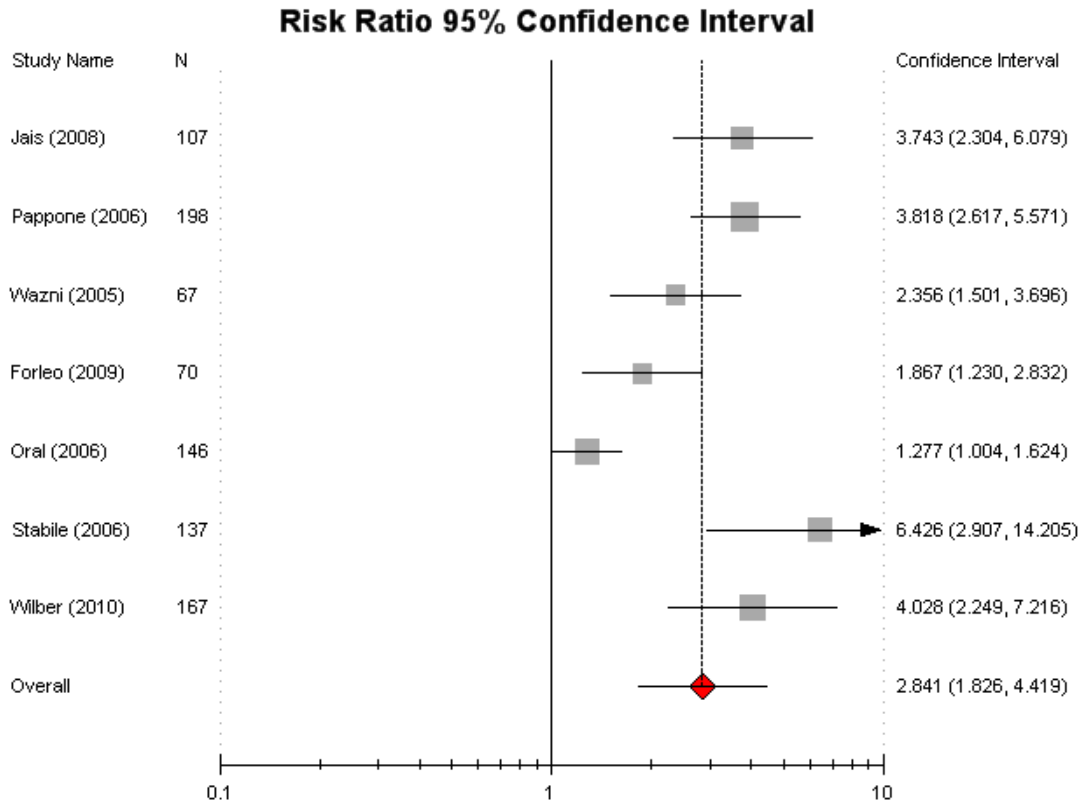
As described earlier, measurement of this outcome in catheter ablation and TOP surgical ablation studies is highly variable, with different interpretations of the outcome and different methods of measurement. In catheter ablation RCTs that focused on freedom from any AF recurrence up to 12 months as measured by Holter monitor, event recorder or transtelephonic EKG, patients undergoing catheter ablation were nearly 3 times as likely to be free from AF (range: 56-87%) relative to those receiving AADs (range: 9-58%); the relative advantage for catheter ablation was more pronounced for patients with paroxysmal AF. While data from comparative trials were not available for TOP surgical ablation, the freedom from AF at 6-12 months in surgical case series was comparable to that seen for catheter ablation (range: 62-88%).

Interpretation of these findings is made difficult by the "point-in-time" nature of the outcome measurement. AF recurrence is not uncommon following either catheter or surgical ablation, and may persist over several years after the initial procedure (Henry,

2010). In addition, studies differ in how "early" recurrence was considered (i.e., freedom from AF at month 12 vs. freedom from any recurrence up to month 12).

Findings from our meta-analysis of the existing RCT data for catheter ablation and AADs suggested a nearly 3-fold greater likelihood of freedom from AF at 9-12 months for catheter ablation (Figure ES1 below); our estimate is somewhat lower than that produced in the AHRQ review of catheter ablation (Ip, 2009) (RR=3.46 vs. 2.84 in our analysis); this may have been a function of the limitation of studies in our meta-analysis to those measuring recurrence using long-term monitoring methods as well as the introduction of additional studies to the analysis (7 vs. 3 in the AHRQ review). Findings from further exploratory analyses indicated that the effects of catheter ablation were more pronounced in studies that had ≥65% of patients with paroxysmal AF than in those with greater numbers of patients with persistent or long-standing persistent AF.

Figure ES1. Meta-analysis of 6-12 month freedom from AF: catheter ablation vs. AADs.



Need for Subsequent Procedures Following Catheter Ablation and TOP Surgical Ablation

Data on repeat ablation for AF recurrence was found in a limited number of RCTs and case series of catheter ablation; rates varied between 10-70%. In some studies, the total number of ablations performed per patient also was reported; this figure ranged between 1.2-2.9 procedures per patient. Findings from an analysis performed by ICER of data from a national private health plan indicates that, over 1-3 years of follow-up, 82% of patients

required a single ablation, while 15%, 2%, and 1% required 2, 3, and 4 procedures respectively. Data are limited on use of subsequent catheter ablation for AF recurrence following TOP surgical ablation. Findings from 2 case series suggest that approximately one-fifth of patients undergoing TOP surgical ablation received subsequent treatment to restore normal sinus rhythm, such as catheter ablation or cardioversion.

Hospitalization and Quality of Life

Evidence from a limited number of RCTs suggests that, compared to treatment with AADs, catheter ablation is associated with reductions in rates of all-cause and cardiovascular hospitalization; however, these comparisons are confounded to some extent by treatment goals. For example, protocols for patients on AADs who suffer recurrent AF may involve immediate admission for cardioversion and/or medication change, while post-ablation patients may initially receive outpatient approaches to managing recurrent AF before consideration of repeat ablation. Similarly, data from a limited number of catheter ablation RCTs and comparative studies also suggest significant improvement in general quality-of-life scores and symptom scales for patients following catheter ablation relative to AADs; findings from a long-term case series also suggest that post-ablation QoL improvement persists independent of the level of ablation success. None of the surgical series report on the impact of TOP procedures on subsequent hospitalization rates; findings from a single surgical series (n=43) suggest significant improvement on quality-of-life and symptom scores at 1 year relative to baseline (Bagge, 2009).

Cessation of Anticoagulation Following Catheter Ablation or TOP Surgical Ablation

The potential for stopping oral anticoagulation following ablation is an important consideration for both patients and clinicians, given the inherent risks and intensive monitoring currently involved. However, available data are extremely limited. Only one catheter ablation RCT reports on cessation of anticoagulation following restoration of normal sinus rhythm (60% vs. 34% for AADs) (Jaïs, 2008). The impact of this change on stroke rates was not measured, however. Data from several case series and cohort studies suggest no detrimental impact of warfarin discontinuation among patients receiving catheter ablation and in NSR, but these studies are limited by restriction to low-risk populations as well as their observational nature. Data from surgical series suggest an inconsistent approach to anticoagulation following surgery.

Clinical Benefits: Amiodarone vs. Dronedarone

Mortality and Stroke

Limited head-to-head data exist with which to judge the differential impact on all-cause mortality for amiodarone vs. dronedarone. In the single head-to-head RCT that has been conducted, the DIONYSOS trial, all-cause mortality was 3.4% for amiodarone vs. 1.4% for dronedarone on an annualized basis, a difference that was not statistically significant (Le Heuzey, 2010). Dronedarone was found to have a significantly lower rate of cardiovascular death vs. placebo in the large, placebo-controlled ATHENA trial (1.5% vs. 2.2% on an annualized basis) (Hohnloser, 2009). In our indirect meta-analysis of multiple amiodarone

and dronedarone trials, the relative risk of all-cause mortality was 1.80 for amiodarone vs. dronedarone, but the difference was not statistically significant (95% CI=0.68, 4.78).

Published studies of amiodarone and dronedarone also provide limited data on stroke rates, with no evidence of benefit for either drug relative to placebo in any studies. Data from an amiodarone RCT showed annual rates of minor and major stroke of approximately 1% annually, which did not differ from placebo (Singh, 2005). Stroke was also infrequently reported in dronedarone trials; differences relative to placebo were observed in a post hoc analysis of the ATHENA trial, which showed a two-thirds lower annual rate of stroke (1.2% vs. 1.8% for placebo) (Connolly, 2009a). Stroke rates were not reported as an outcome measure in the DIONYSOS head-to-head RCT of amiodarone and dronedarone (Le Heuzey, 2010).

Freedom from AF Recurrence

Moderate evidence exists with which to compare rates of freedom from AF, as this was measured in 14 amiodarone and dronedarone trials. Rates ranged from 31-59% for amiodarone and 23-37% for dronedarone. Findings from the head-to-head DIONYSOS trial showed a >50% lower rate of AF recurrence with amiodarone (42.0%) vs. dronedarone (63.5%). Results from our mixed treatment meta-analysis suggest that dronedarone is 70% less likely to maintain normal sinus rhythm at 12 months than amiodarone (see Table ES2 below); these findings are comparable to another meta-analysis published on the comparative effectiveness of these two agents (Piccini, 2009).

Table ES2. Results of mixed treatment comparison of likelihood of freedom from AF at 6-12 months, by agent and comparison.

	Amiodarone	Sotalol	Dronedarone
	Odds Ratio (95% CI)		
Control	5.68 (3.23, 9.66)	2.16 (0.96, 4.20)	1.67 (0.68, 3.66)
Amiodarone		0.39 (0.18, 0.74)	0.31 (0.12, 0.68)
Sotalol			0.88 (0.27, 2.27)

Note: Results are presented as agent in column vs. agent in row
CI: Confidence interval

Hospitalization and Quality of Life

Evidence is limited regarding amiodarone's impact on hospitalization rates when compared to rate control, with data available from a single RCT in our sample (Hohnloser, 2000). The comparison to rate control is highly problematic, however, given that hospitalization is used as a planned element of rhythm control strategies. Hospitalization was assessed as a primary outcome in the ATHENA trial of dronedarone as well as in post hoc comparisons for stroke Hohnloser, 2009; Connolly, 2009a); findings suggested a lower rate of hospitalization with dronedarone compared to placebo.

Data are extremely limited on the impact of amiodarone or dronedarone on quality of life. Amiodarone's impact on quality of life has been evaluated in a single RCT; no significant improvement in quality of life was observed relative to rate control. At present, there are no published QoL data for patients on dronedarone.

Clinical Benefits: Warfarin vs. Dabigatran vs. LAA Exclusion Devices

Only the RE-LY RCT of dabigatran (Connolly, 2009b) and an RCT (PROTECT-AF; Holmes, 2009) of a single LAA exclusion device (WATCHMAN) were included for the comparisons of stroke prevention strategies, as other LAA exclusion studies involved devices not available in the U.S. or those intended for use as a component of an existing ablation procedure (i.e., AtriClip).

Mortality and Stroke

Data from RE-LY indicate no significant differences in the rate of all-cause mortality between dabigatran at 110 mg or 150 mg and warfarin. However, the difference in mortality between the 150 mg dose of dabigatran was nearly statistically significant (3.6% vs. 4.1% per year for warfarin, p=.051) (Connolly, 2009b); the rate of vascular mortality was significantly lower with higher dose dabigatran (2.3% vs. 2.7% with warfarin, p=.04). No reasons were given as to the possible reasons for reduced mortality with dabigatran. While the risk of mortality did not differ in PROTECT-AF, it was observed that lower numbers of deaths due to stroke as well as cardiovascular or unexplained causes occurred in the WATCHMAN arm (Holmes, 2009).

In the RE-LY trial, significant reductions in the risk of hemorrhagic stroke were observed with both doses of dabigatran relative to warfarin (0.10-0.12% vs. 0.38% per year, p<.001 for both comparisons). In addition, the rate of total stroke was reduced by nearly 40% for the higher dose of dabigatran (1.1% vs. 1.7% per year, p<.001). The rate of hemorrhagic stroke in PROTECT-AF also was lower in the WATCHMAN arm relative to warfarin (0.1% vs. 1.6% per year), while the rate of ischemic stroke was higher (2.2% vs. 1.6% respectively); neither comparison was statistically significant. Findings from a subsequent analysis of data from this trial suggested that dabigatran's effects were independent of the quality of warfarin management at each study site, as measured by time in therapeutic range (Wallentin, 2010).

Hospitalization and Quality of Life

The rate of all-cause hospitalization was examined in RE-LY; rates were 19.4%, 20.2%, and 20.8% for dabigatran 110 mg, dabigatran 150 mg, and warfarin respectively (Connolly, 2009b) . These rates differed significantly when compared between the lower dose of dabigatran and warfarin (p=.003). Hospitalization rates were not reported in the WATCHMAN RCT; data on quality of life were not reported in either trial.

Potential Harms

The data reported on harms vary both by treatment strategy and by study; while some types of harms are common to multiple strategies, others are intervention specific. In addition, harms are variably reported in both RCTs and case series, and published studies often lack important detail on severity, resolution, and other important characteristics. Not surprisingly, ranges of certain harms are quite wide when evaluated across studies. A full listing of the rates of major harms for each treatment strategy can be found in Table ES3 on the following page.

Potential Harms: Catheter Ablation

Peri-Operative Mortality and Stroke

Peri-operative death and stroke were very rare events as reported in catheter ablation RCTs and case series. Rates ranged from 0-0.7% (mean: 0.1%) and 0-1.5% (mean: 0.4%) for peri-operative mortality and stroke respectively.

Major and Minor Complications

Rates of complications are highly variable across catheter ablation studies, and reporting of these outcomes is affected by differences in definition and measurement. The most commonly reported major complications in RCTs and comparative cohort studies include major bleeding, cardiac tamponade, moderate-to-severe pulmonary vein stenosis, and worsening heart failure; rates range between 0-6% (mean: 1.3%) across studies. No instances of atrioespohageal fistula, a rare but potentially catastrophic complication of catheter ablation, were observed in any RCTs or comparative cohorts in our sample; rates across case series range from 0-2%. Rates of minor complications, including mild pulmonary vein stenosis, pericardial effusion, and phrenic nerve injury, also varied substantially across studies, but were generally higher than those for major complications (mean: 3.7%; range: 0-30%).

Potential Harms: Thoracopic, Off-Pump Surgical Ablation

Peri-Operative Mortality and Stroke

As with catheter ablation, the incidence of peri-operative mortality appears to be very low with TOP surgical ablation; rates ranged from 0-2% across studies (mean: 0.3%). Similarly, peri-operative stroke appears to be an infrequent occurrence, with a range across studies of 0-3% (mean: 0.8%).

Major and Minor Complications

Data from TOP surgical ablation series are highly variable regarding complications, in terms of both reporting frequency and level of detail. Nevertheless, major complications also appeared to be relatively rare with TOP procedures, averaging 3.8% and ranging from 0-14% across series; the most common of these were major bleeding requiring full thoracotomy or sternotomy to resolve. Minor complications occurred at a somewhat higher rate (mean: 8.2%, range: 6-17% across series); the most frequent of these was permanent

Table ES3. Reported ranges of harms, by treatment strategy.

Intervention/Harm	Mean (SD)	Reported Range
Catheter Ablation		
Peri-operative death	0.1% (0.2%)	0-0.7%
Peri-operative stroke	0.4% (0.5%)	0-1.5%
Major complications	1.3% (2.2%)	0-6%
Minor complications	3.7% (6.7%)	0-30%
TOP		
Peri-operative death	0.3% (0.6%)	0-2%
Peri-operative stroke	0.8% (1.2%)	0-3%
Major complications	3.8% (4.1%)	0-14%
Minor complications	8.2% (6.7%)	0-23%
AADs		
Pulmonary toxicity*		
Amiodarone	0.7% (0.7%)	0-1.6%
Dronedarone	0.1% (0.1%)	0-0.1%
Thyroid toxicity*		
Amiodarone	5.4% (4.4%)	0-12%
Dronedarone	5.5% (6.9%)	0-13%
Any AE leading to drug discontinuation*		
Amiodarone	14.8% (8.4%)	1.6-26.0%
Dronedarone	8.5% (6.0%)	0-17.9%
Stroke Prevention		
Major bleeding*		
Warfarin†	---	2-4%
Dabigatran	---	2.7-3.1%
WATCHMAN	---	3.5%
Procedure safety events*		
WATCHMAN	---	7.4%

NOTE: Means not reported for warfarin (no new evidence synthesized) or dabigatran/WATCHMAN (data from single trials only)
*Annualized rate
†Rate for warfarin inclusive of meta-analysis findings and observed rate in dabigatran and WATCHMAN trials
TOP: Thorascopic, off-pump surgical ablation; AADs: Antiarrhythmic drugs; AE: Adverse effect

pacemaker implantation (range: 2-10%). Other minor complications of note were phrenic nerve injury (range: 0-3%) and pericarditis (range: 0-4%).

Potential Harms: Amiodarone and Dronedarone

Pulmonary Toxicity

As measured in RCTs and comparative studies, the rate of pulmonary toxicity with amiodarone is relatively low, ranging from 0-1.6% on an annualized basis. Long-term follow-up studies and other evidence-based reviews have reported a much wider range of pulmonary toxicity (1-17%); however, many of the higher estimates were for amiodarone at higher dose levels (i.e., ≥400 mg daily). A 200 mg daily maintenance dose is now recommended; at this level, observed rates are very similar to those in our review. Pulmonary toxicity has been reported in only one dronedarone trial, at an annualized rate of 0.1%. In the short-term head-to-head DIONYSOS trial, no pulmonary events were observed in either the amiodarone or dronedarone arms.

Thyroid Toxicity

A higher rate of thyroid toxicity with amiodarone was observed in the DIONYSOS trial (10.4% vs. 1.4% on an annualized basis), although the statistical significance of this finding was not tested (Le Heuzey, 2010). Rates of hyper- or hypothyroidism have ranged from 0-13% (mean: 5.5%) in both amiodarone and dronedarone studies. The range in rates is a product of measurement, with some studies relying on clinical presentation alone and others including abnormal lab values; for example, the dronedarone findings are skewed by results from the EURIDIS/ADONIS trials, which were based on laboratory findings from multiple tests (Singh, 2007); exclusion of these study findings would drop the average annual rate of thyroid toxicity with dronedarone to 1.6%.

Other Adverse Effects

Other potential adverse effects of amiodarone include optic neuropathy/neuritis, skin discoloration, photosensitivity, liver toxicity, tremor, and ataxia. Those effects reported with dronedarone include bradycardia, QT-interval prolongation, nausea, and diarrhea. Annual rates of drug discontinuation from *any* adverse effect have been reported over a similar range for amiodarone (1.6-26.0%) and dronedarone (0-17.9%), although the average rate across studies was higher for amiodarone (15% vs. 8% for dronedarone). Discontinuation due to AEs did not differ significantly in the DIONYSOS trial (17.2% vs. 22.9% for dronedarone and amiodarone, p=.23); in addition, findings of our mixed treatment comparison suggests no significant difference in drug discontinuation between these agents (OR=2.02; 95% CI=0.14, 9.62).

Potential Harms: Warfarin, Dabigatran, and the WATCHMAN

Warfarin

The primary risk of warfarin treatment is serious hemorrhage, particularly intracranial hemorrhage. The risk of serious hemorrhage has been estimated in previous meta-analyses

to be approximately 2% per year; however, this risk is highly dependent on patient, clinician, and health care system variation in maintaining anticoagulation at a therapeutic level.

Dabigatran

RE-LY demonstrated a significantly lower annualized rate of major bleeding for the lower 110 mg dose of dabigatran vs. warfarin (2.7% vs. 3.4%), and a comparable rate of bleeding at the higher 150 mg dose (Connolly, 2009b); rates of major bleeding were higher in RE-LY than in other recent warfarin trials and observational studies, perhaps as a function of a more inclusive bleeding definition. In this study dabigatran was also associated with a higher rate of myocardial infarction, 0.72-0.74% vs. 0.53% for warfarin); this difference was statistically significant for the higher-dose comparison (p=.048). The reason for this adverse finding is not immediately apparent. Although it could be a chance finding, the authors hypothesized that an increased relative risk for MI could be due not to a harmful effect of dabigatran but to warfarin's ability to confer relatively greater protection against ischemic events (Connolly, 2009b).

WATCHMAN

Placement of the WATCHMAN device has been associated with a number of serious complications, most commonly serious pericardial effusion (4.8%) and major bleeding (3.5%). In addition, peri-procedure stroke as reported appears to be more common with WATCHMAN implantation (1.1%) than with either catheter ablation or TOP surgical ablation. Further safety data on the WATCHMAN has recently been requested by the FDA, further delaying the device's approval in the U.S.

Evidence on Comparative Value

Overview

We used data from the systematic review on clinical effectiveness, as well as information from the literature and other sources, to inform a primary cost-utility analysis of management strategies for adults with atrial fibrillation.

Patient Population

The eligible population for the model was adult patients with atrial fibrillation. Given the focus on patients with symptomatic AF, patients in the model were assumed to have moderately severe impact of AF on their quality of life (-0.065 quality-adjusted life years) (Reynolds, 2009). The clinical course is modeled from initiation of each management strategy through to the end of the patients' lifetime. A 5-year time horizon was also evaluated, with results presented in the body of the report.

Our analysis, guided by input from the ERG, focused on three patient scenarios for the comparison of the management strategies:

- *60 year old male patient with paroxysmal AF:*
    - This scenario describes a younger patient with paroxysmal atrial fibrillation and no comorbidity ($CHADS_2$ score = 0) at low risk of stroke.
    - Guidelines recommend aspirin for stroke patients with $CHADS_2 = 0$.

- *65 year old male patient with long-standing persistent AF and heart failure:*
    - This scenario describes a patient with a single comorbid condition, heart failure, at an intermediate risk of stroke ($CHADS_2 = 1$).
    - Heart failure is mild/moderate and controlled (to allow for dronedarone use)
    - Guidelines recommend aspirin or warfarin; aspirin is used in our analyses for patients with $CHADS_2 = 1$ if age is less than 75.

- *75 year old male patient with hypertension and diabetes mellitus and persistent AF:*
    - This scenario describes an older patient with substantial comorbidity at high risk of stroke ($CHADS_2 = 3$).
    - Guidelines recommend adjusted dose warfarin for stroke prevention.

Key Strategy Comparison Sets

Each management strategy has a cardiovascular component for management of heart rhythm or rate and a stroke prevention component. The decision analytic model evaluated 5 key sets of alternative strategies for management of atrial fibrillation:

1. *LA Catheter Ablation (LACA) strategies*
    a. Primary LACA as initial therapeutic intervention
    b. Rhythm control with amiodarone followed by LACA (secondary LACA) for AAD failure
    c. Rhythm control with amiodarone

2. *Thorascopic, off-pump (TOP) surgical ablation for patients with AF not otherwise requiring cardiac surgery for structural heart disease*
    As described in earlier sections of this executive summary, the published evidence on the clinical effectiveness of TOP surgical ablation is extremely limited. The best evidence has been obtained via case series of patients who have largely been referred for surgery after multiple failed LACA attempts. However, there is increasing interest in the possibility of using TOP ablation approaches in lieu of initial attempts at LACA for patients who fail AAD therapy. To explore these questions we compared TOP surgical ablation to LACA for patients with AAD failure, but we wish to emphasize that the model findings should be viewed as highly exploratory. We will frame the results as an attempt to evaluate a hypothetical clinical and policy question: how much more effective than LACA in returning patients to NSR would TOP surgical ablation need to be in order to provide additional QALY benefits at an incremental cost-effectiveness ratio of $100,000.

a. Rhythm control with amiodarone with secondary LACA for AAD failure
b. Rhythm control with amiodarone with thorascopic, off-pump (TOP) surgical ablation for AAD failure. The TOP procedure is assumed to include left atrial appendage excision for stroke prevention.

3. *Dronedarone vs. amiodarone for rhythm control*
    a. Rhythm control with amiodarone
    b. Rhythm control with dronedarone
    c. Rhythm control with dronedarone as the initial agent with amiodarone as a second agent for persistent or recurrent AF.

4. *Dabigatran or guideline based anti-coagulation (warfarin or aspirin) for stroke prevention*
    a. Dabigatran 110 mg for stroke prevention within an amiodarone rhythm control strategy
    b. Dabigatran 150 mg for stroke prevention within an amiodarone rhythm control strategy
    c. Guideline-based anti-coagulation (warfarin or aspirin) within an amiodarone rhythm control strategy

5. *WATCHMAN device or guideline-based anti-coagulation (warfarin or aspirin) for stroke prevention*
    a. WATCHMAN device within a rate control strategy
    b. Guideline-based anti-coagulation (warfarin or aspirin) within a rate control strategy

Model Inputs

Model probabilities (e.g., conversion to NSR, AF recurrence) were obtained from the ICER systematic review and published literature. Published literature also was used to obtain information on utilities (i.e., the value between 0 and 1 placed on quality of life in a particular state of health). Costs of devices and procedures, complications, and drug side effects were based on national Medicare payment rates; drug costs were obtained from publicly-available commercial sources.

The cost estimates for *uncomplicated* major procedures included: (1) LACA = $11,231; (2) TOP surgical ablation = $26,818; (3) WATCHMAN = $11,340 (the device is not yet reimbursed in the US, so the costs for closure of an atrial septal defect were used as a reasonable proxy). Annual costs of treatment were estimated at $434 for amiodarone and $3,120 for dronedarone; costs for the former included those of quarterly thyroid function testing. The annual cost of warfarin was estimated to be $440 vs. $4,734 for dabigatran 110 mg or 150 mg; costs for the former included those of monthly INR testing ($6 per test) and quarterly physician office visits ($51 per visit). Because dabigatran is not yet on the U.S. market, costs were estimated based on published prices from a Canadian online pharmacy (CanadaDrugs.com).

Key Assumptions
In addition to base case model analyses, a number of sensitivity analyses were run to provide additional information on key areas of concern. These are areas that were felt to be of the greatest impact and controversy in multiple discussions with the ERG, and included:

- Impact of AF on quality of life
- Stroke risk following conversion of AF to NSR
- Warfarin use following conversion of AF to NSR
- Impact of chronic warfarin use on quality of life

Other key assumptions for the model are listed in Table ES4 on the following page. The results presented in this Executive Summary reflect only the base case assumptions. Complete results with consideration of sensitivity analyses are provided in the full report.

Table ES4. Key assumptions, atrial fibrillation disease course.

Assumptions	Rationale & Source
Atrial Fibrillation Disease Course	
• Patients' heart rhythm may be NSR or AF and AF patients in NSR may have recurrent episodes of AF.	ACC/AHA/ESC 2006 Guidelines (Fuster, 2006)
• Decreased quality of life while in AF compared to quality of life in NSR.	(Chan, 2006; Gage, 1995; Gage, 1998; Catherwood, 1999; O'Brien, 2005; Reynolds, 2009) ("Prior CEAs") ERG review
AF and Stroke	
• AF patients have an increased risk of stroke. Stroke risk varies by CHADS2 score for AF patients.	(Beyth, 2002; Singer, 2009; Wang, 2003; Wolf, 1991)
• Stroke risk has decreased in recent years. Assume secular trend in stroke risk using ATRIA study.	ERG review (Singer, 2009)
• Stroke outcomes include no disability, mild disability, moderate/severe disability and death	Prior CEAs
• Patients with stroke have increased risk of subsequent stroke	Prior CEAs
• Stroke risk may be lower for AF patients with NSR induced by LA catheter ablation than in AF patients with recurrent AF after LA catheter ablation. Base case will not assume lower risk for post LA catheter ablation patients with NSR.	(Nademanee, 2008; Oral, 2006a; Themistoclakis, 2010)
• Stroke risk is reduced for patients undergoing thorascopic, off-pump surgical ablation as a consequence of LAA excision.	(Blackshear, 1996)
AF and Stroke Prevention	
• Stroke prevention follows the ACC/AHA/ESC guidelines for management of patients with AF	ACC/AHA/ESC 2006 Guidelines (Fuster, 2006)
• Stroke prevention treatment with warfarin, aspirin, dabigatran, and WATCHMAN procedure reduce risk of stroke	(Hart, 1999; Holmes, 2009; van Walraven, 2002)
Stroke Prevention and Hemorrhage	
• Warfarin, aspirin, and dabigatran are associated with an increased risk of hemorrhage	(Connolly, 2009b; Hart, 1999; van Walraven, 2002)
• Hemorrhage may be intracranial (ICH) or non-intracranial	(Hart, 1999; van Walraven, 2002)
• Intracranial hemorrhage outcomes include no disability, mild disability, moderate/severe disability and death	Prior CEAs
AF and Death	
• AF patients have elevated risk of non-stroke and non-hemorrhagic probability of death	Prior CEAs
• AF patients treated with warfarin or aspirin have reduced risk of cardiovascular, non-stroke death that differs for warfarin and aspirin	Prior CEAs
• AF patients with stroke- or ICH-associated disability have increased risk of death	Prior CEAs
• Patients with mild or moderate/severe disability following stroke or intracranial hemorrhage have increased risk of death that varies by severity of disability	Prior CEAs

Summary Model Results

Comparison Set #1: Amiodarone with Secondary Rate Control for AAD failure, Amiodarone with Secondary LACA for AAD failure, and Primary LACA

As can be seen in Table ES5 below, LACA following failure of rhythm control on amiodarone produced higher total QALYs than a strategy of returning to rate control only after recurrence of AF. The QALY advantage was seen in all three patient cohorts, with incremental costs of approximately $15,000. Incremental cost-effectiveness ratios increased with age and comorbidity but were less than $100,000 per QALY for all three cohorts. The difference in QALYs was primarily due to the quality-of-life benefits of return to normal sinus rhythm alone, as our base case assumed no impact on stroke risk from return to normal sinus rhythm and also assumed that anticoagulation would continue as appropriate regardless of whether AF had recurred.

Table ES5. Costs and effectiveness of amiodarone with secondary rate control for AAD failure vs. amiodarone with LACA for AAD failure, by patient cohort.

Strategy	Cost	Incremental Cost	Effectiveness (QALYs)	Incremental Effectiveness (QALYs)	ICER ($/QALYs)
60 M Paroxysmal AF					
Amiodarone-> 2° Rate Control	$20,265		11.12		
Amiodarone -> 2° LA Catheter Ablation	$35,038	$14,773	11.51	0.39	$37,808
65 M CHF and Persistent AF					
Amiodarone-> 2° Rate Control	$20,332		8.67		
Amiodarone -> 2° LA Catheter Ablation	$37,522	$17,190	8.90	0.23	$73,947
75 M DM HTN and Persistent AF					
Amiodarone-> 2° Rate Control	$17,759		5.80		
Amiodarone -> 2° LA Catheter Ablation	$32,081	$14,322	5.94	0.15	$96,846

NOTE: Findings rounded to hundredths
QALY: Quality-adjusted life year; ICER: Incremental cost-effectiveness ratio; AF: Atrial fibrillation
CHF: Congestive heart failure; DM: Diabetes mellitus; HTN: Hypertension

Primary LA Catheter Ablation vs. Amiodarone

Primary LACA compared to long-term rhythm control with amiodarone also produced higher QALYs for all patient cohorts at similar marginal costs that also produced incremental cost-effectiveness ratios less than $100,000 per QALY (see Table ES6 on the following page).

Table ES6. Costs and effectiveness of primary LA catheter ablation vs. rhythm control with amiodarone, by patient cohort.

Strategy	Cost	Incremental Cost	Effectiveness (QALYs)	Incremental Effectiveness (QALYs)	ICER ($/QALYs)
60 M Paroxysmal AF					
Amiodarone -> 2° Rate Control	$20,265		11.12		
Primary LA Catheter Ablation	$34,044	$13,779	11.63	0.51	$26,869
65 M CHF and Persistent AF					
Amiodarone -> 2° Rate Control	$20,332		8.67		
Primary LA Catheter Ablation	$38,245	$17,913	8.96	0.30	$60,804
75 M DM HTN and Persistent AF					
Amiodarone -> 2° Rate Control	$17,759		5.80		
Primary LA Catheter Ablation	$34,410	$16,651	6.00	0.21	$80,615

NOTE: Findings rounded to hundredths
QALY: Quality-adjusted life year; ICER: Incremental cost-effectiveness ratio; AF: Atrial fibrillation
CHF: Congestive heart failure; DM: Diabetes mellitus; HTN: Hypertension

The primary and secondary LACA strategies resulted in a large reduction in AF time and drug toxicity compared to rhythm control with amiodarone. The primary LACA strategy has a lower risk of drug toxicity than the amiodarone-rate control strategy or the secondary LACA strategy. Both the primary and secondary LACA strategies have a modest increase in the risk of stroke compared to rhythm control in our base case analysis, which did not assume a reduction in stroke for patients who are successfully returned to NSR (but does include peri-procedure strokes from ablation).

Comparison Set #2: Secondary LACA for AAD failure vs. Thorascopic, Off-Pump (TOP) Surgical Ablation for AAD Failure

Base Case Results:
In Table ES7 on the following page we show that for all three patient cohorts -- 60 year-old paroxysmal AF, 65 year-old CHF, and 75 year-old multiple comorbidities – our model found that a secondary TOP surgical ablation strategy was more expensive and produced total lifetime QALYs essentially identical to those estimated for a secondary LACA strategy.

The TOP surgical ablation strategy results in more major complications, minor complications, and peri-procedural strokes than LACA. The TOP strategy does result in a reduction in total strokes, however, consistent with the benefits conveyed by left atrial appendage excision. The TOP ablation strategy is also associated with a reduction in intracranial hemorrhage due to the fact that the model assumes discontinuation of warfarin three months following the surgery for all patients successfully converted to NSR. It is important to note again that these findings are considered highly speculative given the sparse data available on TOP surgical ablation outcomes and the lack of head-to-head trials.

Table ES7. Costs and effectiveness of thorascopic, off-pump surgical ablation vs. secondary LA catheter ablation, by patient cohort.

Strategy	Cost	Incremental Cost	Effectiveness (QALYs)	Incremental Effectiveness (QALYs)	ICER ($/QALYs)
60 M Paroxysmal AF					
Amiodarone -> 2° LA Catheter Ablation	$35.038		11.51		
Amiodarone -> 2° TOP Surgical Ablation	$43,976	$8,937	11.46	-0.04	Dominated
65 M CHF and Persistent AF					
Amiodarone -> 2° LA Catheter Ablation	$37,522		8.90		
Amiodarone -> 2° TOP Surgical Ablation	$46,163	$8,641	8.89	-0.02	Dominated
75 M DM HTN and Persistent AF					
Amiodarone -> 2° LA Catheter Ablation	$32,081		5.94		
Amiodarone -> 2° TOP Surgical Ablation	$39,744	$7,663	5.83	-0.12	Dominated

NOTE: Findings rounded to hundredths
QALY: Quality-adjusted life year; ICER: Incremental cost-effectiveness ratio; AF: Atrial fibrillation; LA: Left atrial; TOP: Thorascopic, off-pump; CHF: Congestive heart failure; DM: Diabetes mellitus; HTN: Hypertension

Threshold Analysis of TOP Surgical Ablation Effectiveness at Conversion to NSR

The base case assumption of the model was that the success rate of conversion from AF to NSR following TOP surgical ablation was identical to that following an initial LACA (70% for persistent AF). In an analysis that varied the probability of NSR after TOP surgical ablation from the baseline assumption all the way up to perfect effectiveness (100%), the TOP ablation strategy produced higher QALYs when the probability of NSR was higher than 87%. Even at 100% success, however, the marginal QALY advantage of TOP ablation was so small that incremental cost-effectiveness ratios remained well above $100,000.

Threshold Analysis of TOP Surgical Ablation Stroke Risk Reduction due to Excision of LA Appendage

The base case assumed a 60% reduction in stroke risk due to LA appendage excision based studies suggesting that approximately 60 percent to 90 percent of strokes in AF may be due to thrombi that originate in the LA appendage. TOP surgical ablation would produce higher total QALYs compared to secondary LACA when the reduction in risk of stroke due to LA appendage excision exceeds 68%.

Comparison Set #3: Dronedarone, Amiodarone, and Dronedarone followed by Amiodarone for Recurrent AF

Base Case Results

As shown in Table ES8 on the following page, the dronedarone followed by amiodarone strategy produced the highest total lifetime QALYs in all three of the patient cohorts. The QALY differences were not large, however. The amiodarone strategy had higher total

QALYs and lower costs than the dronedarone alone strategy for all three patient cohorts. The dronedarone followed by amiodarone strategy had higher total lifetime QALYs and higher costs than the amiodarone strategy with incremental costs in the $100,000 to $120,000 range for all three patient scenarios.

The dronedarone alone strategy is dominated (albeit by very small QALY margins) by the other strategies despite the lower drug toxicity of dronedarone because it is less effective at keeping patients out of AF, and the cumulative decrement in quality of life in AF outweighs the benefits of reduced drug toxicity. The dronedarone followed by amiodarone strategy has the lowest time in AF and correspondingly, the highest QALYs. Although this strategy produces more drug toxicity episodes than amiodarone alone because patients with recurrent AF on initial dronedarone are subsequently exposed to amiodarone, the dronedarone followed by amiodarone strategy still produces higher QALYs than rhythm control with amiodarone. In an analysis of time free from AF recurrence, drug toxicity, or death , the median time to recurrent AF, drug toxicity, or death was 5.6 years for the dronedarone followed by amiodarone strategy, 3.7 years for amiodarone, and 2.0 years for the dronedarone alone strategy, confirming the summary QALY benefits observed.

Table ES8. Costs and effectiveness of amiodarone, dronedarone alone, and dronedarone first with amiodarone for recurrent AF, by patient cohort.

Strategy	Cost	Incremental Cost	Effectiveness (QALYs)	Incremental Effectiveness (QALYs)	ICER ($/QALYs)
60 M Paroxysmal AF					
Amiodarone	$ 20,265		11.12		
Dronedarone alone	$27,749	$7,484	11.02	-0.09	Dominated
Dronedarone -> amiodarone	$30,700	$10,435	11.22	0.10	$103,892
65 M CHF and Persistent AF					
Amiodarone	$20,332		8.67		
Dronedarone alone	$27,829	$7,497	8.59	-0.09	Dominated
Dronedarone -> amiodarone	$30,536	$10,204	8.76	0.09	$110,440
75 M DM HTN and Persistent AF					
Amiodarone	$17,759		5.80		
Dronedarone alone	$24,334	$6,575	5.73	-0.06	Dominated
Dronedarone -> amiodarone	$26,560	$8,801	5.87	0.07	$120,398

NOTE: Findings rounded to hundredths
QALY: Quality-adjusted life year; ICER: Incremental cost-effectiveness ratio; AF: Atrial fibrillation
CHF: Congestive heart failure; DM: Diabetes mellitus; HTN: Hypertension

It should be noted that the dronedarone followed by amiodarone strategy was created to explore the potential impact of sequential use of these agents in clinical practice, and was not based on any published data. Additionally, our study did not systematically analyze strategies with sequential use of other AADs, which may also compare favorably with single-drug strategies.

Comparison Set #4: Dabigatran vs. Guideline-directed Warfarin or Aspirin

Base Case Results

Both the dabigatran and warfarin/aspirin strategies were evaluated as components of a rhythm control strategy using amiodarone. Two separate dabigatran strategies were modeled based on data regarding two potential doses: 110 mg and 150 mg.

As can be seen in Table ES9 below, both dabigatran strategies were associated with higher QALYs compared to a guideline-directed warfarin/aspirin strategy across all three patient scenarios due to the reduction in strokes and intracranial hemorrhages associated with dabigatran. The cost for both dabigatran strategies was substantially higher, producing incremental cost-effectiveness ratios that were in the $175,000 to $250,000 per QALY range.

Table ES9. Costs and effectiveness of dabigatran (110 mg and 150 mg doses) vs. warfarin, by patient cohort.

Strategy	Cost	Incremental Cost	Effectiveness (QALYs)	Incremental Effectiveness (QALYs)	ICER ($/QALYs)
60 M Paroxysmal AF					
Warfarin/Aspirin	$20,265		11.12		
Dabigatran 150 mg	$82,780	$62,514	11.42	0.30	$207,760
Dabigatran 110 mg	$83,015	$62,750	11.40	0.29	$220,212
65 M CHF and Persistent AF					
Warfarin/Aspirin	$20,332		8.67		
Dabigatran 150 mg	$72,451	$52,119	8.96	0.29	$178,483
Dabigatran 110 mg	$72,795	$52,463	8.94	0.27	$197,321
75 M DM HTN and Persistent AF					
Warfarin/Aspirin	$17,759		5.80		
Dabigatran 150 mg	$50,944	$33,184	5.97	0.17	$191,757
Dabigatran 110 mg	$51,351	$33,592	5.93	0.14	$244,121

All strategies use amiodarone for rhythm control
NOTE: Findings rounded to hundredths
QALY: Quality-adjusted life year; ICER: Incremental cost-effectiveness ratio; AF: Atrial fibrillation
CHF: Congestive heart failure; DM: Diabetes mellitus; HTN: Hypertension

Analysis of MI Risk with Dabigatran

While our model was not designed to include rates of myocardial infarction (MI) as direct parameter inputs, we explored the potential impact of an increased rate of MI with dabigatran through a sensitivity analysis of a potential increase in MI- or ischemic heart disease-related deaths. For the purposes of brevity, only the MI analysis is presented here; both sensitivity analyses may be found in the full body of the report. For the cohort of men age 65 with CHF and persistent AF, if the relative risk of MI-related deaths was 1.38 based on the point estimate from the trial, both of the dabigatran strategies would still produce higher total lifetime QALYs than the warfarin strategy over the range of the 95% confidence interval around this risk.

Threshold Analysis of Dabigatran Cost

A sensitivity analysis also was conducted to determine the sensitivity of the incremental cost-effectiveness ratios of the dabigatran strategies to the assumed cost of dabigatran. For the cohort of men age 65 with CHF and persistent AF, the incremental cost-effectiveness ratios of the dabigatran 150 mg and dabigatran 110 mg doses would be less than $100,000 per QALY gained if the annual cost of dabigatran was less than $2,899 ($242 per month) and $2,649 ($221 per month), respectively, which is approximately 6-7 times the estimated annual cost of warfarin ($440). Incremental cost-effectiveness would drop below $50,000 per QALY gained at an annual cost of approximately 3 times that of warfarin ($1,500).

Comparison Set #5: WATCHMAN Procedure vs. Guideline-directed Warfarin or Aspirin

Base Case Results

Both of these stroke prevention strategies were assumed to be used within a rate control strategy with atenolol or digoxin. As can be seen in Table ES10 below, in all three patient cohorts the WATCHMAN procedure was associated with substantially higher costs and slightly lower effectiveness as measured by lifetime QALYs.

The results of the model showed that the WATCHMAN procedure reduced numbers of total strokes and intracranial hemorrhages across all three patient cohorts relative to warfarin/aspirin; differences were mitigated with increasing age and comorbidity, however, given the presence of other major stroke risk factors. In addition, the incidence of peri-procedure strokes and major/minor complications further reduced QALYs, leading to the WATCHMAN's domination by warfarin/aspirin for all three patient cohorts.

Table ES10. Costs and effectiveness of WATCHMAN vs. warfarin, by patient cohort.

Strategy	Cost	Incremental Cost	Effectiveness (QALYs)	Incremental Effectiveness (QALYs)	ICER ($/QALYs)
60 M Paroxysmal AF					
Warfarin/Aspirin	$15,299		11.03		
WATCHMAN	$23,053	$7,754	11.01	-0.02	Dominated
65 M CHF and Persistent AF					
Warfarin/Aspirin	$15,721		8.57		
WATCHMAN	$22,659	$6,938	8.56	-0.01	Dominated
75 M CHF and Persistent AF					
Warfarin/Aspirin	$13,792		5.70		
WATCHMAN	$20,625	$6,833	5.60	-0.10	Dominated

All strategies use digoxin/atenolol for rate control
NOTE: Findings rounded to hundredths
QALY: Quality-adjusted life year; ICER: Incremental cost-effectiveness ratio; AF: Atrial fibrillation
CHF: Congestive heart failure; DM: Diabetes mellitus; HTN: Hypertension

ICER Evidence Review Group Deliberation

The ICER Evidence Review Group deliberation (see section starting on page 42 for membership and details) focused on many important issues regarding the evidence provided by the ICER review. Major points of discussion are shown in the numbered points below.

1) *More context should be given to the types of patients for whom these various management strategies are considered potentially appropriate.* The initial draft appraisal document was judged to have inadequately clarified that the clinical community views the selection of catheter ablation vs. AADs as relevant only for patients who are highly symptomatic on rate control alone. Several ERG members also made mention of differences in the candidate populations for some of the major studies described in our review. For example, it was pointed out that highly symptomatic AF was an exclusion criterion in several of the rhythm vs. rate control trials, but that symptomatic AF is the major reason that patients undergo catheter or surgical ablation. In addition, patients undergoing surgical ablation have often failed catheter ablation previously. Finally, it was also suggested that the AAD strategies employed in the catheter ablation trials did not include amiodarone. The report has been revised to set additional context around the rationale for the comparisons of focus and to highlight the symptomatic patient as the linchpin of the analyses; the surgical ablation category has also been refined to address this concern (see #2 below). Finally, the catheter ablation RCTs were examined to assess whether amiodarone was made available by study protocol. With few exceptions, amiodarone was available, and was utilized by 60-65% of patients in these studies.

2) *The report does not clearly articulate what is meant by "minimally-invasive surgical ablation" and including it as an option in the modeling analyses does not convey adequately that the paucity of data on surgical techniques raises questions about whether surgical ablation should be offered as a reasonable option for patients who have not failed multiple attempts at catheter ablation.* This term was used in the initial draft appraisal to try to capture that set of surgical ablation techniques that were most likely to be considered by patients and clinicians as options for treatment in lieu of an initial catheter ablation. However, this term was felt to be confusing, as there is no agreed-upon standard for what constitutes minimally-invasive surgery for AF. It was agreed that the policy interest was in identifying surgical procedures that would be offered as alternatives to catheter ablation, as opposed to those procedures that would be reserved for salvage therapy after failed catheter ablation. Following the ERG meeting we had subsequent discussions with clinicians that identified thorascopic, off-pump (TOP) procedures as those most likely to be positioned as catheter ablation alternatives, as these would avoid both thoracotomy and bypass. The data synthesis has been revised to focus on these procedures; to provide relevant comparisons, however, data from recent systematic reviews of "cut and sew" as well as alternative Maze procedures are also included in the report. The comparative value section of the appraisal has been revised to include greater

discussion of the limitations of the data on surgical ablation and frames the cost-utility analyses as more hypothetical and exploratory in nature.

3) *From the patient's perspective, one key question regarding surgical ablation is "how many attempts at repeat catheter ablation should I undergo before turning instead to surgery?"* This specific question was not addressed in the appraisal, and unfortunately we were unable to find any published evidence that would shed light on this important question. We have included specific mention of this issue in our research recommendations.

4) *The appraisal fails to convey the limitations inherent in interpreting differences in rates of "freedom from AF" across studies.* The revised appraisal document includes new language explaining the limitations of the surrogate outcome measures used to compare ablation with AADs.

5) *The risks associated with amiodarone use appear to have been downplayed.* It was pointed out that, due to toxicity concerns, amiodarone is considered a 2nd-line agent for most AF patient types, and that Singh's adaptation of the ACC/AHA/ESC guideline flowchart unfairly depicts dronedarone as a 2nd-line agent. The report has been revised to highlight the concerns associated with amiodarone use, replace the Singh adaptation with the original guideline flowchart, and to highlight that amiodarone's use in AF, while widespread, is in fact off-label. In addition, a new strategy has been developed for the decision-analytic model that features 1st-line use of dronedarone followed by amiodarone for dronedarone failure, to approximate how these agents might be used in typical practice.

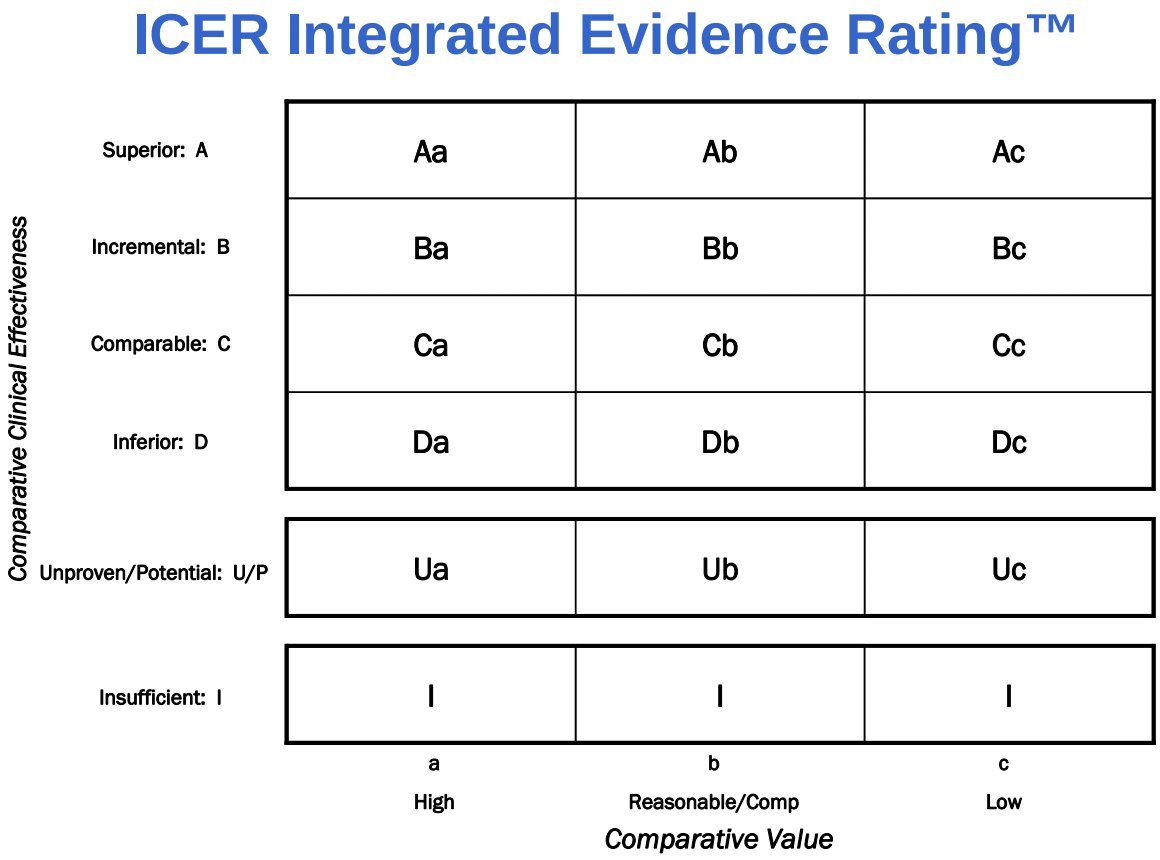
6) *Meta-analytic estimates subject to heterogeneity should have such heterogeneity explored.* The report has been revised to include findings from meta-regression as well as multiple tests and analyses of publication bias where relevant.

7) *The appraisal should provide more context on complication rates, including explanations of outlier studies.* The report has been revised to add measures of central tendency and variance to previously presented ranges of complication rates, with further explanation of outlier values where warranted.

8) *The model assumption that warfarin's cardioprotective effects do not extend to dabigatran is flawed.* While warfarin does have documented evidence of protection against ischemic events, this was not felt to be a reason to assume that dabigatran does not offer similar protection. The base case assumption has been changed to set cardioprotection for the two agents to be equal. However, it was also noted that the higher rate of myocardial infarction observed in the dabigatran arms in the RE-LY trial might be considered a harm; accordingly, a sensitivity analysis was conducted to explore this.

ICER Integrated Evidence Ratings™: Rhythm Control and Stroke Prevention Strategies for Patients with Atrial Fibrillation

The ICER integrated evidence rating matrix is shown below; a detailed explanation of the methodology underpinning this rating system can be found beginning on page 38. Ratings for each comparison set and patient population of interest are shown in tables on the following pages rather than illustrated in the body of the matrix figure itself. Although the input of the Evidence Review Group helps inform ICER's consideration of the evidence, the final ratings are ultimately a judgment made solely by ICER, and individual members of the ERG should not be viewed in any way as having endorsed the ratings described below.



ICER Integrated Evidence Ratings for Comparison Set #1:
Catheter Ablation vs. AADs

	Patient Population		
Comparison Set/Intervention	**Age 60 Male Paroxysmal AF**	**Age 65 Male w/CHF Persistent AF**	**Age 75 Male w/DM, HTN Persistent AF**
Amiodarone-->LACA vs.			
Long-term Amiodarone	Ba	Ub	I
Primary LACA vs.			
Long-term Amiodarone	Ua	Ub	I

LACA: Left Atrial Catheter Ablation; AF: Atrial Fibrillation; CHF: Congestive Heart Failure; DM: Diabetes Mellitus HTN: Hypertension

Comparative Clinical Effectiveness. The use of catheter ablation has been primarily studied in younger patients with paroxysmal AF. While data on long-term outcomes such as mortality and stroke risk are lacking, and better knowledge of the durability of treatment effects is needed, there is consistent high-quality evidence pointing to higher rates of return to NSR at 6 and 12 months among patients treated with catheter ablation. Among patients who have at least a moderate negative impact on quality of life from their AF, the patient group at the core of the scope of this appraisal, ICER made the judgment that there is a high level of certainty in a rating of incremental net health benefit for catheter ablation compared to AAD use. There was consideration of whether the net health benefit should be rated as "superior," but assuming that the primary benefit is the reduction in symptoms, and not reduced stroke rate or decreased early mortality, ICER chose the rating of "incremental."

There is more limited evidence for patients with persistent AF and CHF, but ICER felt that the existing evidence included the experience of enough patients of this type to represent moderate certainty in an incremental benefit as well (a rating of "unproven with potential"). In contrast, ICER felt that evidence does not exist to help make a reasonable judgment on the balance of risks and benefits for much older patients with multiple comorbidities. The rating for this patient category was therefore "insufficient."

Ratings of comparative clinical effectiveness for primary LACA are challenging because for some patients – those who will not ever respond well to AADs – earlier ablation would be very likely to provide even higher net health benefits than waiting to perform ablation until after a trial of AADs. On the other hand, some patients will begin AADs and have wholly satisfactory control of their symptoms, and thus never need to undergo the risks of ablation. An overall rating for primary LACA thus must take both of these possible scenarios into account. Given that there is less direct data to judge the net health benefits of primary LACA, ICER judged that it had moderate certainty that the net health benefit for 60 or 65-year-old patients would be incremental or better. For the 75-year-old with multiple comorbidities, however, the lack of evidence led us to select an "insufficient" rating.

Comparative Value. The comparative value rating for secondary catheter ablation among 60-year-old ("younger") patients was based largely on the model findings confirming lifetime

QALY benefits for younger patients at relatively low marginal costs. For older patients with some level of comorbidity the model suggests that the net health benefit gain is lower, and therefore the higher cost for these patients was judged by ICER to represent a reasonable value compared to long-term AAD use. Among the oldest patients with comorbidities the lack of sufficient certainty about net clinical benefits led ICER to decline to assign a comparative value rating.

ICER Integrated Evidence Ratings for Comparison Set #2:
TOP Surgical Ablation vs. Catheter Ablation

	Patient Population		
Comparison Set/Intervention	**Age 60 Male Paroxysmal AF**	**Age 65 Male w/CHF Persistent AF**	**Age 75 Male w/DM, HTN Persistent AF**
Amiodarone-->TOP Surgical Ablation vs.			
Amiodarone-->LACA	I	I	I

LACA: Left Atrial Catheter Ablation; TOP: Thorascopic, Off-Pump; AF: Atrial Fibrillation; CHF: Congestive Heart Failure; DM: Diabetes Mellitus; HTN: Hypertension

Comparative Clinical Effectiveness. The use of thorascopic, off-pump (TOP) surgical ablation techniques is an emerging treatment approach. With only a limited number of case series in the published literature, and continued wide variation in patient selection and surgical technique, ICER judged that the evidence was insufficient to assign a rating of a comparative net clinical benefit for TOP surgical ablation in relation to AAD use (or catheter ablation).

ICER Integrated Evidence Ratings for Comparison Set #3:
Dronedarone vs. Amiodarone

	Patient Population		
Comparison Set/Intervention	**Age 60 Male Paroxysmal AF**	**Age 65 Male w/CHF Persistent AF**	**Age 75 Male w/DM, HTN Persistent AF**
Dronedarone vs.			
Long-term Amiodarone	Cb	Cb	Cb
Dronedarone-->Amiodarone vs.			
Long-term Amiodarone	Ub	Ub	Ub

AF: Atrial Fibrillation; CHF: Congestive Heart Failure; DM: Diabetes Mellitus; HTN: Hypertension

Comparative Clinical Effectiveness. Although head-to-head data for dronedarone and amiodarone are limited to a single RCT, the findings of this study, when combined with evidence accumulated from RCTs of these drugs vs. placebo and multiple observational studies, allows a high level of certainty that the comparative net health benefit of these two drugs is essentially "comparable." The central tradeoff that ICER believes makes the net health benefits "comparable" is this: dronedarone is less effective than amiodarone at

maintaining patients in NSR, but it offers a lower risk of serious long-term toxicity. There is some chance that further research and longer-term clinical experience will uncover new risks associated with dronedarone, but given that it is a very similar molecule to amiodarone, the chances of this seem lower than for most new cardiovascular drugs.

ICER gave a separate rating to a specific strategy suggested by the ERG as a common current clinical approach: start patients on dronedarone and only switch them to amiodarone (or another AAD) if dronedarone is inadequate at controlling symptoms. For this strategy there is admittedly no direct evidence from clinical trials, but the available data on dronedarone and amiodarone can be extrapolated with moderate certainty to this stepped approach, and ICER gave it a rating of "unproven with potential." There was no significant difference in the clinical literature or model results for the likely net health benefits of this strategy across different patient age and comorbidity categories.

Comparative Value. Dronedarone is a new medication with a price much higher than amiodarone, but when evaluated as the cornerstone of a treatment strategy over the lifetime of a patient, the incremental costs of dronedarone compared to amiodarone are relatively low. In part this is because over time many patients will "fail" both medications and will either move onto other medications, seek catheter ablation, or settle for rate control strategies alone. Given the range of incremental cost-effectiveness ratios produced by the economic model, a "reasonable/comparable" rating was assigned to strategies of dronedarone alone and dronedarone followed by amiodarone.

ICER Integrated Evidence Ratings for Comparison Set #4:
Dabigatran and LAA Occlusive Devices vs. Guideline-directed Warfarin/Aspirin

	Patient Population		
Comparison Set/Intervention	**Age 60 Male Paroxysmal AF**	**Age 65 Male w/CHF Persistent AF**	**Age 75 Male w/DM, HTN Persistent AF**
Dabigatran (both doses) vs.			
Warfarin/Aspirin	Uc	Uc	Uc
WATCHMAN vs.			
Warfarin/Aspirin	I	I	I

AF: Atrial Fibrillation; CHF: Congestive Heart Failure; DM: Diabetes Mellitus; HTN: Hypertension

Comparative Clinical Effectiveness. The RE-LY RCT of dabigatran is the sole source of comparative evidence for the clinical effectiveness of this new drug. Although a single RCT would not usually provide enough certainty to merit any rating of comparative clinical effectiveness, ICER's judgment was that RE-LY produced unusually persuasive findings. The study was very large, well-designed, and produced highly consistent findings across drug doses; in addition, subsequent analyses of trial data suggested that dabigatran's performance was comparable to that of warfarin irrespective of whether warfarin use was well- or poorly-managed at each center. Accordingly, despite the presence of only one

RCT, we judged the level of certainty to be moderate in an incremental or superior net health benefit for dabigatran, the "unproven with potential" ICER rating. There are still questions about the possible higher comparative risk of MI that was seen among patients on dabigatran in the RE-LY study, but even with this considered, ICER felt the "unproven with potential" rating was appropriate. There seemed to be no reason to give a different rating for different patient categories.

In contrast to RE-LY, the single RCT of LAA occlusive devices, the PROTECT-AF trial of the WATCHMAN, was a small non-inferiority study whose results have left significant unanswered questions around implantation success and procedure safety. ICER felt the state of evidence was "insufficient" to be able to render a reasonable judgment of whether the comparative net health benefit of WATCHMAN is higher, comparable, or lower than that of guideline-directed warfarin and aspirin. This uncertainty pertains to all patient categories.

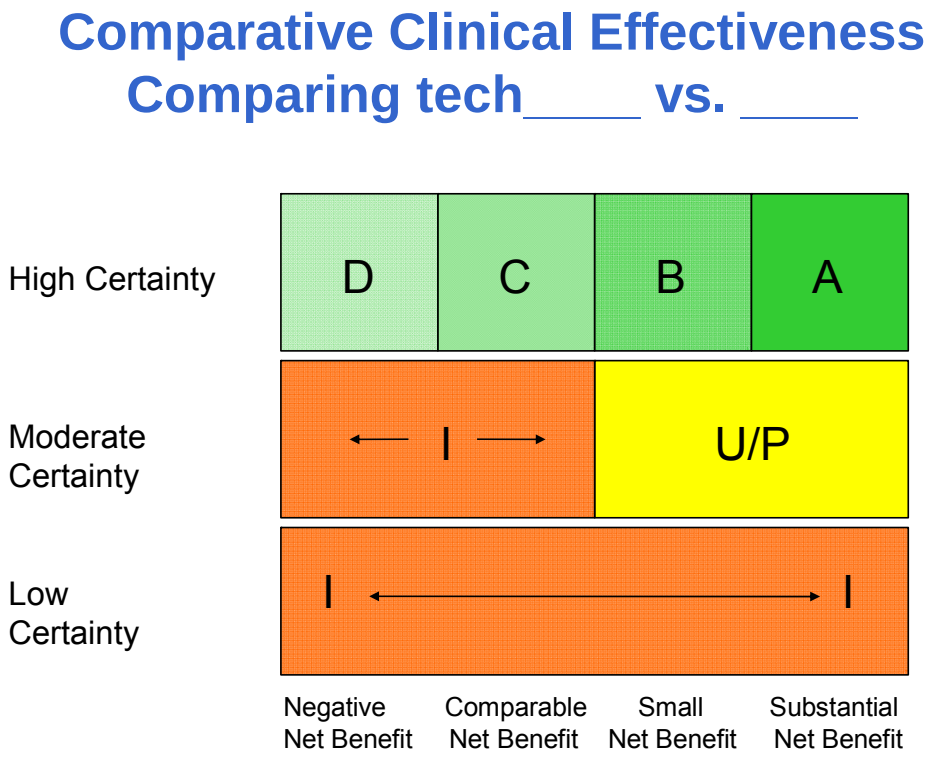
Comparative Value. Based on international benchmarking, our analysis of comparative value assumed a price for dabigatran approximately 10 times that of warfarin. At this price the marginal cost over a patient's lifetime of treatment with dabigatran are sizable. Even with the model findings of a net QALY gain for dabigatran, the extremely high cost led ICER to judge the comparative value of dabigatran to be "low." However, this rating is very sensitive to the assumed price of dabigatran; if the price of dabigatran is only 6 times as high as warfarin, ICER believes the incremental lifetime costs would merit a "reasonable/comparable" value rating. And, if the price for dabigatran is assumed to be 3 times that of warfarin or less, ICER believes that this drug would provide its benefits at a "high" value.

Methodology: ICER Integrated Evidence Rating™

The ICER Integrated Evidence Rating™ is shown on page 33. It is constructed as a matrix, with a vertical axis denoting the possible categories for a rating of comparative clinical effectiveness, and the horizontal axis divided into 3 possible rating categories for comparative value. It is important to note that these ratings are specified as comparing specific uses of medical interventions; that is, there may be different ratings for different uses of a test, treatment, or other intervention depending on the specified indication and patient population(s).

Level of Certainty in a Comparative Net Health Benefit

The underlying approach to ICER's rating of comparative clinical effectiveness mirrors that developed by the United States Preventive Services Task Force (USPSTF) in its most recent methods documents, and is dependent upon a joint judgment of the level of certainty provided by the body of evidence and a categorical judgment of the magnitude of the comparative net health benefit (Sawaya, 2007). To render this 2-part judgment both explicit and transparent, ICER uses a "Comparative Clinical Effectiveness Matrix" very similar to that used by the USPSTF. This matrix, depicted below, was developed independently (although with some overlap in participants with the USPSTF effort) and pilot-tested specifically for comparative clinical effectiveness assessments by a multistakeholder evidence-based medicine roadmap group (Berger, 2009; Forum, 2006).



A = "Superior" - High certainty of a moderate-large net health benefit
B = "Incremental" - High certainty of a small net health benefit
C = "Comparable" - High certainty of a comparable net health benefit
D = "Inferior" - High certainty of an inferior net health benefit
U/P = "Unproven with Potential" - Moderate certainty of a small or moderate-large net health benefit
This category is meant to reflect technologies whose evidence provides:

1) High certainty of *at least* comparable net health benefit
2) Moderate certainty suggesting a small or moderate-large net health benefit

I = "Insufficient" - The evidence does not provide high certainty that the net health benefit of the technology is at least comparable to that provided by the comparator(s).

The vertical axis of the comparative clinical effectiveness matrix rates the level of certainty that the evidence provides in the precision of the net health benefit. There are 3 categories: high, moderate, and low, the same categories used by the USPSTF. While the vertical axis represents a judgment of certainty, the horizontal axis of the Comparative Clinical Effectiveness Matrix displays gradients of the estimated net health benefit provided by a health intervention compared with the net health benefit of the selected comparator intervention. The categories for comparative net health benefit begin at the far left with "negative"; as the estimate of net health benefit increases, the rating moves to "comparable," then to "small net benefit," and culminates with a rating of "substantial" comparative net health benefit.

The term comparative "net" health benefit is used because of the importance attached to an explicit judgment of the overall balance of benefits and risks between an intervention and its selected comparator(s). The rating of net health benefit on the horizontal axis of the Comparative Clinical Effectiveness Matrix represents the best conceptual "point estimate" ICER can make given its interpretation of the existing evidence. As with the approach taken by the USPSTF, ICER has at this time no set definition of the boundaries between "comparable," "small," and "substantial" comparative net health benefit. For example, if the results of the appraisal include an estimate of a small lifetime quality-adjusted life year (QALY) advantage for one intervention compared with another, balanced against known greater short-term risks, whether or not these findings should be judged as conferring a comparative net health benefit will depend on many features of the relative certainty of the benefits and harms, as well as value judgments of the importance to patients of small QALY gains over a lifetime. Despite the variability that will attend these judgments, presenting a categorical judgment of net health benefit serves an important goal: it enhances understanding of the underlying evidence by forcing the review team to justify its rating. The review team must describe more concretely than they might otherwise their view of how the disparate findings of a systematic review and decision model sum up. The review team's justification can be debated and disagreed with, but in all cases it will give decision makers a more clear insight into the key issues they should consider when summing up the evidence and applying it to particular clinical actions or policies.

Summary Rating of Comparative Clinical Effectiveness

As shown in the figure above, the Comparative Clinical Effectiveness Matrix maps the 3 categories of certainty upon the categories of comparative net health benefit to define a

summary rating of comparative clinical effectiveness. Here, the relationship between level of certainty and magnitude of net health benefit comes into sharper relief. With a high level of certainty, the point estimate of net health benefit in one category is relatively assured, and therefore each cell in the matrix on the row of high certainty has a distinct label. A technology whose evidence base provides high certainty of a moderate-to-high net health benefit is rated to have "superior" comparative clinical effectiveness. As the net health benefit diminishes, the rating of comparative clinical effectiveness shifts to "incremental," then "comparable," and finally "inferior."

When the level of certainty in the comparative net health benefit is only moderate, however, uncertainty about either benefits or harms is such that the precision of the net health benefit is significantly reduced. This lack of precision is akin to a broader "conceptual confidence interval," and is illustrated in the matrix by the broader summary categories of Unproven with Potential (U/P) and Insufficient (I).

The U/P category is a particularly important element of the Comparative Clinical Effectiveness Matrix. This category is intended to indicate a judgment that the available evidence can only yield moderate certainty in the comparative net health benefit at the population level, but that the best estimate is that there is either a small or substantial net benefit. Moderate certainty implies that the point estimate of net health benefit is unlikely to shift more than one category in either direction; thus, a U/P rating implies a judgment that there is relatively high certainty that the comparative net health benefit is comparable or better, and a correspondingly relatively small possibility that future evidence would demonstrate that the true net comparative benefit of the intervention being assessed is inferior to its comparator.

The final summary category of comparative clinical effectiveness is the "I" category that sweeps from the moderate certainty of a point estimate of comparable or inferior net health benefit into the entire bottom row in which certainty in net health benefit is so low that there remains a reasonable probability that the true net health benefit is inferior; in other words, that the intervention being evaluated produces a net harm for many or most patients.

Rating Comparative Value

The rating of comparative clinical effectiveness can stand alone, to be discussed and applied by decision makers, but it also forms the first of the 2 parts of the ICER Integrated Evidence Rating. The second component is a rating of "comparative value." ICER rates the use of interventions for particular patient populations as having "high," "reasonable or comparable," or "low" comparative value.

ICER does not employ a single measure of cost effectiveness, such as the incremental cost-effectiveness ratio, for assignment of a rating of comparative value, and therefore does not rely on a formal cost-effectiveness threshold. Instead, the rating of comparative value is informed by multiple measures of potential economic impact.

To determine a final rating of "high," "reasonable/ comparable," or "low" value, ICER considers all of the economic findings, including the relative uncertainty of model findings as explored through multiple deterministic sensitivity analyses and a probabilistic sensitivity analysis. To aid transparency, ICER provides general guidance that incremental cost per QALY ratios of less than approximately $50,000 will often be considered as indicative of a "high" value intervention; incremental cost per QALYs from about $50,000 to $150,000 would often fit within a designation as "reasonable" values; and incremental cost per QALYs above $150,000 would be more likely to suggest "low" value interventions. This general guidance is based upon previous academic work benchmarks modified by ICER's interpretation of evidence on the role medical inflation and societal willingness to pay should have in creating cost-effectiveness thresholds (Braithwaite, 2008; King, 2005). While there is a limited normative or empiric basis for the loose boundaries ICER presents, these boundaries also reflect input from stakeholders in today's health care system on how best to present incremental cost-effectiveness ratios within broad categories that can be widely understood, gain relative consensus, and be actionable.

Integrated Ratings

The ICER Integrated Evidence Rating™ combines the individual ratings given for comparative clinical effectiveness and comparative value. The overall purpose of the integrated ratings is to highlight the separate considerations that go into each element but to combine them for the purposes of conveying that clinical benefits provided by technologies come at varying relative values based on their cost and their impact on the outcomes of care and the health care system.

Evidence Review Group Members

The Evidence Review Group (ERG) is an independent group brought together by ICER and composed of academic experts, patients, clinicians, epidemiologists, ethicists, and medical policy representatives of stakeholder groups including health plans and manufacturers.

The purpose of the ERG is to guide and help interpret the entire appraisal process. Members of the ERG are first convened to function as a "scoping committee" for the appraisal. During this phase the key questions for the appraisal are outlined, including elements such as the appropriate comparator technologies, patient outcomes of interest, patient subpopulations for which clinical and cost-effectiveness may vary systematically, time horizon for outcomes, and key aspects of the existing data that must be taken into account during the appraisal. The ERG may be divided into sub-committees that advise the ICER appraisal team at the mid-point of the appraisal on the early findings and challenges encountered. All of the ERG members listed below participated in scoping and/or mid-cycle activities, but not all were able to participate in the final ERG meeting.

At the final ERG meeting, members are asked to declare any interests in the technology or its comparator(s), or other potential influences on their expertise. The ERG meeting allows for in-depth deliberation on the findings of the ICER appraisal document and provides an opportunity for comment on the determination of the ICER integrated evidence rating. Although the ERG helps guide the final determination of the ICER Integrated Evidence Rating™, the final rating is ultimately a judgment made by ICER, and individual members of the ERG should not be viewed in any way as having endorsed this appraisal.

ERG Participant Name and Affiliation	**Potential Influences on Judgment**
Hugh Calkins, MD Professor, Medicine, Johns Hopkins University Heart & Vascular Institute Cardiology Director, Arrhythmia Service; Director, Electrophysiology Lab Johns Hopkins Medical Center	Electrophysiologist; helped develop consensus statement on catheter and surgical ablation of atrial fibrillation; consultant to multiple manufacturers
David Callans, MD Professor, Medicine, The University of Pennsylvania Director, Electrophysiology Laboratory, Dept. of Medicine Hospital of The University of Pennsylvania	Conducts clinical research on AF; speaker at industry-funded events; family members affected by AF
Ralph J. Damiano Jr., MD Professor, Surgery, Washington University of St. Louis Chief, Cardiac Surgery Washington University Medical Center	Surgeon who treats patients with AF; research funded by the National Institutes of Health; has received industry support for research
Bob Deyermond Patient/Consumer Representative	Did not attend meeting

Michele DiPalo Director, Health Services Evaluation Blue Cross & Blue Shield of Massachusetts	Did not attend meeting
Afshin Ehsan, MD Assistant Professor of Surgery, Tufts University Associate Director, Cardiothoracic Surgery Residency Program Surgical Director, Heart Failure and Transplant Program Director, Cardiac Surgery Intensive Care Unit Tufts Medical Center	Surgeon who treats patients with AF
Marthe Gold, MD, MPH Professor & Chair, Community Health and Social Medicine City College of New York	Did not attend meeting
E. Kevin Heist, MD, PhD Assistant Professor, Medicine, Harvard University Cardiologist, Cardiac Unit, Department of Medicine Massachusetts General Hospital	Conducts clinical research in AF; has received honoraria and research grants from industry
Mellanie True Hills Patient/Consumer Representative Founder and CEO, StopAfib.org/American Foundation for Women's Health	AF survivor (surgery 5 years ago); founder (volunteer) of StopAfib.org, a patient advocacy organization; StopAfib.org receives donations and grants from multiple drug and device manufacturers
Mark Hlatky, MD Professor, Health Research & Policy Health Services Research; Professor, Medicine, Stanford University Director, Stanford-Kaiser Cardiovascular Outcomes Research Center Stanford Hospital & Clinics	Consultant to industry; serves on medical advisory board of Blue Cross Blue Shield Technology Evaluation Center (TEC)
Robert McDonough, MD Senior Medical Director, Clinical Research and Policy Development Aetna, Inc.	Develops clinical policies for private payer; family members affected by AF
Steven McQuillan, MS Vice President, Clinical & Regulatory Affairs AF Solutions Medtronic, Inc.	Has conducted clinical research in AF; employed by manufacturer of devices used to treat AF

Peter Neumann, ScD Professor of Medicine, Tufts University School of Medicine Director, Evaluation of Value and Risk in Health, Institute for Clinical Research and Health Policy Studies, Tufts Medical Center	Receives funding from diverse sources, including industry; funding is unrestricted
Rita Redberg, MD, MSc, FACC Professor, Clinical Medicine, University of California, San Francisco Director, Women's Cardiovascular Services ,Division of Cardiology UCSF Medical Center	Did not attend meeting
Alan Rosenberg, MD Vice President of Medical Policy, Technology Assessment and Credentialing Programs Wellpoint, Inc.	Employed by private payer; serves on medical advisory board of BCBS TEC; member of AHRQ stakeholder group; bias toward production of better evidence to guide decision-making
Daniel E. Singer, MD Professor of Medicine, Harvard Medical School Professor in the Department of Epidemiology, Harvard School of Public Health Chief, Clinical Epidemiology Unit, General Medicine Division, Massachusetts General Hospital	Consultant to multiple manufacturers; has patients with AF
Joseph Smith, MD, PhD Chief Medical and Science Officer West Wireless Health Institute	Previously employed by Johnson & Johnson and Boston Scientific; bias toward use of evidence to reduce healthcare costs
Mintu Turakhia, MD, MS Director, Cardiac Electrophysiology Palo Alto VA Healthcare System Investigator, Stanford/VA Center for Health Care Evaluation Cardiac Electrophysiology Section, Department of Medicine Stanford University	Has received honoraria and research support from manufacturers
Marcia Yaross, PhD Vice President, Worldwide Clinical, Regulatory and Health Policy Biosense Webster, Inc.	Employed by manufacturer of products for catheter ablation

APPRAISAL OVERVIEW

RHYTHM CONTROL AND STROKE PREVENTION STRATEGIES FOR PATIENTS WITH ATRIAL FIBRILLATION

The overview is written by members of ICER's research team. The overview summarizes the evidence and views that have been considered by ICER and highlights key issues and uncertainties.

Final Scope

Atrial fibrillation (AF) is the most common cardiac arrhythmia in the US population. Recent guidelines suggest that rate control medications be continued for long-term management in most AF patients, with the addition of rhythm control medications for patients who remain symptomatic despite adequate rate control, or for those with special considerations such as degree of symptoms, younger age, or higher activity levels (Camm, 2010). For patients such as these, the choice among rhythm control strategies becomes a paramount clinical concern, and given the number and variety of options, the comparative effectiveness of rhythm control strategies is a key question for clinical and policy decision-making.

Management of all patients with AF also involves a stroke prevention component. This is most often accomplished using an oral antithrombotic medication such as warfarin or aspirin; other approaches, such as use of the direct thrombin inhibitor dabigatran or the LAA exclusion device known as the WATCHMAN, are currently under consideration by the FDA as future alternatives for stroke prevention in AF.

This appraisal sought to evaluate the comparative clinical effectiveness and comparative value of alternative rhythm control and stroke prevention strategies for AF patients with moderate-to-severe symptoms. The final scope of this appraisal, described using the Populations, Interventions, Comparators, Outcomes, Timing, and Setting (PICOTS) format (Counsell, 1997), is presented below:

- **Patient Populations**: paroxysmal, persistent, and long-standing persistent AF with and without comorbidity

- **Interventions:** AF management--catheter ablation, thorascopic, off-pump surgical ablation (TOP), antiarrhythmic drugs; Stroke prevention—dabigatran, left atrial appendage exclusion devices

- **Comparators:** AF management—AAD therapy, with amiodarone as the primary representative from this set of drugs, was the comparator for catheter and surgical ablation strategies. For stroke prevention strategies the comparator was guideline-directed use of warfarin and aspirin

- **Outcomes:** Mortality, ischemic/hemorrhagic stroke, freedom from AF, hospitalization, quality of life, procedural complications, drug-related adverse events

- **Timing:** Follow-up durations of 6+ months

- **Setting:** Inpatient/outpatient, primary practice, cardiac electrophysiology, cardiovascular surgery

Objective and Methods:
The objective of this report is to appraise the comparative clinical effectiveness and comparative value of multiple management options for atrial fibrillation. To support this appraisal we report the results of a systematic review of the published literature and the findings from a *de novo* decision analysis. From the outset of this effort the research team has been aided by in the input of a national Evidence Review Group (ERG) composed of clinical and methodological experts, patient experts, and representatives from private insurers and manufacturers. Input from the ERG was used to help identify the comparisons that serve as the focus for this review:

- Rhythm control with left atrial catheter ablation (LACA) vs. anti-arrhythmic drugs
- Rhythm control with LACA vs. thorascopic, off-pump (TOP) surgical ablation
- Rhythm control with amiodarone vs. dronedarone
- Stroke prevention with warfarin/aspirin vs. dabigatran
- Stroke prevention with warfarin/aspirin vs. left atrial appendage (LAA) exclusion devices

Key Areas of Focus

1) The impact of AF management options on stroke, cardiovascular and all-cause mortality, recurrence of AF, and quality of life

2) The relative rates of complications and side effects between management options

3) The effects of modifications to AF management (e.g., discontinuation of warfarin) on short- and long-term outcomes

4) The relative performance of each management options in certain "prototypical" AF populations (e.g., younger patients with paroxysmal AF, older patients with persistent AF and cardiovascular comorbidity)

5) The cost-effectiveness and budget impact of multiple management options for AF relative to standard care

Key Considerations Highlighted by the Evidence Review Group:

1. Key patient populations: ERG members noted that the effectiveness of each treatment option appraised varies substantially with the clinical characteristics of the patient population studied. In addition to type of AF, other factors thought to affect performance include demographics (age, sex), risk factors for stroke as defined by $CHADS_2$ or other mechanisms, and other comorbidities, underscoring the need to identify and highlight stratified analyses of interest.

2. AF "burden": While the expectation was that the literature on this topic is relatively scant, the ERG felt that some attempt should be made to quantify the burden of AF based on the time spent experiencing symptoms rather than the "time until first recurrence" framework that has been employed in most studies.

3. Practice variability: It was noted that ablation approaches and techniques, both surgical and catheter-based, vary significantly by center, and that the review should recognize this lack of standardization, as well as the potential association between level of clinician experience and training and patient outcomes.

4. Anticoagulation: Given the uncertainty regarding continuation of anticoagulation after ablation, the ERG suggested that the ICER clinical and economic model consider multiple stroke prevention strategies that vary in duration.

5. Ethical considerations: At the outset of the appraisal there appeared to be no distinctive ethical issues regarding the patient populations or the interpretation of results from cost-effectiveness analyses.

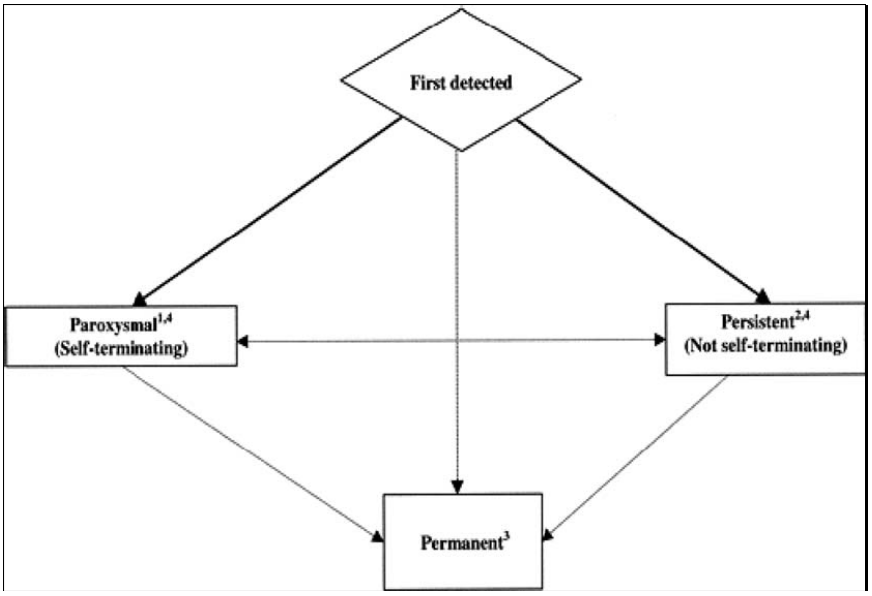
1. Background

1.1 The Condition

Atrial fibrillation (AF) is the most common cardiac arrhythmia in the US population (Fuster, 2006). AF occurs when rapid, disorganized electrical signals cause the atria (the two upper chambers of the heart) to "fibrillate", or contract quickly and irregularly. This in turn causes some blood to pool in the atria rather than be pumped completely into the ventricles. AF can be asymptomatic but it may also be associated with several bothersome symptoms, including shortness of breath, difficulty with exercise, palpitations, general fatigue, dizziness, and confusion.

Importantly, AF is the second-leading cause of stroke, after atherosclerosis (Heron, 2009); the risk of stroke among those with AF is estimated to be fivefold higher than in patients without this disorder (National Stroke Association, 2010). AF and congestive heart failure are also highly associated; about two-thirds of patients with CHF over age 65 are likely to have AF (Savelieva, 2004), and the presence of AF increases CHF severity (Maisel, 2003). In the symptomatic patient, the goals of treatment are therefore twofold: (1) to reduce AF symptoms and its contribution to comorbidity; and (2) to prevent stroke.

The clinical presentation of AF is categorized based on the time course of AF episodes, as illustrated below:



Source: Fuster, 2006

AF is classified as "paroxysmal" when episodes last 7 days or less and terminate spontaneously. "Persistent" AF occurs when episodes do not self-terminate and last longer than 7 days; this classification also includes a "long-standing" category, described as persistent AF for longer than one year. Finally, "permanent" AF describes a situation in which restoration of sinus rhythm is no longer considered possible. As noted in the

schematic on the previous page, these categories are not mutually exclusive; patients are typically classified according to their most frequent presentation.

The epidemiology of AF as well as the changing demographic in the US suggest a significant and growing health-system burden, as the prevalence of AF increases substantially with age (Feinberg, 1995) . An estimated 2.6 million Americans are currently diagnosed with AF, a number that is expected to grow nearly threefold by 2050 (Go, 2001). A study of temporal trends in AF hospital admission indicates a 60% rise in hospitalization rates from the early 1980s to the early 1990s, independent of changes in other risk factors (Friberg, 2003). Total annual costs of AF treatment are already estimated to amount to nearly $7 billion in the US (Coyne, 2006). Not surprisingly, there is significant interest on the part of patients, clinicians, policymakers, and other stakeholders in evaluating the clinical and economic impact of management options for AF.

2. The Alternative Treatment Strategies

As mentioned previously, the two overarching goals of treatment for AF are (a) reduction or elimination of symptoms; and (b) stroke prevention. The major strategies employed to achieve these goals are presented in the sections that follow.

2.1 Management of Atrial Fibrillation

Following a diagnosis of AF, initial restoration of normal heart rhythm is typically attempted through either electrical or pharmacologic cardioversion. This is usually a temporary solution, however, as 20-30% of patients do not convert immediately to sinus rhythm, and AF recurs in many patients who have initial success (Crandall, 2009).

Rate control with medications is often considered to be the most appropriate initial strategy for AF management, as it is well-accepted that slowing ventricular response both at rest and during activity will result in symptom improvement and likely reduce the risk of cardiovascular events (Dorian, 2010). Recent guidelines suggest that rate control medications be continued for long-term management in most AF patients, with the addition of rhythm control medications for patients who remain symptomatic despite adequate rate control, or for those with special considerations such as degree of symptoms, younger age, or higher activity levels (Camm, 2010). For patients such as these, the choice among rhythm control strategies becomes a paramount clinical concern, and given the number and variety of options, the comparative effectiveness of rhythm control strategies is a key question for clinical and policy decision-making.

There has been much debate regarding the relative merits of rate vs. rhythm control strategies; findings from several large-scale clinical trials suggest that these strategies do not differ in broad populations in their impact on morbidity and quality of life (Carlsson, 2003; Hohnloser, 2000; Van Gelder, 2002). While no statistical differences in overall mortality were noted in these studies, stratified findings from the largest of these trials (AFFIRM) suggested a higher rate of non-cardiovascular mortality for rhythm control (Wyse, 2002). However, additional stratified analyses from this trial indicated that the presence of normal sinus rhythm was associated with a nearly 50% reduction in mortality (Corley, 2004). The arguments for and against rate-control and rhythm-control strategies have also been complicated by recent findings that more lenient rate-control dosing protocols may produce better quality of life than traditional protocols that have sought to keep the heart rate below 80 beats per minute (Van Gelder, 2010). Thus, the question of whether rate control or rhythm control is superior remains controversial, and clinical guidelines emphasize the importance of individualization of treatment approach.

Despite the uncertainties regarding the relative risks and benefits of rate-control and rhythm-control strategies, restoration of normal sinus rhythm remains a key clinical goal for many patients, particularly among patients who suffer significant symptoms while in AF. The major strategies for restoration and maintenance of sinus rhythm that were included in the scope of this appraisal are reviewed in detail below. Rate-control strategies, a cornerstone of management of patients in AF, were not subjected to formal systematic

review because the most policy-relevant questions driving this appraisal centered on rhythm control strategies employing newer drugs and procedures in the patient with moderate-to-severe AF symptoms. Nevertheless, a rate control strategy was included as one of the options evaluated in the decision analytic model (see Section 8).

Antiarrhythmic Drugs

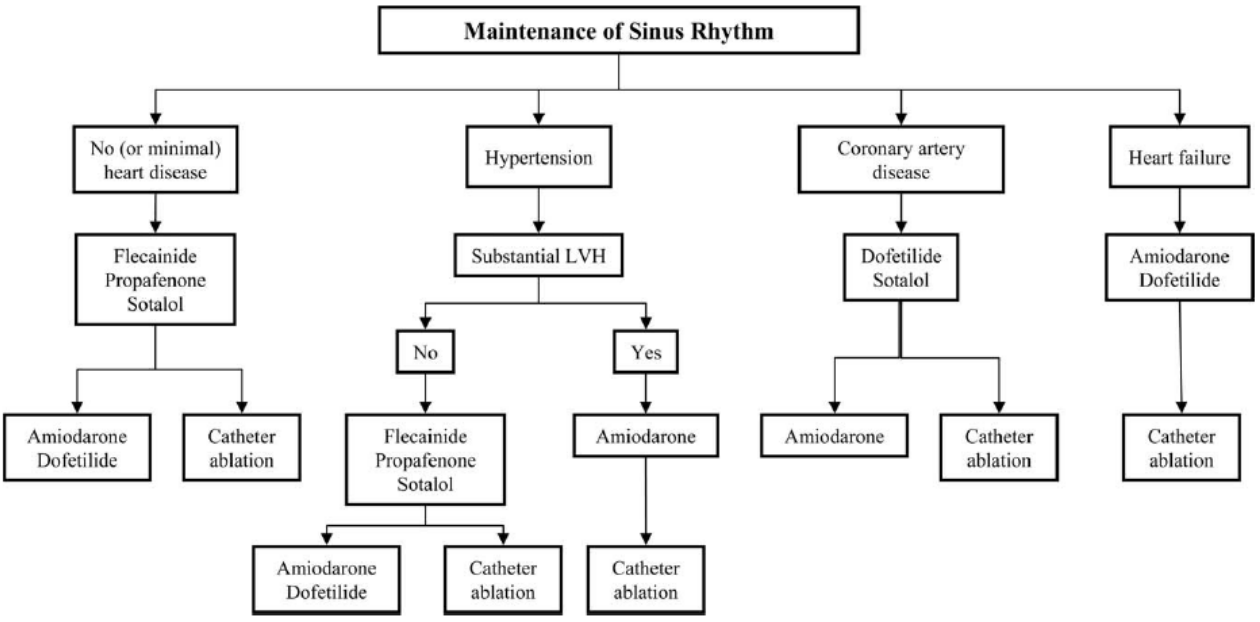
Antiarrhythmic drugs (AADs) may be used to try to maintain sinus rhythm after electrical cardioversion, or they may be initiated independently (Gopinathannair, 2009). Many AADs are also known to have rate-control properties (Zimetbaum, 2007). It should be noted that AF recurrence is frequent even with the most effective AADs; in this context, success of rhythm control therapies is typically defined by reduction in the frequency and severity of symptoms, not by their elimination (Fuster, 2006).

There are many options among AADs, and the available drugs have differing levels and types of side effects (Reiffel, 2009). Among all AADs, amiodarone, although it is technically "off-label" for use in treating AF, is generally viewed as the most effective available drug at maintaining sinus rhythm. Amiodarone is frequently used in patients with underlying structural heart disease, as the risk of proarrhythmia (increased frequency and/or severity of atrial arrhythmias) in patients with heart disease is much lower with amiodarone than with other AADs (Zimetbaum, 2007). However, amiodarone's relative effectiveness is counter-balanced by its potential to cause severe side effects such as thyroid dysfunction and pulmonary fibrosis, particularly with long-term use. Because of these risks, for many patients with AF amiodarone is considered a second-line agent, used only if another AAD fails to control the rhythm adequately.

Other common AADs include flecainide, dofetilide, propafenone, and ibutilide. Although not generally as effective as amiodarone at sustaining normal sinus rhythm, because these drugs offer lower risks for some long-term toxicities, they may be considered first-line agents for selected patients. Recently, a new non-iodinated amiodarone analogue, dronedarone, was approved by the FDA for use in patients with AF without severe heart failure (Stiles, 2009). The absence of iodine in dronedarone is thought to render the drug less toxic, but its comparative effectiveness vs. amiodarone and its optimal role in AF management is still controversial (Chan, 2009; Singh, 2010). Recently, reports have surfaced regarding incident cases of torsades de pointes and worsening CHF for patients on dronedarone, but their association with dronedarone use is still under investigation (FDA Adverse Event Reporting System, 2010).

Guidelines published in 2006 from a joint task force of the American College of Cardiology, American Heart Association, and European Society of Cardiology recommended AAD treatment for patients in AF who have troublesome symptoms, who have a good chance of remaining in sinus rhythm, and who can tolerate AAD drugs. The guidelines stressed the importance of choosing an AAD based on individual characteristics of the patient. The graphic on the following page depicts first- and second-line agents for particular types of patients. While dronedarone was introduced after the publication of these guidelines, it would likely be considered to be another options for first-line use in all patient types other

than patients with recently decompensated CHF. Note that the potential role of catheter ablation is also highlighted in the graphic.



Source: Fuster, 2006

Catheter Ablation

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 (Crandall, 2009). 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) (Callahan, 2009). The pulmonary vein is a common source of abnormal electrical activity that can trigger AF; the goal of PVI is therefore to create scars in the cardiac tissue that will interrupt all electrical communication between the pulmonary vein and the atria. Other sites of ablation may include the ligament of Marshall and the superior vena cava, although these are most frequently ablated as an adjunct to PVI rather than a substitute (Callahan, 2009). 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 (Crandall, 2009).

Catheter ablation is performed in an electrophysiology (EP) lab. In most cases the location of catheter insertion is either the neck or groin area. One or more diagnostic catheters are inserted into the blood vessel and are moved toward the heart. The physician follows the catheter's progress via a special monitor connected to a fluoroscopic camera. The

diagnostic catheters are used to study the arrhythmia. Once the physician determines the location of the cardiac tissue where abnormal rhythms can be sustained, this area can be ablated. Catheter ablation usually results in a same-day discharge or single overnight hospital stay. Rare but serious complications can occur, including stroke during the procedure, cardiac tamponade, and atrioesophageal fistula from the energy source. Some level of atrial fibrillation or flutter is not unexpected immediately following ablation, but this often gradually diminishes over several weeks; as such, the success of catheter ablation is typically not assessed until after a "blanking period", generally 3 months in duration (Calkins, 2007).

Proponents of catheter ablation argue that, by "curing" AF, the procedure provides permanent symptom relief and may produce electroanatomic remodeling of the atrial space, thereby reducing the risk of recurrence (Pappone, 2001). Others contend that the idea of a "cure" is oversold; recurrence of AF remains common after ablation, requiring multiple repeat ablations in many patients. Moreover, there remain questions about whether ablation offers significant long-term improvements in quality of life compared to rate-control strategies; and, even after a successful ablation, current guidelines recommend continuation of antithrombotic therapy based on patients' underlying risks for stroke.

Surgical Ablation

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 the use of surgical ablation as a treatment for AF among patients with no other indication for cardiac surgery.

There are three major types of surgical techniques used in the treatment of AF. Like catheter ablation, all approaches seek to interrupt abnormal electrical impulses that cause AF, but surgical techniques also involve excision or exclusion of the left atrial appendage (LAA), which is thought to be the location of 60-90% of the thrombi that cause AF-related strokes (Blackshear, 1996):

4. **"Cox-Maze III" –** This procedure, which involves a full thoracotomy and cardiopulmonary bypass, is the original, "cut and sew" approach to surgical ablation of AF (Lee, 2009b). 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. The Cox-Maze, which is now in its third generation (i.e., Cox-Maze III), is a technically demanding procedure; as a result, only a limited number of centers worldwide perform it.

5. **"Cox-Maze IV" –** This procedure involves a smaller, "mini-thoracotomy" and cardiopulmonary bypass. The traditional cardiac incisions of the Cox-Maze III are replaced by radiofrequency and/or cryothermal lesions; in addition, isolation of the right and left pulmonary veins is accomplished using a slightly different method

(Lall, 2007). This procedure is considered simpler to perform and is associated with reduced operating-room time relative to Cox-Maze III (Melby, 2006b).

6. **Thorascopic "Off-Pump" (TOP) Approaches –** This procedure is done on a "beating heart" – the heart is not arrested via bypass. Use of a thorascope (a video telescope) helps surgeons guide the energy source to the atria. Radiofrequency energy applied to the outside of the heart (epicardial ablation) is used for lesion creation. This approach has many variants, but commonly involves pulmonary vein isolation at a minimum, as well as other potential ablation lines. Bipolar radiofrequency energy is typically employed, in contrast to the unipolar energy employed in catheter ablation.

All forms of surgical ablation require an inpatient stay in the hospital; the length of stay will vary depending on whether other cardiac surgical procedures are performed. All surgical approaches carry small risks of serious complications, including stroke, tamponade, coronary artery injury, phrenic nerve paralysis, and esophageal perforation (Lee, 2009a), in addition to traditional surgical risks (e.g., MI, infection). In addition, as with catheter ablation, temporary recurrence of AF in the 3-6 months post-surgery is common, and many patients receive AADs during this period to aid in the return to sinus rhythm.

Proponents of surgical ablation describe several advantages over catheter-based ablation techniques. First, removal of the left atrial appendage has been conservatively estimated to remove the source of approximately 50% of thromboembolic events in patients with chronic AF (Blackshear, 1996). In addition, some advocates believe the use of bipolar radiofrequency energy produces more effective lesions than unipolar energy (Bugge, 2005). On the other hand, it is argued that effective management of AF can be accomplished through non-invasive means for many patients, and the additional risks posed by surgery may outweigh any potential clinical benefits offered by surgery.

The field of surgical ablation continues to evolve rapidly, and there are widely varying techniques used by different surgeons and surgical centers. Until recently, surgical ablation was performed by a relatively small number of centers given the complexity of the Cox-Maze procedures, and most patients referred for surgery were seeking an alternative after one or more failed catheter ablation attempts. As expertise and less-invasive TOP approaches have spread, however, there has been growing interest in the possibility of using surgical ablation as a primary treatment for highly symptomatic patients with AF for whom rate control is not an option and who have failed or are not suitable candidates for AAD therapy. Therefore, while evidence on all forms of surgical ablation is presented in this review, we emphasize evidence on TOP approaches as potential alternatives to catheter ablation or AAD therapy among patients who are not undergoing concurrent cardiac surgery for other indications.

Several new innovations of ablation techniques have been reported. The division of cardiothoracic surgery at Ohio State University has recently produced a thorascopically-based electrophysiologic replication of the Cox Maze left atrial lesion pattern; findings from a series of 48 patients undergoing this procedure have recently been published (Sirak, 2010). In addition, a combined endocardial and epicardial "hybrid" procedure has been

developed that involves both surgery and cardiac electrophysiology; preliminary findings showing high success rates were reported at the 2010 meeting of the Heart Rhythm Society (StopAfib.org, 2010).

2.2 Prevention of Stroke

Because AF is such a significant risk factor for thrombotic stroke, clinical guidelines recommend the use of antithrombotic therapy to prevent blood clot formation in all patients with AF, regardless of the strategy used to manage AF symptoms and restore sinus rhythm (Singer, 2008). Standard, guideline-directed treatment is available for this purpose; in addition, several new treatment options are emerging. All are described in detail below.

Standard Care

Clinical guidelines link the choice of anti-thrombotic therapy to the patient's stroke risk. A well-accepted framework for measuring stroke risk in AF is the $CHADS_2$ score (Gage, 2001), based on the presence of the following risk factors:

- Congestive heart failure
- Hypertension
- Age ≥75 years
- Diabetes mellitus
- Prior stroke/transient ischemic attack (TIA)

Risk is scored on a 0-6 scale using one point for each of the first four risk factors, and two points for prior stroke/TIA. Guideline recommendations call for the long-term use of aspirin (75-325 mg daily) for patients at lower stroke risk ($CHADS_2$ scores of 0 or 1). For all other patients, long-term use of anticoagulants is recommended. Warfarin, which has been shown to be highly effective in preventing stroke in a variety of populations with AF, is the most common anticoagulant used in the US for this purpose, as well as for other conditions such as deep vein thrombosis and pulmonary embolism (Go, 2001).

While warfarin's effectiveness has been well-documented, its use is also associated with significant risks (Hylek, 2009). Warfarin dosing varies by individual, and must be monitored frequently by blood test to ensure that the level of anticoagulant effect as measured by the international normalized ratio (INR) is neither too low nor too high. If the INR is too low, the patient is at increased risk for thrombotic stroke; if the INR is too high, there is an increased risk of major bleeding, including into the brain (hemorrhagic stroke). Warfarin treatment is also complicated by interactions with other drugs, alcohol, and certain foods.

Because of the complex nature of long-term warfarin use, alternative means of stroke prevention among patients with AF have been developed. Two such strategies are currently under consideration by the FDA and are summarized below.

Dabigatran Extexilate

Dabigatran extexilate is an orally administered direct-acting thrombin inhibitor (Kalus, 2009). It has been approved by the European Medicines Agency for use in the prevention of venous thromboembolism following total hip and total knee surgery. Dabigatran differs substantially from warfarin in that it offers once-daily fixed dosing without requirement for laboratory monitoring. Dabigatran is also not significantly affected by interactions with food and has a shorter half life than warfarin (Hylek, 2009). On September 20, 2010, the FDA's cardiovascular and renal drugs advisory committee voted unanimously to recommend dabigatran's approval (Drahl, 2010).

While dabigatran is the first new agent to be considered by the FDA for stroke prevention in AF, other agents may soon become available as well. For example, findings from the AVERROES trial were recently presented at the European Society of Cardiology's 2010 meeting; this trial randomized nearly 6,000 patients with AF who were not considered suitable candidates for warfarin to receive apixaban, an experimental oral selective Factor Xa inhibitor, or aspirin (Connolly, 2010). The trial was terminated early due to substantially lower rates of stroke or systemic embolism in apixaban patients; rates of major bleeding did not differ between the two arms. Like dabigatran, apixaban can be used without requirement for laboratory monitoring. Other Factor Xa inhibitors currently being tested in AF include betrixaban, edoxaban, and rivaroxaban (Nainggolan, 2010).

Left Atrial Appendage Exclusion

An alternative to surgical excision of the left atrial appendage is device-based exclusion. In the United States, the FDA recently gave 510 (k) clearance to the AtriClip® Gillinov-Cosgrove device for use during surgical ablation procedures. Findings from clinical testing suggest a high rate of confirmed LAA exclusion with no related safety events; stroke rates were not measured in this study, however, and no comparison group was included (AtriCure, 2010).

Another device close to potential FDA approval is the WATCHMAN, an expandable nitinol (a nickel–titanium alloy) cage covered with a porous fabric (Fountain, 2006). When implanted in the left atrial appendage, it acts as a filter to block the formation of clots. In April 2009, based on the result of a randomized clinical trial, the FDA circulatory systems device advisory panel voted for approval of the WATCHMAN. However, several safeguards were recommended, including implantation of the WATCHMAN only in centers with adequate surgical backup and extensive follow-up of patients in current trials (O'Riordan, 2010). In March 2010, the FDA requested that the manufacturer design and conduct a confirmatory study on the WATCHMAN's safety and effectiveness (Atritech, 2010); the manufacturer expects to begin the study later this year, which will likely delay final regulatory approval by an additional year or more.

While the AtriClip and WATCHMAN are the first devices to submit for FDA approval, multiple devices are on the market in Europe and other locations. The AMPLATZER® Cardiac Plug system received European CE mark approval in December 2008; a Phase I trial vs. warfarin has just started recruiting patients in the U.S. (AGA Medical, 2010a).

3. Clinical Guidelines

3.1. Antiarrhythmic Drugs

- The European Society of Cardiology (2010)
  http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-afib-FT.pdf
  Amiodarone is more effective at maintaining sinus rhythm than sotalol, propafenone, flecainide, or dronedarone, but because of its toxicity should generally be used when other agents have failed or are contraindicated. Dronedarone should be considered for reducing cardiovascular hospitalization in patients with nonpermanent AF and cardiovascular risk factors.

- 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
  - Amiodarone and Class 1C AADs are both appropriate for pharmacological cardioversion.
  - 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.
  - Among patients with persistent AF, AAD therapy is not required among patients who have undergone successful ablation and cardioversion. Class 1C agents, amiodarone, or sotalol can be administered if beta blocker therapy fails to control symptoms.

3.2 Catheter Ablation

- The European Society of Cardiology (2010)
  http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-afib-FT.pdf
  Catheter ablation for paroxysmal AF should be considered for patients who have previously failed a trial of anti-arrhythmic medication. Ablation of persistent symptomatic AF that is refractory to anti-arrhythmic medication should be considered a treatment option.

- Heart Rhythm Society Task Force on Catheter and Surgical Ablation of Atrial Fibrillation (HRS, 2007) http://www.hrsonline.org/News/Media/press-releases/upload/HR-and-Euro-Copy-for-Print.pdf
  The Task Force considers the following indications to be appropriate for catheter ablation:
  - Symptomatic AF refractory or intolerant to at least one Class 1 or Class 3 AAD; or
  - 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 thrombi.

- 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
  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.

3.3 Surgical Ablation

- The European Society of Cardiology (2010) http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-afib-FT.pdf
  Surgical ablation should be considered in patients with symptomatic AF undergoing cardiac surgery, as well as in patients with asymptomatic AF if feasible and performed with minimal risk. Minimally-invasive surgical ablation without concomitant cardiac surgery is feasible and may be performed in patients with symptomatic AF after failure of catheter ablation.

- 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 AAD treatment has failed and the patient requires further treatment.

- Heart Rhythm Society Task Force on Catheter and Surgical Ablation of Atrial Fibrillation (HRS, 2007) http://www.hrsonline.org/News/Media/press-releases/upload/HR-and-Euro-Copy-for-Print.pdf
  The Task Force considers the following indications to be appropriate for surgical ablation:

- Symptomatic atrial fibrillation in patients who are undergoing other cardiac surgery;
- Selected 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.

- The National Collaborating Centre for Chronic Conditions (NCCCC, 2006) http://www.nice.org.uk/nicemedia/pdf/cg036fullguideline.pdf
  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.

3.4 Stroke Prevention

- American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (ACCP, 2008)
  http://chestjournal.chestpubs.org/content/133/6_suppl/546S.full.pdf+html
  - In all patients with AF, the ACCP recommends long-term treatment with aspirin or a vitamin K antagonist 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; those with no risk factors should receive aspirin.

- 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
  - 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 anticoagulation.

- The National Collaborating Centre for Chronic Conditions (NCC-CC, 2006)
  http://guidance.nice.org.uk/CG36
  - 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.

4. Medicare and Representative Private Insurer Coverage Policies

4.1. Antiarrhythmic Drugs

Dronedarone

- Centers for Medicare and Medicaid Services (CMS): CMS does not have a national coverage decision on dronedarone at this time.

- Tufts: Dronedarone is listed as a "Tier 3" (non-preferred) AAD on the Tufts formulary.

- Wellpoint/Anthem: Dronedarone is listed as a "Tier 3" (non-preferred) AAD on the Anthem national drug list.

- Others: Most other private payers with published policies, including Aetna, Harvard Pilgrim, Regence, and Humana, list dronedarone as a "Tier 2" (preferred, branded) AAD on their formularies.

4.2. Catheter Ablation

- Centers for Medicare and Medicaid Services (CMS)**:** Medicare does not currently have a national coverage decision for the use of catheter ablation in the treatment of atrial fibrillation. The procedure is reimbursed, however, by all local Medicare contractors. 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 AAD 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 AADs, or has a contraindication to the appropriate therapy

4.3 Surgical Ablation

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

- CIGNA: The Maze procedure is covered when performed during cardiopulmonary bypass with or without concomitant surgery in patients who have medically refractory, intermittent 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 minimally-invasive procedures are considered medically necessary for the following situations:
    - The patient is suffering hemodynamic consequences of chronic atrial fibrillation.
    - The patient cannot tolerate the side effects of drug therapy.
    - The patient is at high risk for thromboembolism due to:
        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 minimally-invasive procedures are considered medically necessary for drug-resistant atrial fibrillation. 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.

4.4 Stroke Prevention

There are generally no coverage limitations on the use of aspirin or warfarin for anticoagulation (other than clinical indications and contraindications). The AtriClip has only been recently approved, and has therefore not been addressed yet by public and private payers in the United States. Dabigatran and the WATCHMAN are not yet FDA-approved.

5. Previous Systematic Reviews/Tech Assessments

5.1 Medical Management

Dronedarone

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

- National Institute for Health and Clinical Excellence (NICE, 2010)
  http://www.nice.org.uk/nicemedia/live/11750/49792/49792.pdf
  NICE has issued a final appraisal determination which revised its original recommendation that dronedarone should not be used to treat atrial fibrillation. The revised guidance recommends that dronedarone may be used only in patients with additional cardiovascular risk factors whose AF is not controlled by first-line therapy and who do not have unstable NYHA class III or IV heart failure. The original conclusion that dronedarone is not as effective as other AADs in preventing AF recurrence still remains. However, NICE has accepted evidence that dronedarone does not lead to an increase in mortality relative to the AADs to which it was compared.

5.2 Catheter Ablation

- Canadian Agency for Drugs and Technologies in Health (CADTH, 2010)
  http://www.cadth.ca/media/pdf/H0491_Ablation_Procedures_with_Atrial_Fibrillation_tr_e.pdf
  Catheter ablation was found to be superior to medical treatment for the maintenance of sinus rhythm up to one year, particularly in patients with paroxysmal AF. There was insufficient evidence on (a) first-line use of catheter ablation; (b) long-term outcomes of ablation procedures; (c) adverse events of ablation; and (d) effectiveness in patients with congestive heart failure; (e) outcomes in comparison to surgical techniques; and (f) effectiveness of repeated catheter ablations.

- California Technology Assessment Forum (CTAF, 2010)
  http://www.ctaf.org/UserFiles/File/2010%20June/RFAafrib%20final%20draft.pdf
  Radiofrequency catheter ablation as a treatment for paroxysmal, drug-refractory AF does not meet CTAF criteria 4 (the technology must be as least as beneficial as available alternatives) or 5 (improvement in health outcomes must be attainable outside of investigational settings).

- Agency for Healthcare Research and Quality (AHRQ, 2009)
  http://effectivehealthcare.ahrq.gov/ehc/products/51/114/2009_0623RadiofrequencyFinal.pdf
  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.

- Blue Cross Blue Shield Association Technology Evaluation Center (TEC, 2009)
  http://www.bcbs.com/blueresources/tec/vols/23/radiofrequency_catheter_ablation.pdf
  Radiofrequency catheter ablation of the pulmonary veins as a treatment for atrial fibrillation meets the TEC criteria for:

  * patients with symptomatic paroxysmal or persistent atrial fibrillation who have failed antiarrhythmic medications, as an alternative to continued medical management; and

  * patients with class II or III congestive heart failure and symptomatic atrial fibrillation in whom heart rate is poorly controlled by standard medications, as an alternative to AV nodal ablation and pacemaker insertion.

- Health Technology Assessment NIHR HTA Programme (2008)
  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 are some data to suggest that 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 National Institute for Health and Clinical Excellence (NICE, 2006)
  http://www.nice.org.uk/nicemedia/pdf/ip/IPG168guidance.pdf
  The evidence on the safety and efficacy of percutaneous radiofrequency 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 AADs or when medical therapy is contraindicated because of co-morbidities or drug intolerance.

5.3 Surgical Ablation

- Toronto: Medical Advisory Secretariat, Ontario Ministry of Health and Long-Term Care (MAS, 2006)
  http://www.health.gov.on.ca/english/providers/program/mas/tech/reviews/pdf/rev_af_030106.pdf

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, 2009)
  http://www.nice.org.uk/nicemedia/live/11964/42871/42871.pdf
  There is limited short-term evidence from the experience of a small number of patients on the efficacy of thoracoscopic epicardial radiofrequency ablation. Evidence on safety indicates there is a low incidence of serious complications but this is based on a limited number of patients. This procedure should only be used when appropriate arrangements are in place for consent, clinical governance, and audit.

- National Institute for Health and Clinical Excellence (NICE, 2005)
  http://www.nice.org.uk/nicemedia/pdf/ip/IPG121guidance.pdf
  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).

5.4 Stroke Prevention

Dabigatran

There are no publically available technology assessments of dabigatran for the prevention of stroke among 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 extexilate 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.

- National Institute for Health and Clinical Excellence (NICE, 2008)
  http://www.nice.org.uk/nicemedia/pdf/TA157GuidanceWord.pdf
  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.

LAA Exclusion Devices

- National Institute for Health and Clinical Excellence (NICE, 2010) http://www.nice.org.uk/nicemedia/live/11216/49407/49407.pdf
  Percutaneous exclusion of the left atrial appendage is efficacious in reducing the risk of thromboembolic complications associated with non-valvular AF. There is a risk of life-threatening complications with the procedure, but the incidence is low. Therefore, this procedure may be used provided that normal arrangements are in place for clinical guidance, consent, and audit, patient selection is carefully performed by a multidisciplinary team, centers performing the procedure have appropriate training and experience, and on-site cardiac surgical backup is available.

6. Ongoing Clinical Studies

Trial Sponsor /Title	Design	Primary Outcomes	Populations	Variables	Comments
Sanofi-Aventis, NCT01026090/Dronedarone Pattern of Use in Patients Scheduled for Elective Cardioversion (ELECTRA)	RCT	AF recurrence within 6 months	• N = 500 • 18 Years and older	Dronedarone vs. Placebo	Estimated Study Completion Date: June 2011
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	• N = 400 • Age >18 Years old	Pulmonary Vein Isolation vs. Antiarrhythmic Drugs per ACC/AHA 2006 Guidelines for the Management of Patients with AF	Estimated Study Completion Date: *Unknown*
Mayo Clinic, NCT00911508/ Ablation Versus Antiarrhythmic (AA) Drug Therapy for AF - Pivotal Trial (CABANA)	RCT	Reducing total mortality in patients with untreated or incompletely treated AF	• N = 3000 • 18 Years to 90 Years	Pharmacologic Therapy Rate and/or Rhythm Control vs. NAVI-STAR Thermo-cool (Left Atrial Catheter Ablation)	Estimated Study Completion Date: September 2015
Virginia Commonwealth University | AtriCure, Inc., NCT00747838/ A Multicenter Data Registry for Outcomes From Surgical Treatment of Atrial Arrhythmias	Prospective Cohort Study	Minimally invasive surgical treatment for control of atrial fibrillation	• N = 5000 • 18 Years and older	Minimally Invasive Maze Procedure	Study Completion Date: *Unknown*
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);	• N = 6200 • 18 Years and older	Dabigatran etexilate vs. warfarin	Active but not recruiting; estimated primary completion date is July 2011
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

7. The Evidence

7.1 Systematic Literature Review

Objectives
The primary objectives of the systematic review were to:

- Evaluate and compare the published evidence on the effects of catheter ablation, surgical ablation, and antiarrhythmic drugs on stroke, cardiovascular mortality, all-cause mortality, and health-related quality of life in patients with moderate-to-severe symptoms of AF;

- Evaluate and compare the clinical benefits of these therapies in terms of intermediate and other outcomes, including freedom from AF recurrence, hospitalization, subsequent treatment, and requirements for anticoagulation;

- Evaluate and compare the potential harms of these therapies, including procedure-related fatalities, major and minor complications, and drug-related adverse events; and

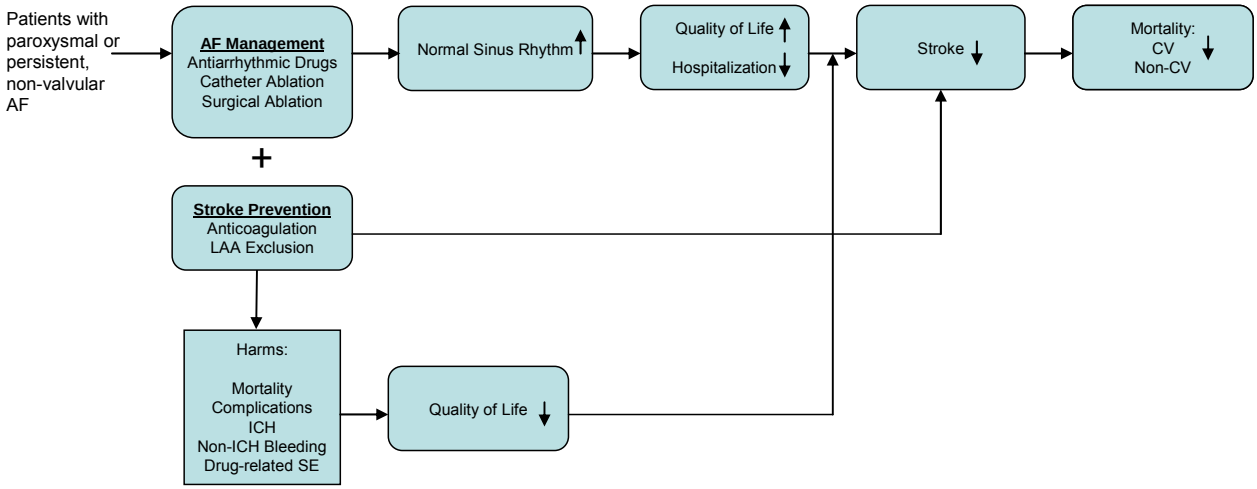
- Evaluate and compare the effects of warfarin, dabigatran, and left atrial appendage (LAA) exclusion devices on rates of ischemic stroke, hemorrhagic stroke, and other major bleeding.

Our recording of data on potential harms of either catheter-based or surgical ablation included "peri-procedure" fatalities or strokes occurring during the procedure or within 30 days following. While the types of major and minor complications differed somewhat by ablation approach, we defined major complications as those requiring reoperation or other major intervention (e.g., thoracotomy) to correct, while we defined minor complications as transient conditions or those requiring minimal intervention. We also examined major categories of drug-related adverse events, as well as rates of drug discontinuation due to any adverse event.

While not part of the systematic review, published studies of the economic impact of these management options are summarized in Section 8 to provide additional context for the ICER economic model.

Analytic Framework
The analytic framework for this review is shown in the Figure on the following page. Note that the figure is intended to convey the conceptual links involved in evaluating outcomes of these management options, and are not intended to depict a clinical pathway that all patients would transit through. This framework also does not represent the clinical pathways as they were constructed for the decision analytic model (see Section 8).

Analytic Framework: Strategies to Restore Normal Sinus Rhythm in Atrial Fibrillation



AF: Atrial fibrillation; CV: Cardiovascular; LAA: Left atrial appendage; ICH: Intracranial hemorrhage; SE: Side effects

There are little to no data directly demonstrating the impact of AF management strategies on ischemic stroke or cardiovascular and overall patient mortality, so judgments about the effectiveness of these interventions must rest almost exclusively upon surrogate endpoints as well as evaluation of treatment-associated risks. In contrast, evidence on stroke prevention strategies contains direct measures of ischemic stroke rates as well as specific harms (i.e., intracranial hemorrhage, other major bleeding).

There is considerable debate about how much credence to place in comparisons across studies of surrogate outcome measures for the treatment of AF. Study measurements of normal sinus rhythm or "freedom from AF" are typically constructed as point-in-time measurements and may not capture previous or subsequent episodes of AF recurrence. Some studies focus on symptomatic AF alone while others include asymptomatic AF; measurement of AF itself can vary widely, from single in-office electrocardiograms, to longer Holter examinations; and, in addition, may also incorporate patient-reported episodes of AF. It has been noted that the more diligently AF is sought, the more is found, and so comparisons across studies using different methods is fraught with the risk that differences in AF recurrence may be nothing but measurement artifact (Henry, 2010).

Moreover, it must be acknowledged that measures of AF by themselves cannot tell us the degree to which AF episodes, particularly short ones, impact quality of life or other outcomes of interest to patients. Some patients have both symptomatic and asymptomatic episodes of AF, and even patients who have recurrent symptomatic AF following treatment may nevertheless be satisfied and have increased quality of life because the incidence of symptomatic episodes may be far lower than was experienced previously.

For all these reasons, clinical and policy decision-makers should be aware that evidence on the outcomes of treatment for AF is almost exclusively limited to surrogate outcomes that are difficult to compare and that can be over-interpreted; it is thus very important to maintain respect for the tenuous links between the components of the analytic framework for the evaluation of AF treatment options.

Patient Populations

Where possible, information on the impact of the interventions of focus in key patient subpopulations was sought. The ERG defined 3 patient populations of interest for this appraisal:

- Younger patients with paroxysmal AF and limited/no comorbidities
- Older patients with persistent/long-standing persistent AF and comorbidity
- Older patients with symptomatic left ventricular dysfunction in whom return to sinus rhythm may improve cardiac function, quality of life, and length of life

In addition, there was interest in understanding whether any evidence of differential treatment effects existed for populations stratified by sex, race/ethnicity, or type of AF generally. Finally, because there is always concern when innovative technologies such as surgical or catheter ablation are introduced regarding the correlation between level of clinician experience and/or training and patient outcomes, information was sought regarding the impact of procedure "learning curve" on important measures of effectiveness and harm.

Methods

This review included studies of the benefits and harms of management options among adults (i.e., aged 18 years or older) with atrial fibrillation. Because AHRQ recently completed a review of catheter ablation for AF in July 2009 (Ip, 2009), the ICER appraisal sought to build off this effort by including all RCTs and comparative cohort studies from the AHRQ review that compared PVI-based catheter ablation to AAD treatment. We then abstracted studies published after AHRQ's review timeframe through May 2010. In order to ensure consistency between the 2 reviews, study eligibility criteria for our literature search on catheter ablation were designed to match the AHRQ review as closely as possible. We compared summary findings of the AHRQ review with those obtained on analyses including subsequent literature and noted any differences in findings or conclusions.

In the broader literature search for this appraisal, to ensure that the evidence included represented outcomes for patients with AF, studies that included the following populations were excluded from analyses:

- Other arrhythmias or atrial flutter
- Type of AF other than paroxysmal, persistent, or long-standing persistent (e.g., temporary AF following major surgery)

- Specific cardiovascular conditions likely to affect downstream risks independently (e.g., congenital heart disease, hypertrophic cardiomyopathy, Wolff-Parkinson-White syndrome)

This appraisal focuses on interventions aimed at long-term restoration of sinus rhythm. Therefore, rate control strategies were not included in the scope of the systematic review.

The electronic databases we searched as part of the systematic review included MEDLINE, EMBASE, and *The Cochrane Library* (including the Database of Abstracts of Reviews of Effects [DARE]) for health technology assessments (HTAs), systematic reviews, and primary studies. Reference lists of all eligible studies were also searched. The search strategies used for MEDLINE, EMBASE, and *The Cochrane Library* are shown in Appendix A.

The search included studies published during the period January 2000 – May 2010; this timeframe was recommended by the ICER Evidence Review Group (ERG) to be generally consistent with the advent of ablation techniques and the modernization of antiarrhythmic drug therapy. Other major eligibility criteria included:

- Minimum of 6 months of follow-up post-intervention
- English-language only
- Effectiveness studies: ≥25 patients per study arm
- Retrospective cohort studies for harms: ≥100 study subjects

Treatments of Focus

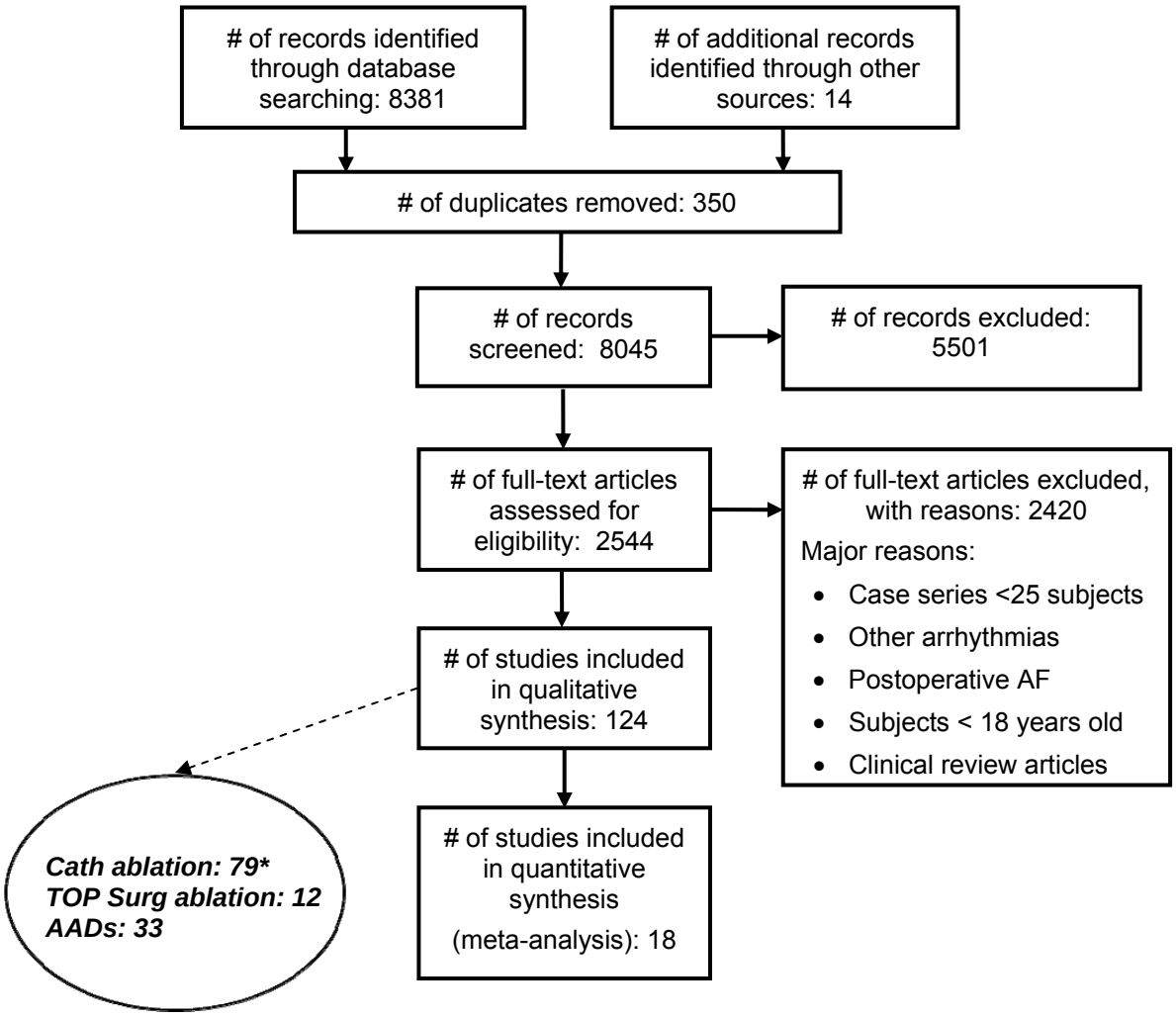
Because the focus of this appraisal was on the treatment of AF as the primary condition of interest, surgical or catheter-based ablation approaches that were concomitant to other major cardiovascular procedures (e.g., CABG, valve replacement) were excluded from analysis. All studies of catheter-based PVI were included, with or without additional lesion sets, since the ERG suggested that pulmonary vein isolation (PVI) is a critical component of nearly all catheter-based approaches.

In addition, because the focus of attention was on treatment approaches that would be targeted at similar candidate patient populations, abstraction of data on surgical ablation was limited to studies of thorascopic, off-pump (TOP) procedures for stand-alone AF, as bypass-based Maze or other surgical approaches are typically a therapy of "last resort" (i.e., after failure of both drug therapy and catheter ablation). Nevertheless, relevant findings from prior systematic reviews of Maze or other forms of surgical ablation for stand-alone AF were reported as a point of comparison.

Finally, in order to have a manageable number of treatment options to compare, and based on guidance from the ERG, detailed analyses of antiarrhythmic therapy were limited to studies of amiodarone, as it is widely believed to be the most effective at restoring sinus rhythm; and dronedarone, a new agent that is being promoted as a potentially safer alternative to amiodarone.

Studies were not restricted by instrumentation, manufacturer, or outcome measurement technique. Figure 1 below shows a flow chart of the results of all searches for primary studies (n=124). Of the 79 catheter ablation studies, 12 were from the previous AHRQ review and 67 were newly-abstracted as part of this appraisal.

Figure 1. PRISMA flow chart showing results of literature search.



*Data included on 12 studies from AHRQ review; 67 studies newly-abstracted
TOP: Thorascopic, off-pump; AADs: Antiarrhythmic drugs

7.2 Data Analyses

Measures of Clinical Benefit

Mortality & Stroke
Data were collected where reported on both cardiovascular and overall (all-cause) mortality. Survival rates were only abstracted if reported on an annualized basis or if annualized rates could be constructed from available data. Mortality during follow-up was distinguished from fatalities occurring within 30 days of catheter ablation or TOP surgical ablation, as these were considered peri-operative events.

Similarly, data were collected on the rates of ischemic, hemorrhagic, and overall stroke during follow-up. Data on annualized rates of stroke were abstracted or calculated as with mortality above; in addition, attempts were made to distinguish peri-operative stroke from stroke recorded during follow-up.

Freedom from AF
Published studies of rhythm control strategies for AF have used a wide variety of measures to document the presence and significance of AF. Because these variations in study methods could lead to apparent but spurious differences in key outcomes, we compared reported rates of "freedom from AF" across different studies only if AF was documented using both of the following two approaches: (1) use of Holter monitors, event recorders, or transtelephonic EKG to record the presence of AF; and (2) use of actuarial or Kaplan-Meier techniques for calculation of the measure, or alternatively, reporting of the measure at timepoints (e.g., 6 months, 1 year) with data available from all study subjects. Evidence tables presented in Appendix B highlight the studies that are included and excluded for this and other measures.

Hospitalization
Rates of hospitalization were recorded as annualized rates if reported as such or if annualized rates could be constructed. Where feasible, we reported separate rates for AF, cardiovascular, and all-cause hospitalization.

Quality of Life
Data on health-related quality of life as well as AF symptom severity and frequency were recorded as reported at multiple timepoints.

Potential Harms

Surgical/Catheter Ablation, LAA Exclusion
Peri-procedure deaths and strokes were classified as those occurring during catheter ablation or TOP surgical ablation or within 30 days following the procedure. Surgery-related complications were recorded as "major" or "minor" based on a discrete list of complication types; a specific classification scheme (e.g., Clavien) was *not* used, as such schemes were infrequently employed in the studies we evaluated. Major complications

were those that were felt to require re-exploration of the ablation site or a significant new clinical intervention, and included:

- Major hemorrhage
- Deep vein thrombosis and/or pulmonary embolism
- Respiratory failure with prolonged ICU stay or ventilator dependency
- Renal failure with dialysis
- Other organ failure
- Myocardial infarction and/or stroke
- Other conditions (e.g., AE fistula, tamponade) requiring conversion to full thoracotomy

Minor complications were recorded as a single category based on classification as "minor" or "not requiring major invasive treatment" in comparative or other case series. While a discrete set of minor complications was not analyzed, a representative list of the most frequently reported minor complications can be found below:

- Minor procedure requirement (e.g., pericardiocentesis, thoracentesis)
- Pneumothorax (chest tube only)
- Coagulation
- Wound infection
- Phlebitis

A separate recording was made for two selected minor complications, based on their potential to affect long-term quality of life and consequent utility for the modeling effort. These were phrenic nerve injury with subsequent diaphragmatic paralysis, and permanent pacemaker implant.

Rates of repeat ablation were recorded when available; where feasible, repeat ablation rates were stratified based on occurrence during the post-procedure "blanking period" (i.e., 2-3 months post-procedure) vs. during follow-up. Separate analyses were conducted using data from a national payer on the incidence of single vs. multiple ablation episodes as well as the elapsed time between episodes over 1-3 years of follow-up. Rates of "retreatment" following TOP surgical ablation were also abstracted, including subsequent catheter ablation as well as AAD therapy.

Antiarrhythmic Drug Therapy

Drug-related adverse events were recorded categorically based on the event types most commonly associated with amiodarone and dronedarone (e.g., pulmonary toxicity, thyroid toxicity). Rates of any adverse event requiring study drug discontinuation also were recorded. All rates were annualized as described previously.

Dabigatran and Warfarin

The rate of major bleeding (other than hemorrhagic stroke) was recorded for each of these anti-thrombotic agents and reported on an annualized basis (warfarin was the control agent

in both the dabigatran and WATCHMAN trials). We also recorded rates of study discontinuation due to any adverse events when the data were available.

Study Quality

We used standardized criteria to rate the quality of each included RCT or comparative cohort study, using the categories "good", "fair", or "poor". Our methods were based on the criteria employed by the U.S. Preventive Services Task Force (AHRQ, 2008), as described below:

- ***Good:*** Comparable groups are assembled initially and maintained throughout the study (follow-up of at least 80%); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; important outcomes are considered; and appropriate attention to confounders in analysis.

- ***Fair:*** Generally comparable groups are assembled initially but some question remains whether minor/moderate differences occurred in follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for.

- ***Poor:*** Any of the following problems exist: (1) groups assembled initially are not close to being comparable or maintained throughout the study; (2) unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); and (3) key confounders are given little or no attention.

Case series were not graded for study quality, as these reports are generally considered to be poor-quality evidence by the technology assessment community.

Data Synthesis

Treatment Effects

Where feasible, estimates of treatment effect were synthesized using meta-analysis. When direct evidence was deemed to be sufficient, random-effects models were generated based on head-to-head data. Data were deemed to be sufficient if (a) the number of eligible fair or good-quality RCTs was 3 or more; and (b) the measure of interest was reported using uniform methods. The rate ratio (RR) was the measure of choice for generating pooled estimates of effect. Studies rated "poor" were not included in meta-analyses, regardless of design. Finally, while cohort and case series studies were not candidates for meta-analyses of treatment effect, qualitative findings from these studies as well as studies similarly identified in the AHRQ review are described for each measure of interest.

Where direct evidence was not available, indirect and mixed treatment comparisons were considered. Indirect treatment comparisons were defined as comparisons of two or more

interventions to a common standard, and were conducted using the adjusted indirect comparisons method (Bucher, 1997). Mixed treatment comparisons (MTC) were defined as comparisons of both direct and indirect evidence, and were performed utilizing Bayesian hierarchical modeling techniques (Brooks, 1998). The WinBUGs software code for conducting MTC methods for random effects models is available on the following website: https://www.bris.ac.uk/cobm/research/mpes/mtc.html (University of Bristol, 2009). Findings were expressed as relative risks or odds ratios as appropriate. Heterogeneity was assessed via chi-squared analysis for indirect comparisons; meta-regression was used to explore heterogeneity in mixed treatment comparisons, including assessment of covariate-by-treatment interactions.

Model Parameter Estimation
Meta-analysis also was employed to generate estimates for the decision analytic model. Random-effects models were employed using the DerSimonian-Laird method (DerSimonian, 1986) with inverse variance weighting, given expected variability in study design and population; pooled rates were generated along with 95% confidence intervals. Heterogeneity was assessed via the tau-squared statistic, as well as observations regarding overlap in the estimates by treatment type and the width of the analysis-generated confidence interval.

Given the high potential for publication or other evidence dissemination bias from the type of evidence reviewed (i.e., mostly small, single-center studies), estimates were subjected to multiple tests of such bias. Specifically, rank correlation-tau and Egger's regression were performed and assessed for significance; if either result was significant, the trim-and-fill method was employed to adjust the pooled estimate.

Meta-analyses were conducted using METAANALYST v2.0 (Wallace, 2009), WinBUGS v1.4 (Lunn, 2000), and MIX v1.7 (Bax, 2006).

7.3 Results

Evidence Quality
The most abundant data identified were for catheter ablation (79 studies; N=19,831), followed by AADs (33 studies; N=39,978) and TOP surgical ablation (12 studies; N=662). Only the RE-LY RCT of dabigatran (Connolly, 2009b) and an RCT of a single LAA exclusion device (WATCHMAN) (Holmes, 2009) were included for the "stroke prevention" category, as other LAA exclusion studies involved devices not available in the U.S. or those intended for use as a component of an existing ablation procedure (i.e., AtriClip). Of the 124 studies identified, a total of 46 were RCTs (N=28, 16, 0, and 2 for AADs, catheter ablation, TOP surgical ablation, and stroke prevention respectively); of the 16 RCTs identified for catheter ablation, 6 were previously included in the AHRQ review (Ip, 2009), and 10 were newly-abstracted. As shown in Table 1 on the following page, patients in the catheter ablation and TOP surgical ablation studies tended to be younger, more likely to be male, and more likely to have paroxysmal AF than patients receiving AADs.

Table 1. Patient characteristics in atrial fibrillation studies, by type of intervention.

	Estimate (unweighted average across studies)		
Intervention	**% Paroxysmal AF**	**% Male**	**Age (y)**
Catheter Ablation	66.0	76.3	57.0
TOP Surgical Ablation	52.9	70.4	58.9
AADs	30.0	64.2	65.0

AF: Atrial fibrillation; TOP: Thorascopic off-pump; AADs: Antiarrhythmic drugs

Study characteristics are summarized in Appendix B, Table B1. Ratings of evidence quality for RCTs and comparative cohort studies are shown in the Table 2 below. The dabigatran RCT was considered a good-quality study, while the WATCHMAN RCT was considered "fair" (some imbalance noted between treatment groups in important confounders).

Table 2. Study quality, by type of study and intervention.

	Type of Study		
Intervention	**RCT**	**Comparative Cohort**	**Case Series**
Catheter Ablation	**16**	**20**	**43**
Good	*3*	*6*	--
Fair	*5*	*10*	--
Poor	*8*	*4*	--
TOP Surgical Ablation	**0**	**1**	**11**
Good	--	--	**--**
Fair	--	*1*	**--**
Poor	--	--	--
AADs	**28**	**2**	**3**
Good	*15*	*0*	**--**
Fair	*7*	*0*	**--**
Poor	*6*	*2*	--
Stroke Prevention*	**2**	**0**	**0**
Good	*1*	**--**	**--**
Fair	*1*	**--**	**--**
Poor	--	**--**	**--**

*Limited to studies of dabigatran and WATCHMAN only
TOP: Thorascopic off-pump; AADs: Antiarrhythmic drugs

The amount of evidence for TOP surgical ablation is quite limited. There are primarily case series data available on the outcomes of TOP surgical ablation, making neither direct nor indirect comparisons with other AF management options feasible; the one comparative

cohort study involved a Cox-Maze III control group, not a comparison to the other interventions of interest. In addition, the case series data available are marked by variability in surgical approach and ablation technique, lack of standardized measurement of outcomes, and a relatively brief duration of follow-up (3-12 months in most circumstances).

While RCT data as well as other comparative data were more widely available for catheter ablation, these data were not without limitations. As with TOP surgical ablation, variability in technique, approach, and patient populations made it difficult to draw conclusions across studies. For example, procedure success was defined by a single ablation procedure in some studies, while in others additional ablation attempts or re-initiation of AADs were allowed in determinations of return to sinus rhythm. In addition, while analyses of freedom from AF in this review included only those studies employing some form of extended monitoring, even these monitoring methods may significantly overstate freedom from AF. An analysis of quarterly Holter monitoring vs. a reference method using an implantable continuous monitoring device in 45 patients indicated sensitivity and negative predictive value of only 60% and 64% respectively for the Holter method (Hanke, 2009). Finally, while the level of procedure experience varied for both TOP surgical ablation and catheter ablation across centers, we found no studies that attempted to evaluate the impact of procedure "learning curve" on measures of effectiveness or harm.

In addition, some variability was observed in the types of AADs made available by study protocol in the catheter ablation RCTs, making comparisons to the evidence generated for our AADs of primary focus (amiodarone and dronedarone) potentially problematic. However, while amiodarone was infrequently used or excluded by protocol in two RCTs (Wazni, 2005; Wilber, 2010), it was the only comparator in another (Oral, 2006) and was used on either a first- or second-line basis by 60-65% of patients in the remaining studies.

In addition to the study differences by intervention noted previously, other more subtle differences in candidate populations for each treatment may also complicate comparisons. For example, while the general policy construct that positions TOP surgical ablation and catheter ablation as competing for the same set of patients may be reasonable, the percentage of surgical patients in the included case series who failed previous catheter ablation attempts was substantial in some studies. Previous catheter ablation was a protocol *requirement* in one TOP surgical ablation study (Castella, 2010); in the others, the proportion with failed prior catheter ablation ranged from 5-42% (mean: 24%). Also, the presence of highly symptomatic AF, a target indication for catheter or surgical ablation, was a protocol exclusion for some of the rhythm vs. rate control RCTs (Wyse, 2002; van Gelder, 2002), while other RCTs included a broader spectrum of patients (Roy, 2008; Hohnloser, 2000; Carlsson, 2003).

There was wide variation in the measurement and reporting of patient characteristics and outcomes; of the 16 catheter ablation RCTs identified for this appraisal, none met all of the criteria set forth by the Heart Rhythm Society (Calkins, 2007) for quality RCTs. Moreover, outcomes were generally captured for a relatively short time period, and many studies also saw significant patient crossover, both from drug to procedure and from procedure back to

drugs when adequate control of AF was not achieved or maintained with the first therapeutic modality.

Key Studies
Despite the variability in the quality of available data, several studies will be described here as "key" studies on the basis of their citation in multiple editorials and reviews. These studies are considered notable due to some combination of high quality study design, size and representativeness of patient population, and recent publication date. Summaries of their key findings are provided below and on the following page.

Antiarrhythmic Drugs

Le Heuzey, the DIONYSOS study (2010): This is the only published RCT to date involving a head-to-head comparison of dronedarone and amiodarone. A total of 504 amiodarone-naïve patients, aged 64 years on average, were assigned to receive dronedarone 400 mg twice-daily or amiodarone (600 mg daily for 28 days, then 200 mg daily thereafter). After a median of 7 months of follow-up, the proportion reaching the composite study endpoint of AF recurrence or premature study discontinuation was 75.1% for dronedarone vs. 58.8% for amiodarone (Hazard Ratio [HR]=1.59, 95% Confidence Interval [CI]=1.28, 1.98), due primarily to AF recurrence. Premature drug discontinuation was lower with dronedarone (10.4% vs. 13.3%), although the significance of this difference was not tested; differences were due primarily to lower rates of thyroid, neurologic, skin, and ocular events. No pulmonary toxicity was observed in either arm, presumably because of the relatively short duration of follow-up.

Kober, the ANDROMEDA study (2008): A total of 627 patients with a median age of 72 years were randomized to receive dronedarone 400 mg or placebo twice daily to evaluate dronedarone's utility treating CHF (approximately 20% of patients also had AF). The trial was prematurely discontinued after 7 months due to excess mortality in the dronedarone group (8.1% vs. 3.8% for placebo, p=.03), primarily caused by worsening heart failure. In addition, a higher rate of increased serum creatinine was observed in the dronedarone group (2.6% vs. 0%, p=.01). Both findings have affected the eventual labeling for dronedarone use in atrial fibrillation: therapy is contraindicated in patients with NYHA Class IV heart failure or Class II-III heart failure with recent decompensation and/or hospitalization, and serum creatinine monitoring is recommended with long-term dronedarone use (Sanofi-Aventis, 2009).

Singh, the EURIDIS/ADONIS studies (2007): These sister placebo-controlled trials, conducted in European and non-European settings respectively, evaluated the impact of dronedarone on prevention of AF recurrence in 828 patients; mean age was 64 years, 70% were male. Data were pooled from the 2 trials, which used an identical protocol. The median time to first recurrence was over twice as long in the dronedarone group (116 vs. 53 days, p=.01). At 12 months, the likelihood of any AF recurrence was 64% in the dronedarone group vs. 75% for placebo (HR=0.75; 95% CI=0.65, 0.87). The only adverse event found to occur with significantly greater frequency with dronedarone was elevation of serum creatinine (2.4% vs. 0.2% for placebo, p=.004).

Hohnloser, the ATHENA study (2009): This study evaluated dronedarone's impact on the rate of cardiovascular hospitalization or death in over 4,600 patients with AF and additional risk factors for death (e.g., older age, diabetes, previous stroke/TIA). In contrast to the ANDROMEDA study population, patients with NYHA Class IV or recently decompensated heart failure were excluded from ATHENA. Over a mean of 21 months of follow-up, 32% of patients in the dronedarone group had a first cardiovascular hospitalization or death vs. 39% for placebo (HR=0.76, 95% CI=0.69, 0.84). There was a reduced rate of death from cardiovascular causes in the dronedarone group (2.7% vs. 3.9%, p=.03), due primarily to a lower number of deaths from arrhythmias. Dronedarone was associated with significantly higher rates of QT interval prolongation, bradycardia, nausea, diarrhea, rash, and elevated serum creatinine. The rate of drug discontinuation was high with both dronedarone and placebo (>30%).

AFFIRM Investigators (2003): This study, a substudy of the larger AFFIRM rate- vs. rhythm-control study, compared the benefits and harms among the different AADs used in the rhythm-control arm of this large RCT. Specific comparisons were made for amiodarone vs. class I agents, sotalol vs. class I agents, and amiodarone vs. sotalol. Amiodarone was more effective than either sotalol or class I agents, as approximately two-thirds of amiodarone patients achieved "treatment success" (i.e., alive, in NSR, on drug, with no additional cardioversion at 1 year). In contrast, success rates with class I agents and sotalol ranged between 23-38%. However, the rate of side effects causing discontinuation was somewhat higher with amiodarone vs. sotalol, and the rate of severe pulmonary and ocular events was highest with amiodarone.

Catheter Ablation

Wilber (2010): This multicenter RCT compared PVI ablation to AAD therapy among 167 patients with paroxysmal AF (mean age 56 years). The study was notable for use of a pragmatic definition of treatment failure, which included not only documented electrocardiographic recurrence of AF but also the need for repeat ablation after the blanking period, lack of confirmation of entrance block following ablation, changes in the drug regimen after blanking, and drug discontinuation due to adverse events. At 9 months, 34% of catheter ablation patients had suffered treatment failure vs. 84% of AAD patients (HR=0.30; 95% CI=0.19, 0.47), a rate driven primarily by drug discontinuation in the AAD group and recurrent AF in both groups. The rate of major adverse events was lower in the catheter ablation group (4.9% vs. 8.8% for AADs), although statistical significance was not tested. Adverse events included pericardial effusion, pulmonary edema, pneumonia, vascular complications, and heart failure in the catheter ablation group, and life threatening arrhythmias as well as disabling drug intolerance in the AAD group.

Themistoclakis (2010): This multicenter cohort study compared the outcomes of approximately 2,700 patients whose oral anticoagulation therapy (OAT) was stopped 3-6 months after PVI ablation to the outcomes of ~700 patients who continued OAT according to guidelines. Patients were followed for a mean of 2 years; the annual rate of total stroke in the off-OAT group was 0.03 per 100 person-years vs. 0.38 in the on-OAT group (p=.002).

There was no attempt to control for between-group differences; as such, on-OAT patients tended to be older, more likely to have persistent AF, and more likely to have one or more stroke risk factors than their off-OAT counterparts. This study contains the best long-term data on the outcomes of patients who discontinue OAT and shows remarkably low stroke rates. Critics of this study suggest that it provides limited information to guide practice, as 87% of off-OAT patients had $CHADS_2$ scores of 0 or 1 (in which OAT is not recommended or is optional).

Wokhlu (2010): This case series from the Mayo Clinic investigated the long-term impact of catheter ablation on quality of life and symptoms. A total of 502 patients were enrolled; 323 had ≥2 years of follow-up. Patients had significant increases in SF-36 mental and physical component summary scores beginning at 3 months after ablation and remaining constant through 24 months; interestingly, similar improvements in QoL were seen in patients who were AF-free with or without AADs as well as patients with AF recurrence. A different pattern was observed with symptom scores, where improvements in symptoms were significantly greater in AF-free patients not on AADs relative to those on AADs or those with recurrence.

Pappone (2003): In this large Italian multicenter cohort study, nearly 1,200 patients underwent catheter ablation or received AAD therapy and were followed for a median of 2.5 years. Findings with regard to the risk of AF recurrence were similar to other ablation RCTs (HR=0.30; 95% CI=0.24, 0.37). However, ablation appeared to also have a protective effect with regard to all-cause mortality and the incidence of morbid events such as heart failure and stroke (HRs of 0.46 and 0.45 respectively) after controlling for between-group differences. In a separate analysis, maintenance of sinus rhythm by any means (i.e., catheter ablation or AADs) was also associated with rates of all-cause mortality and morbid events that were 65-75% lower for patients in NSR vs. those in AF.

Thorascopic Off-Pump Surgical Ablation

Han (2009): In this case series, a total of 45 patients underwent thorascopic PVI and ligament of Marshall ablation with removal of the left atrial appendage and were followed for a mean of 17 months. The study was notable for its documentation of activity following failed TOP surgical ablation. The primary endpoint was monitor-documented recurrence of any atrial arrhythmia by 12 months; 67% of patients were recurrence-free at this point. Of the 15 patients with recurrence, 8 were recommended to have follow-up catheter ablation. Half of these patients had no recurrence following catheter ablation, while the others required additional drug therapy or had unsuccessful treatment.

Stroke Prevention

Connolly, the RE-LY study (2009): This non-inferiority trial randomized over 18,000 patients (mean age: 72 years) to receive dabigatran at one of two daily doses (110 or 150 mg) or adjusted-dose warfarin. Patients were followed for a median of 2 years. The annual rate of stroke did not differ between 110 mg dabigatran and warfarin; however, the stroke rate was significantly lower for patients on the 150 mg dose (Relative Risk [RR}=0.66; 95% CI=0.53,

0.82). The rate of hemorrhagic stroke was significantly reduced for *both* dabigatran doses relative to warfarin (0.10-0.12% vs. 0.38%, p<.001). The rate of other major bleeding was significantly reduced in the 110 mg group vs. warfarin (2.7% vs. 3.4%, p=.003), while this rate did not differ from warfarin in the high-dose group (3.1% vs. 3.4%, p=.31). Adverse events were similar between the two groups, with the exception of myocardial infarction; rates were 0.72-0.74% per year in the dabigatran groups vs. 0.53% among those receiving warfarin, a difference that neared statistical significance in comparison to the 110 mg dose (p=.07) and reached significance with the 150 mg dose (p=.048).

Holmes (2009): The WATCHMAN RCT was a non-inferiority trial that randomized 707 AF patients (mean age: 72 years, 67% with $CHADS_2$ 1 or 2) in a 2:1 ratio to receive the WATCHMAN and warfarin discontinuation after 45 days, or to continuous adjusted-dose warfarin therapy. Patients were followed for a mean of 1.5 years; the primary endpoint was a composite of stroke, cardiovascular death, and systemic embolism. Implantation was successful in 88% of patients in the WATCHMAN group. Rates of the primary efficacy outcome were 3.0 vs. 4.9 per 100 person-years in the WATCHMAN and warfarin arms respectively (RR=0.62; 95% Credible Interval [CrI]=0.35, 1.25), correlating with a probability of non-inferiority of the WATCHMAN of >99.9%. Some differences were noted in the rate of stroke. The rate of ischemic stroke was higher with the WATCHMAN (2.2 vs. 1.6 per 100 person-years) although this was not significant (RR=1.34; 95% CrI=0.60, 4.29); the difference was driven primarily by strokes occurring during the implantation procedure (one-third of all ischemic strokes in the WATCHMAN arm). In contrast, the rate of hemorrhagic stroke was significantly lower in the WATCHMAN arm (0.1 vs. 1.6 per 100 person-years; RR=0.09; 95% CrI=0.00, 0.45); all of the hemorrhagic strokes in the warfarin arm occurred in patients with therapeutic INR levels. The rate of adverse events was higher with the WATCHMAN (7.4 vs. 4.4 per 100 person-years; RR=1.69; 95% CrI=1.01, 3.19), primarily as a result of pericardial effusion requiring pericardiocentesis or surgery.

Clinical Benefits

1. AADs vs. Catheter Ablation vs. Minimally Invasive Surgical Ablation

Mortality

Given the short-term time frames for nearly all studies, data on the impact of different management options for AF rhythm control on cardiovascular mortality or overall mortality are extremely limited. While the large Pappone cohort study suggests significantly lower mortality rates for catheter ablation vs. AADs over a median time span of 2.5 years, this study is vulnerable to significant selection bias and no such difference in mortality has been observed in RCTs. The small body of evidence on TOP surgical ablation includes too few deaths to be useful in judging potential differences in short or long-term mortality compared to AADs or catheter ablation.

A total of 4 clinical trials of catheter ablation vs. AADs have reported rates of all-cause mortality over 9-12 months follow-up. In all, only 7 deaths were reported among 562 patients (3 vs. 4 for catheter ablation and AADs, respectively). Mortality is similarly infrequently reported in the TOP surgical ablation literature. A single death during follow-up was reported in the 12 available surgical studies over a mean of 13 months of observation.

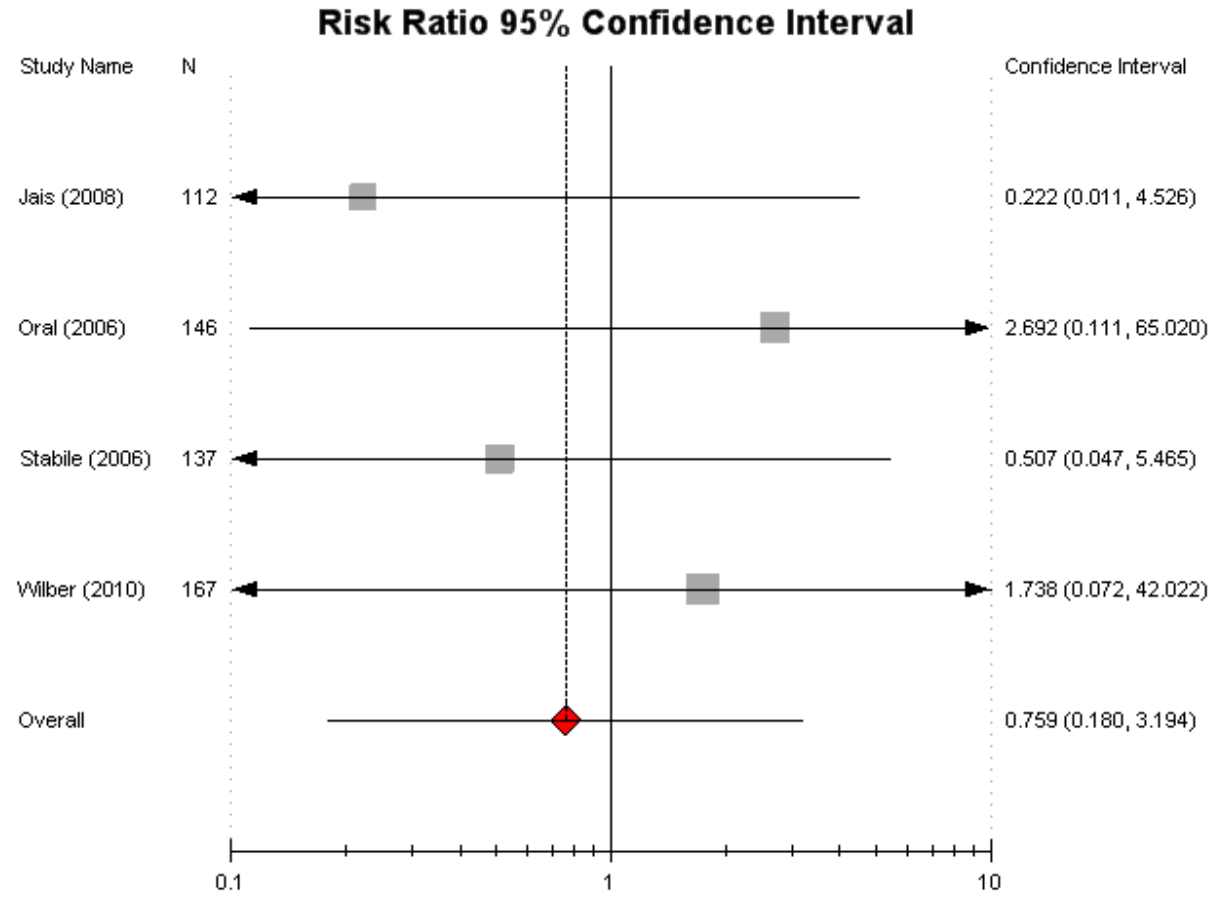
As described previously, the Pappone cohort study's findings suggested significantly lower mortality rates for catheter ablation relative to AADs. While the findings are intriguing, and the analyses controlled for observed differences between groups, the possibility of residual selection biases and unobserved group differences (including differences in monitoring and follow-up) cannot be ruled out. Mortality rates in catheter ablation case series and cohorts ranged from 0-2.5% on an annualized basis (see Appendix B, Table B2).

No data were identified with which to evaluate the impact of either catheter ablation or TOP surgical ablation in key clinical or demographic subpopulations, with the exception of a single catheter ablation cohort study comparing outcomes for 717 patients aged <80 years vs. 35 patients aged ≥80 years (Bunch, 2009). At 12 months, a total of 5 deaths had occurred, all in the younger cohort. Comparisons were limited however, by the small size of the older cohort and the potential for referral bias in those individuals (i.e., referral for ablation only in healthier elderly).

No comparison with the findings of the AHRQ review on ablation was feasible, as mortality was not a measure of interest in that review.

Findings from random-effects meta-analysis of eligible RCTs indicated no significant mortality effect for catheter ablation, as shown in Figure 2 on the following page and in Appendix C, Figure C1 (RR=0.76; 95% CI=0.18, 3.19, p=.66); heterogeneity analyses suggested that this was a homogeneous effect (tau-squared = 0.00). No meta-analysis of surgical data was performed, as no relevant comparative data were available for TOP surgical ablation.

Figure 2. Meta-analysis of all-cause mortality for catheter ablation vs. AADs.



Stroke Rates

Data with which to compare the impact of AADs, catheter ablation, and TOP surgical ablation on the rate of stroke are extremely limited by the short follow-up times available. Data on long-term stroke rates with catheter ablation were available only from cohort studies and case series; annual rates ranged from 0-5%. As with mortality, stroke was infrequently reported in surgical series, and only as a peri-operative event.

Available evidence for long-term stroke rates was even more scant than that for mortality. Data were available on long-term stroke only from cohort studies and case series of catheter ablation. In the largest of these studies, a total of 3,265 patients were followed for a mean of 3 years post-ablation; the annual rate of stroke was 0.3% (Patel, 2010). Rates in the other studies ranged from 0-5% annually (Appendix B, Table B3). The highest rate observed came from a series of 56 patients undergoing PVI who were followed for an average of 13 months (Mangrum, 2002); 3 patients had strokes within the first year (4.9% annualized), all of whom were elderly, and 2 of whom had a prior stroke or TIA. None of the surgical series provided data on strokes observed during follow-up; reported strokes were limited to those that occurred operatively or within 30 days following the procedure.

Rates of stroke were reported by key subgroup in 2 catheter ablation cohort studies. In the Bunch study described above, a total of 4 strokes had occurred at one year, all in the younger cohort (Bunch, 2009). Additionally, findings from a cohort study comparing outcomes of PVI ablation among 2,747 men and 518 women over a mean of 24 months of follow-up (Patel, 2010) showed no difference in the rate of stroke (0.8% vs. 0.6% for women and men respectively, p=.76), although no clear distinction is made between peri-operative strokes and those occurring during follow-up.

Due to the lack of comparative data for catheter ablation/AADs and TOP surgical ablation, we did not perform a meta-analysis of long-term rates of stroke. A meta-analysis of stroke rates from 6 catheter ablation RCTs was performed in the AHRQ review, as this review did not make a distinction between strokes occurring during the peri-operative period and those occurring later in follow-up (Ip, 2009). Findings suggested no significant difference in the rate of stroke between catheter ablation and AADs (Risk Difference [RD] = 0.6%; 95% CI = -1.2%, 2.3%); all strokes in the catheter ablation arms occurred intra- or peri-operatively.

Freedom from AF Recurrence

As previously described, measurement of freedom from AF recurrence in catheter ablation RCTs is highly variable, with different interpretations of the outcome and different methods of measurement. In RCTs that focused on freedom from any AF recurrence up to 12 months as measured by long-term monitoring, patients undergoing catheter ablation were nearly 3 times as likely to be free from AF (range: 56-87%) relative to those receiving AADs (range: 9-58%); the advantage for ablation was more pronounced among patients with paroxysmal AF. While comparative data were unavailable for TOP surgical ablation, freedom from AF at 6-12 months was comparable to that seen for catheter ablation (range: 62-88%). Findings from our meta-analysis suggest a 3-fold greater likelihood of freedom from AF at 9-12 months for catheter ablation relative to AADs.

We sought information on multiple measures of AF burden from available RCTs, including freedom from AF, frequency of recurrence, and time in AF (also characterized as AF burden in some studies). Freedom from AF and/or maintenance of normal sinus rhythm at 6-12 months was the most commonly reported outcome, although there was much variability in how this measure was defined across studies. In some studies, the measure was interpreted as freedom from any AF recurrence during the intervening timeframe; in others, the measure simply represented the proportion free from AF at the timepoint of interest, regardless of prior recurrence. Measurement of AF also differed; in some studies, AF was recorded based on long-term measurement using Holter monitors, event recorders, or transtelephonic EKG. In others, point-in-time EKG testing was performed, and still other studies relied on patient measurement of symptoms alone. Finally, some studies defined patients who required AADs post-ablation as treatment successes if patients were in normal sinus rhythm, while others required that patients be off AADs for ablation to be considered successful.

These different methods likely contribute to the substantial variation in the reported rates of freedom from AF in the catheter ablation and TOP surgical ablation literature. Among patients undergoing catheter ablation, rates ranged from 56-87% at 6-12 months of follow-

up ; the corresponding range among those receiving AADs was 9-58% (Appendix B, Table B4). Rates in case series and cohort studies of catheter ablation were even more variable, ranging from 21-98%. Reported rates in TOP surgical ablation series and cohort studies were similar to those for catheter ablation RCTs, ranging from 62-88% at 6-17 months of follow-up. As with the RCTs, rates were influenced by the distribution of type of AF, patient demographic and other characteristics, and the measurement method used to detect AF. As a point of comparison, findings from a previous systematic review comparing "cut and sew" Maze procedures to ablation using radiofrequency, microwave, or cryothermal energy indicated mean rates of freedom from AF of 84.9% and 78.3% for the 2 groups respectively (Khargi, 2007).

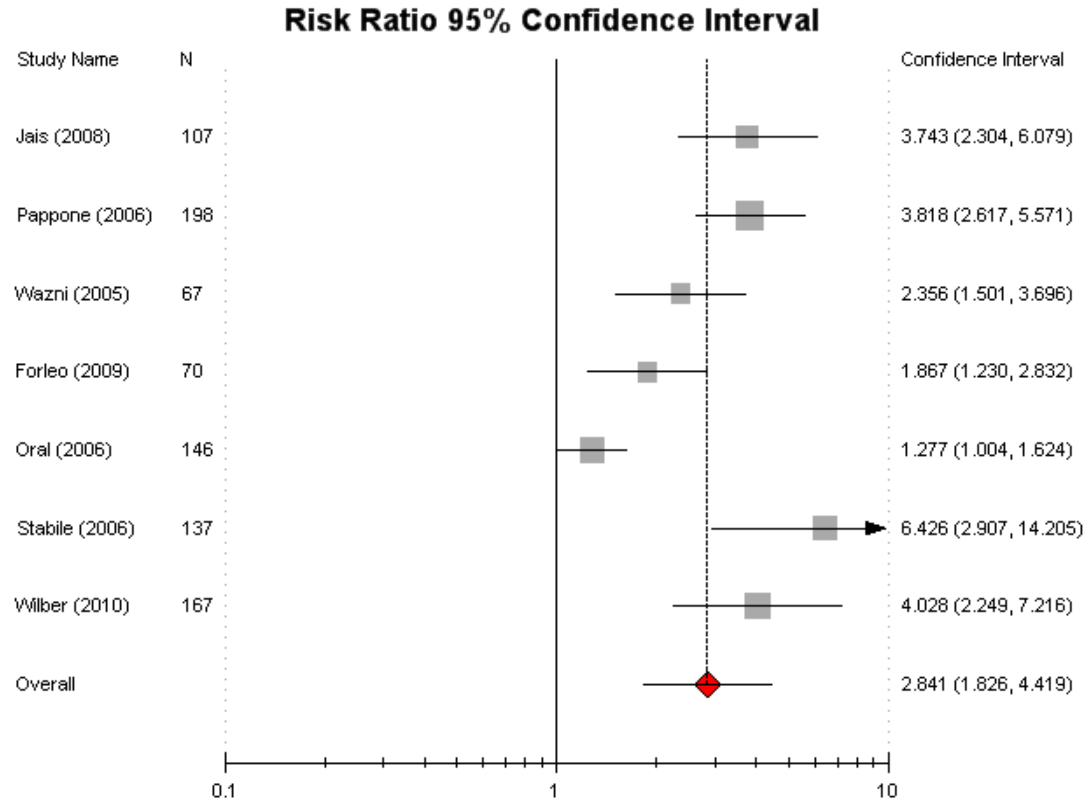
One of the RCTs included in the meta-analysis reported the results of first-line use of catheter ablation (Wazni, 2005). Patients (96% paroxysmal AF, mean age 54 years, mean duration of symptoms 4 months) received either PVI ablation or AAD therapy and were followed for 1 year. Rates of freedom from AF at 1 year were 87% for catheter ablation vs. 37% for AADs ($p<.001$).

Freedom from AF was also assessed for important subgroups in 2 catheter ablation cohort studies. In the age-stratified cohort study described previously (Bunch, 2009), freedom from AF at one year was found not to differ by age category (78% vs. 75% for age <80 vs. ≥80 years, $p=.78$). Within these age groups, freedom from AF was also assessed separately for paroxysmal and persistent AF; again, findings did not differ significantly for either AF type ($p=.44$ for paroxysmal and $p=.74$ for persistent AF, respectively).

Rates of freedom from AF have been shown to differ, however, by sex. In a case series study that evaluated outcomes in 3,265 patients undergoing catheter ablation (Patel, 2010), Kaplan-Meier estimates for freedom from AF at 24 months were significantly lower for women compared to men (68.5% vs. 77.5%, $p<.001$). Factors associated with failed ablation in females included higher BMI, non-paroxysmal AF, and triggers for AF not located in the pulmonary vein.

Findings from a random-effects meta-analysis of the impact of catheter ablation vs. AADs on freedom from AF can be found in Figure 3 on the following page as well as in Appendix C, Figure C2. A total of 7 RCTs reported data on freedom from any AF recurrence at 9-12 months using long-term measurement tools. Those receiving catheter ablation were nearly 3 times as likely to be free from AF as those in the AAD arms (pooled RR: 2.84; 95% CI: 1.83, 4.42); moderate statistical heterogeneity was observed (tau-squared=0.29). This estimate is somewhat lower than that produced in the AHRQ review (pooled RR: 3.46; 95% CI: 1.97, 6.09), which may have been a function of the limitation of studies in our meta-analysis to those measuring recurrence using long-term monitoring methods as well as the introduction of additional studies to the analysis (7 vs. 3 in the AHRQ review).

Figure 3. Meta-analysis of short-term freedom from AF for catheter ablation vs. AADs.



Mixed effects meta-regression was then performed to explore possible factors that could explain observed heterogeneity, including the percentage of paroxysmal AF, mean or median patient age, and the percentage of males. Regression plots and model specifications can be found in Appendix F. Only the percentage of paroxysmal patients was significantly associated with the freedom from AF outcome ($p<.0001$); the decision was therefore made to examine findings stratified by studies of primarily paroxysmal patients vs. those with mixed AF types. When stratified by type of AF, catheter ablation was more effective in populations that were ≥65% paroxysmal (RR: 3.38; 95% CI: 2.65, 4.32), compared to those that were comprised of a more even mix of paroxysmal, persistent, and long-standing persistent AF (RR: 2.24; 95% CI: 1.11, 4.53) (see Appendix C, Figures C3 and C4).

The potential for publication bias to affect these findings was also explored using multiple tests and analyses (Appendix E). While the rank correlation tau-b test did not find a significant correlation between effect size and variance across studies ($p=0.37$), Egger's regression test for asymmetry of the funnel plot was significant ($p=.02$). Accordingly, the automatic trim-and-fill method was used to impute study findings that would result in a symmetrical funnel plot. While the effects of catheter ablation were mitigated somewhat, this procedure remained more than twice as likely to result in freedom of AF as AAD therapy (RR: 2.37; 95% CI=1.60, 3.51). In addition, findings from the fail-safe N test suggested that a relatively large number of studies with "null" findings (N=231) would need to exist to change this primary conclusion.

Finally, while not yet published in a peer-review journal, findings from the pilot phase of the long-term CABANA trial were presented at the 2010 Scientific Sessions of the American College of Cardiology (CardioSource News, 2010b). The trial is notable for its size (n=3000), broad inclusion criteria (e.g., both paroxysmal and persistent AF, multiple risk factors for stroke), and its focus on "hard" endpoints such as total mortality and disabling stroke. Data from the 60-patient pilot phase were short-term, however, and focused on symptomatic AF recurrence only. At 12 months, a higher percentage of patients were free from AF in the catheter ablation arm (65% vs. 41% for AADs). The rate of recurrence of AF after 12 months was high in both groups, however (55% vs. 69% for AADs). Findings from the full study are expected in 2015.

Need for Subsequent Procedures Following Catheter Ablation and TOP Surgical Ablation
Requirements for repeat catheter ablation ranged widely in catheter ablation RCTs and series; between 10-70% of patients required one or more repeat ablations. Studies varied in terms of the level of detail provided on the timing and distribution of repeat procedures. Recent data obtained by ICER from a national private health plan showed repeat ablation episodes within 12-18 months for 18% of patients undergoing a first ablation: 15% of all patients had 2 ablations, 2% had 3 ablations, and 1% had 4 separate ablation episodes. While data on TOP surgical ablation are limited, data from case series suggest that approximately one-fifth of patients require retreatment with catheter ablation, cardioversion, or other treatment following surgery.

Data on repeat ablation are presented in Appendix B, Table B8. A total of 13 catheter ablation studies (3 RCTs, 10 case series) provided information on the frequency and number of ablation procedures. In general, the proportion of patients requiring repeat procedures or the total number of procedures performed was reported; very little information was provided on the distribution and/or timing of repeat ablation. The proportion of patients requiring repeat procedures varied substantially in these studies; on average, approximately 30% of patients required a repeat procedure (range: 10-70%). The total number of procedures performed per patient also ranged widely (1.2-2.9), with patients on average requiring 1.5 ablation procedures.

Recent data obtained from a large national private health plan suggest a somewhat lower rate of repeat ablation. Over a follow-up period ranging from 1-3 years, 82% of patients had a claim for a single instance of ablation; corresponding rates for 2, 3, and 4 instances were 15%, 2%, and 1% respectively (data on file, ICER, 2010). Most patients with a second ablation had this procedure performed within 12-18 months of the initial procedure.

Requirements for subsequent procedures following TOP surgical ablation are reported in 2 case series. A series of 45 patients undergoing thorascopic PVI, ligament of Marshall ablation, and removal of the left atrial appendage (Han, 2009) showed a rate of AF recurrence of 33% (n=15). Of the 15 patients with recurrence, 8 received catheter ablation with or without additional AAD therapy; 50% of these patients had further recurrence or moved into persistent AF. Findings from a series of 32 patients undergoing thorascopic PVI and extended lesion sets (Sirak, 2008) indicated that 5 patients (15.6%) required cardioversion 3 months following surgery.

Data are not available with which to judge the impact of catheter ablation or TOP surgical ablation on requirements for subsequent procedures across key patient subgroups. Meta-analysis on these measures was not conducted, as data by definition were not comparative (i.e., no similar measure was evaluated for AAD patients). The rate of repeat ablation was not specifically addressed as an outcome in the AHRQ review (Ip, 2009).

Hospitalization

Evidence from a limited number of RCTs suggests that catheter ablation is associated with 75-85% lower rates of all-cause and cardiovascular hospitalization in comparison to AADs; however, these comparisons are confounded to some extent by treatment goals (e.g., cardioversion or therapy change in the AAD group). Hospitalization was not measured in TOP surgical ablation case series.

Readmission to hospital was assessed in 3 RCTs of catheter ablation and AADs (Appendix B, Table B5). In 2 of these studies, the percentage of patients hospitalized during follow-up differed significantly during follow-up in favor of catheter ablation (8-9% vs. 34-54%, $p \leq .01$ in both studies). In the other RCT, the total number of hospitalizations only was measured; this also differed significantly in favor of catheter ablation (24 vs. 167, $p < .001$). Hospitalization rates among patients in catheter ablation cohort studies and case series were 2-4% annually. Neither rates of rehospitalization nor total hospital admissions were measured in TOP surgical ablation series or cohort studies.

Even in RCTs, comparisons of hospitalization rates between catheter ablation and AADs can be misleading due to differences in clinical practice and treatment goals. For example, in a trial of first-line catheter ablation vs. AAD treatment (Wazni, 2005), hospitalizations were three times more frequent among AAD patients than among those receiving ablation in the 2 months following randomization; however, clinical protocol during this period appeared to involve rehospitalization for cardioversion and medication adjustment for AAD patients experiencing AF recurrence, but no rehospitalization for ablation recipients whose AF had recurred. While hospitalizations also were less frequent for catheter ablation during follow-up (9% vs. 54%, $p < .001$), the reasons for these hospitalizations are not given.

The effects of catheter ablation or TOP surgical ablation on hospitalization rates were not evaluated according to any of the key patient subgroups for our analysis. Meta-analyses on hospitalization were not conducted, as the minimum number of fair-to-good quality studies evaluating this measure using a uniform method was not reached. Conclusions from the AHRQ review were similar to those above, citing a low level of evidence and confounding by health-system practices, severity of symptoms, and other concerns (Ip, 2009).

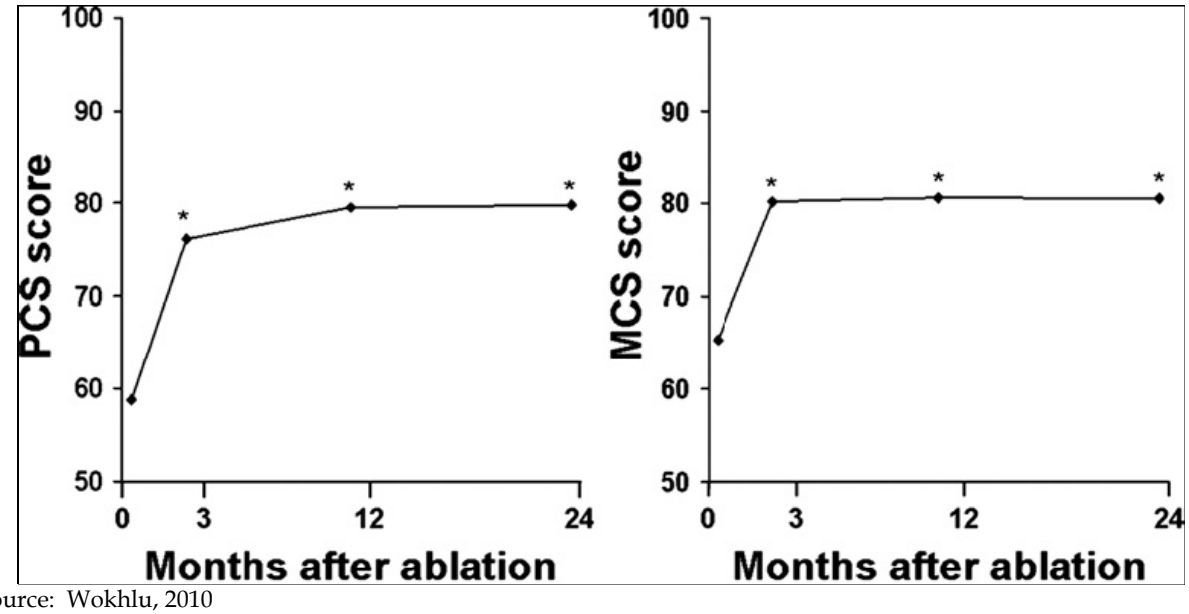
Quality of Life

Data from a limited number of RCTs and comparative cohort studies suggest significant improvement in general quality-of-life scores and symptom scales for catheter ablation relative to AADs; findings from a long-term case series also suggest that post-ablation QoL improvement persists independent of the level of ablation success. Findings from a single surgical series suggest a positive impact of TOP surgical ablation on quality of life.

Data on quality of life and symptom frequency were captured in 3 RCTs and one comparative cohort study involving catheter ablation and AADs (Appendix B, Table B6). Quality of life has not been measured in any study of minimally-invasive surgical ablation. The available studies differed in terms of instrument, domains measured, and/or measurement timepoints, making comparisons across studies problematic. Generally, however, improvements in quality of life as well as symptom frequency and severity were generally significantly greater among patients receiving catheter ablation relative to AADs. For example, improvements in the physical and mental summary scores of the SF-36 were generally observed in both catheter ablation and AAD treatment arms; however, net improvements for catheter ablation vs. AADs ranged from 3-20 points at 3 months and from 3-7 points at 12 months. Symptoms were assessed primarily using the AF Symptom Frequency and Severity Checklist (Bubien, 1996); improvements of 7-10 and 4-9 points for frequency and severity were reported relative to AADs.

Recent findings from a series of 323 patients followed for 2 years post-catheter ablation, >90% of whom had previously failed AAD therapy, suggests some durability in QoL improvement (Wokhlu, 2010). As shown in Figure 4 below, significant improvements over baseline were seen in both SF-36 mental and physical summary scores as early as 3 months after catheter ablation, and remained generally constant through 2 years.

Figure 4. Changes in quality of life among 323 patients undergoing catheter ablation.



Source: Wokhlu, 2010
PCS: Physical component summary score, SF-36; MCS: Mental component summary score, SF-36

Interestingly, the improvements in quality of life in this study did not differ significantly by ablation outcome. Significant improvements were noted among patients in normal sinus rhythm who had discontinued AADs, those in NSR controlled on AADs, and patients with recurrent AF.

The impact of TOP surgical ablation on quality of life was measured in a single series of 43 patients at Uppsala University Hospital in Sweden (Bagge, 2009). At 12 months of follow-up, quality of life was significantly improved over baseline on all SF-36 subscales except for bodily pain. In addition, 12-month QoL scores were not found to significantly differ from those of the general Swedish population for bodily pain, social functioning, role limitation due to emotional problems, and mental health. Overall symptom severity also improved significantly at 12 months, by a mean (SD) of 10.7 (4.8) points, driven primarily by improvements in fatigue, lack of energy, and dyspnea. In contrast, findings from a meta-analysis of randomized and nonrandomized studies of surgical ablation performed as an adjunct to other cardiovascular procedures suggest no impact of surgical ablation on quality of life relative to nonablation controls at 3-12 months (Ad, 2010).

The relative impact on quality of life of catheter ablation vs. AADs has not been evaluated across age, sex, or other key subpopulations of interest except by type of AF. In one study, the Wokhlu series described above, the type of AF (paroxysmal vs. non-paroxysmal) was not found to significantly affect total SF-36 score (mean improvement 13.4 vs. 15.5 points, p=.31).

We did not conduct meta-analyses on quality of life or symptoms due to the lack of uniform measures and timepoints in fair-to-good quality studies.

The conclusions of the AHRQ review with respect to the impact of catheter ablation on the quality of life were similar to ours, although similar cautionary language was used regarding nonuniformity in instruments, domains, and measurement timepoints.

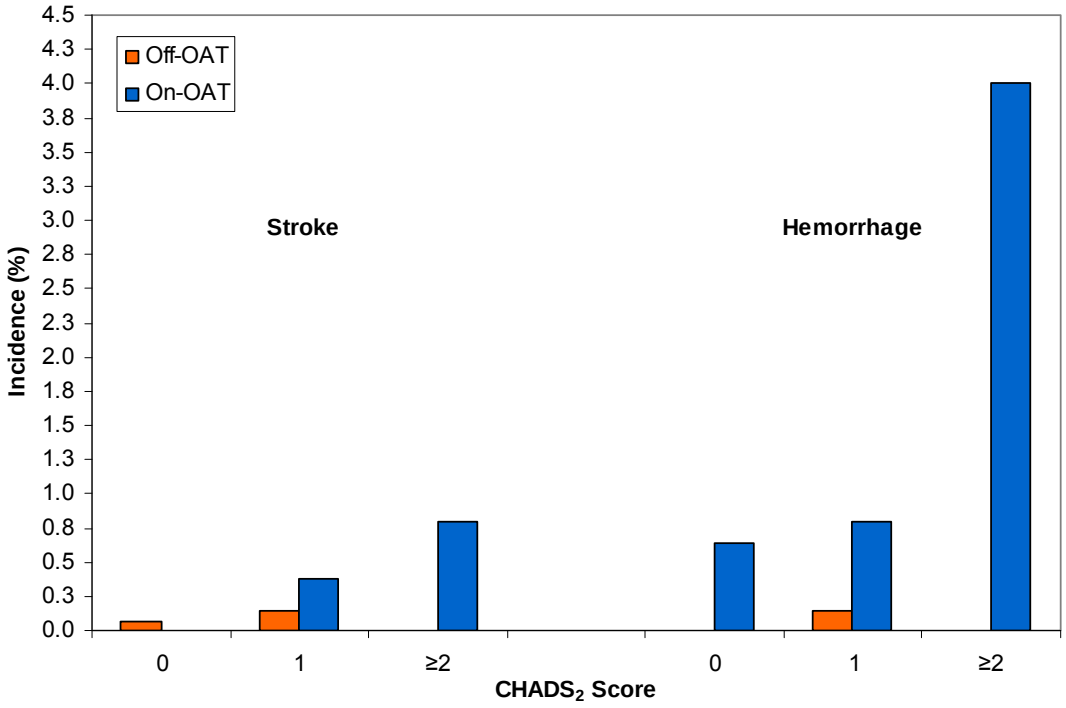
Cessation of Anticoagulation Following Ablation

Only one catheter ablation RCT reports on observed rates of cessation of anticoagulation following restoration of normal sinus rhythm (60% vs. 34% for AADs). The impact of this change on stroke rates was not evaluated, however. Data from several case series and cohort studies suggest no detrimental impact of warfarin discontinuation among patients in NSR after catheter ablation, but these studies are limited by restriction to low-risk populations as well as their observational nature. Data from surgical case series suggest an inconsistent approach to anticoagulation following surgery.

There have been no RCTs in which the safety of cessation of anticoagulation following ablation has been explicitly tested, and only extremely limited data exist on the relative rates of patients who have selected to discontinue anticoagulation after returning to NSR in either ablation or AAD cohorts (Appendix B, Table B7). One RCT of catheter ablation reported significantly more patients in the ablation arm discontinued oral anticoagulation (59.6% vs. 34.0% for AADs, p=.01); no detail is provided, however, on the reasons for discontinuation or the impact of this therapeutic change on rates of stroke (Jaïs, 2008). In addition, while significance testing was not performed on patient characteristics, patients in the AAD arm appeared to be older and more likely to have diabetes, hypertension, and a history of embolic events, which may have affected decisions to discontinue anticoagulation therapy.

Additional data are available from purely observational studies. The largest of these involved a comparison of stroke rates for nearly 2,700 patients who discontinued warfarin 3-6 months following catheter ablation vs. ~700 patients who remained on guideline-directed anticoagulation (Themistoclakis, 2010); patients were followed for approximately 2 years. Findings indicated a very low rate of stroke in both groups, which did not differ significantly (0.07% vs. 0.45% for off- vs. on-anticoagulation, p=.06). Results are difficult to interpret, as over 80% of the study population was at extremely low risk of stroke ($CHADS_2$ scores of 0 or 1), for which anticoagulation is not indicated or is optional. Findings for stroke and major hemorrhage are reported by $CHADS_2$ score in Figure 5 below.

Figure 5. Incidence of stroke and major bleeding, by $CHADS_2$ score, among patients on- vs. off-anticoagulation following catheter ablation.



Source: Themistoclakis, 2010
OAT: Oral anticoagulation therapy

Catheter ablation case series data are notable for high rates of cessation of anticoagulation and low or minimal rates of stroke in these patients; however, it is worth noting that initial discontinuation of warfarin often does not persist. For example, findings from one study suggest a 91% rate of discontinuation of warfarin 3 months following PVI (Rossillo, 2008); however, one-third of these patients had a subsequent AF recurrence and were restarted on warfarin.

Given that minimally-invasive surgical ablation involves exclusion or excision of the left atrial appendage, it would seem that warfarin discontinuation might be common with these approaches. However, protocols for discontinuation appear to be very inconsistent. One protocol involves discontinuation of warfarin 3 months post-operatively in all patients with

normal sinus rhythm (Melby, 2006a), while others describe discontinuation only in patients at very low stroke risk (Han, 2009) or at the discretion of the referring cardiologist (Yilmaz, 2010). As a result, rates of discontinuation in the surgical literature vary widely, ranging from 47-91% in the studies that report such rates.
Data were not available to evaluate the impact of cessation of anticoagulation in key subgroups of patients. Meta-analyses of the impact of treatment on cessation of anticoagulation were not conducted due to a lack of comparative data on the measure. Conclusions on avoiding anticoagulation were similar in the AHRQ review, citing the same RCT and describing a low level of evidence regarding the possibility of stopping anticoagulation after catheter ablation (Ip, 2009).

2. Amiodarone vs. Dronedarone

Mortality
Limited head-to-head data exist with which to judge the differential impact on all-cause mortality of amiodarone vs. dronedarone. In the single head-to-head RCT that has been conducted (DIONYSOS), all-cause mortality was 3.4% for amiodarone vs. 1.4% for dronedarone on an annualized basis, a difference that was not statistically significant. Dronedarone was found to have a significantly lower rate of cardiovascular death vs. placebo in the ATHENA trial (1.5% vs. 2.2% on an annualized basis), but has also been associated with increased mortality in patients with severe heart failure, leading to its non-approval for use in CHF and a warning on its label. In indirect meta-analyses comparing multiple amiodarone and dronedarone trials, the relative risk of all-cause mortality was 1.80 for amiodarone vs. dronedarone, but the difference was not statistically significant.

Limited direct evidence exists on the impact of amiodarone vs. dronedarone on mortality (Appendix B, Table B2). In the head-to-head DIONYSOS trial (Le Heuzey, 2010), a total of 2 and 5 deaths were observed in the dronedarone and amiodarone arms respectively during the on-treatment period (annualized rates: 1.4% vs. 3.4% respectively), but the difference was not statistically significant (RR=2.44; 95% CI=0.48, 12.60). Adverse events associated with these deaths included pulmonary embolism, sepsis, probable MI, and sudden or unwitnessed death.

Information on mortality by cause was also available in the ATHENA placebo-controlled trial of dronedarone (Hohnloser, 2009); as mentioned previously, the ATHENA trial excluded patients with NYHA Class IV or recently decompensated CHF, in response to concerns raised by the ANDROMEDA trial (see below). In this study, the annual rate of all-cause mortality did not differ significantly (2.9% vs. 3.4% for dronedarone and placebo respectively, p=.18). A significant difference was noted, however, in the rate of death from cardiovascular causes (1.5% vs. 2.2% respectively; p=.03). A significant difference was also observed in the rate of death due to cardiac arrhythmias (0.6% vs. 1.2%; p=.01).

As described previously, a finding of increased mortality vs. placebo led to the premature discontinuation of the ANDROMEDA trial of dronedarone among patients with CHF

(Kober, 2008); approximately 20% of study subjects also had AF. Over a median follow-up of 2 months, a total of 25 dronedarone patients died (8.1%) vs. 12 in the placebo group (3.8%), a significant difference (HR=2.13; 95% CI=1.07, 4.25; p=.03); excess mortality was primarily due to worsening heart failure. As a result of these findings, the FDA issued a non-approval for dronedarone for this indication, and a warning on its eventual label that it should not be used in severe CHF or moderate CHF with decompensation or requiring hospitalization (Sanofi-Aventis, 2009).

Despite amiodarone's well-recognized toxicities, RCTs of amiodarone have largely not found any significant differences in mortality between this agent and control, regardless of whether the comparison is to other AADs, rate control, or placebo. A significant reduction in all-cause mortality was observed for amiodarone in the AFFIRM substudy that focused on amiodarone (AFFIRM Investigators, 2003); over a mean of 46 months of follow-up, the annual mortality rate was 2.5% for amiodarone vs. 5.8% for class IC agents (p=.008). Mortality did not differ between amiodarone and sotalol (3.0% vs. 5.0%, p=.081).

The only study documenting a significant increase in mortality with amiodarone was a retrospective cohort study documenting short- and long-term mortality in patients with AF who had experienced MI and survived to hospital discharge (Kilborn, 2002); patients prescribed amiodarone were compared to those not prescribed any AAD. No difference in 30-day mortality was observed; at 12 months, mortality was significantly higher in the amiodarone group (35.6% vs. 31.6% for amiodarone vs. control, p=.001). However, in multivariable analyses controlling for clinical and demographic differences between groups, this difference became nonsignificant (Odds Ratio [OR]=1.04; 95% CI=0.92, 1.18).

Because mortality was not a pre-specified primary endpoint in the amiodarone or dronedarone trials, there are no data with which to examine the differential impact of these agents in key patient subgroups.

We conducted an indirect treatment comparison of all-cause mortality for amiodarone and dronedarone that focused on placebo-controlled studies only and excluded the DIONYSOS trial (n=8). Results are displayed in Figures 6a and 6b on the following page (see also Appendix C, Figures C5 and C6). Findings were not significant in either case; directionally, however, results suggested increased risk for amiodarone and decreased risk for dronedarone. Results from the indirect treatment comparison suggested a relative risk for all-cause mortality of 1.80 for amiodarone vs. dronedarone, a lower figure than in the DIONYSOS study, but directionally similar; however, findings were not statistically significant (95% CI=0.68, 4.78). Note that, while mixed treatment comparisons were considered, differences in the duration of follow-up, numbers of studies with no fatalities, numbers of patients studied, and patient characteristics between the dronedarone and amiodarone cohorts were deemed to be too great to produce reliable findings.

Figure 6a. Pooled estimate of impact of amiodarone on all-cause mortality.

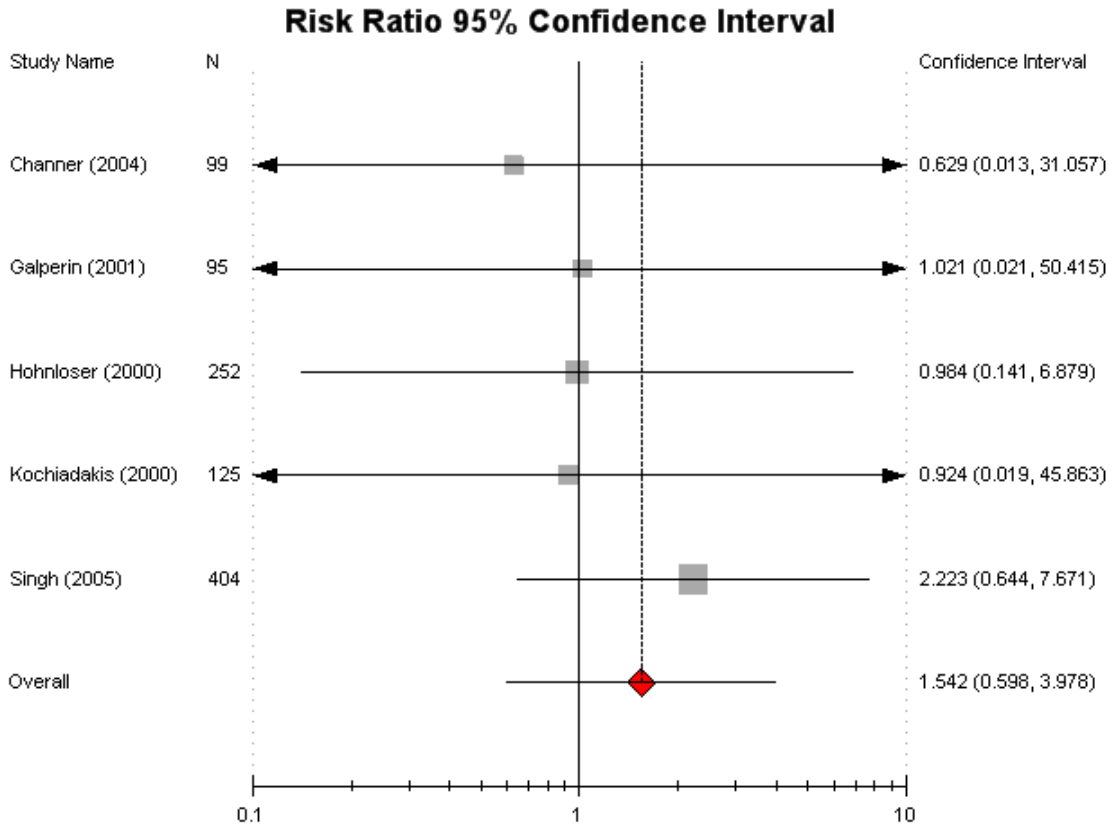
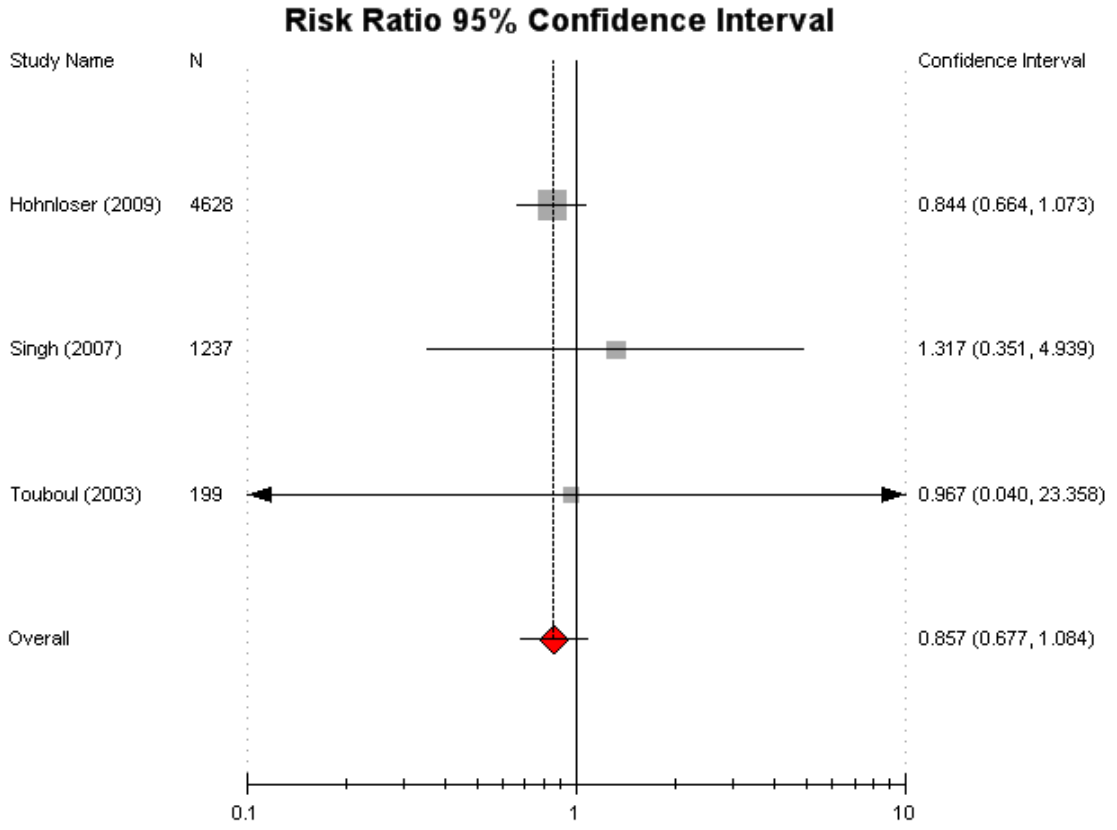


Figure 6b. Pooled estimate of impact of dronedarone on all-cause mortality.



Stroke Rates

There are no data directly comparing stroke rates between amiodarone and dronedarone, and available studies provide limited data suggesting no benefit of either drug vs. placebo. Data from an amiodarone RCT showed annual rates of minor and major stroke of approximately 1% annually, which did not differ from placebo. Stroke was also infrequently reported in dronedarone trials; differences relative to placebo were observed in a post hoc analysis of the ATHENA trial, which showed a two-thirds reduction in the annual rate of stroke (1.2% vs. 1.8% for placebo).

Data on stroke rates among patients on amiodarone or dronedarone are reported in Appendix B, Table B3. Information on stroke rates was not reported in the head-to-head DIONYSOS trial (Le Heuzey, 2010). An RCT examining the impact of amiodarone, sotalol, or placebo on restoration of sinus rhythm (the SAFE-T study) randomized a total of 665 patients and followed them for a mean of 13 months (Singh, 2005). Neither the rates of minor stroke (1.19, 0.68, and 0.96 per 100 patient-years for amiodarone, sotalol, and placebo, p=.67) nor major stroke (0.87, 2.03, and 0.95 per 100 patient-years respectively, p=.36) differed significantly among these groups. In the only other amiodarone RCT reporting stroke rates (the GEFACA study), no strokes were observed in either the amiodarone or placebo arms over a mean of 16 months of follow-up (Galperin, 2001).

Information on stroke rates was reported in 2 dronedarone trials. In the ATHENA trial, rates of total, hemorrhagic, and ischemic stroke were evaluated in a post hoc analysis of hospitalization and other clinical records as well as adverse event reports (Connolly, 2009a). The annual rate of stroke-related hospitalization did not differ between groups (1.0% vs. 1.4% for dronedarone vs. placebo, p=.082); nonsignificant differences also were noted in the rate of ischemic stroke (0.9% vs. 1.3%, p=.081) and hemorrhagic stroke (0.2% in both arms, p=.987). However, when total stroke in all settings was evaluated, the annual rate was significantly lower among patients on dronedarone (1.2% vs. 1.8% for placebo, p=.027). Stroke rates also were reported in the combined findings of the EURIDIS/ADONIS trials (Singh, 2007) . At one year of follow-up, a total of 4 strokes were observed in the dronedarone arm (0.5%) as compared to 3 in those randomized to placebo (0.7%), a difference that was not statistically significant (p=.69).

As with mortality, stroke was not a pre-specified primary endpoint in any of these trials, and so there are no data to differentiate the effects of these agents in key patient subgroups. No meta-analysis on stroke was performed, as there was not sufficient study volume for either agent to do so.

Freedom from AF Recurrence

Moderate evidence exists with which to compare rates of freedom from AF at 6-12 months, as this was measured in 14 amiodarone and dronedarone trials, including the head-to-head DIONYSOS trial, with rates ranging from 31-59% for amiodarone and 23-37% for dronedarone. Findings from the DIONYSOS trial showed a significantly lower rate of AF recurrence with amiodarone vs. dronedarone (42.0% vs. 63.5%). Results from a mixed

treatment meta-analysis suggest that dronedarone is significantly less likely to maintain normal sinus rhythm at 12 months than amiodarone.

Freedom from AF was measured in 9 and 4 amiodarone and dronedarone trials respectively, as well as in the head-to-head DIONYSOS trial (Appendix B, Table B4). Rates of this measure at 6-12 months of follow-up ranged between 31-59% and 23-37% for amiodarone and dronedarone respectively. In the DIONYSOS trial (Le Heuzey, 2010), which focused on the incidence of AF recurrence, which was estimated to be 63.5% and 42.0% for dronedarone and amiodarone, resulting in a greater than 50% relative reduction in the estimated likelihood of recurrence at 12 months (OR=0.44; 95% CI=0.30, 0.64).

Data from the combined report of the EURIDIS/ADONIS trials of dronedarone are available to examine dronedarone's impact on AF recurrence across patient subgroups. In particular, freedom from AF was evaluated in patients who met criteria for moderate-to-severe heart failure (Singh, 2007). Dronedarone was associated with a significantly lower rate of AF recurrence in patients with and without heart failure, but its protective effects appeared to be greater in those with this comorbidity (HR=0.59; 95% CI=0.42, 0.83) vs. those without (HR=0.81; 95% CI=0.69, 0.95). However, the difference between these two subgroups was not statistically significant (p=.10 for interaction).

We conducted a mixed treatment comparison that combined data from 11 amiodarone and dronedarone trials, including the DIONYSOS study as well as trials comparing these agents to sotalol as well as placebo or other control agents (e.g., class IC AADs, rate control agents). Findings are displayed in matrix format in Table 3 below as well as in Appendix C in Table C1). The results showed a significantly lower likelihood of freedom from AF at 6-12 months for dronedarone relative to amiodarone (OR=0.31; 95% CI=0.12, 0.68); similar findings were observed in a recent meta-analysis comparing freedom from AF for these two agents (OR=0.16; 95% CI=0.06, 0.42) (Piccini, 2009).

Table 3. Results of mixed treatment comparison of likelihood of freedom from AF at 6-12 months, by agent and comparison.

	Amiodarone	Sotalol	Dronedarone
	Odds Ratio (95% CI)		
Control	5.68 (3.23, 9.66)	2.16 (0.96, 4.20)	1.67 (0.68, 3.66)
Amiodarone		0.39 (0.18, 0.74)	0.31 (0.12, 0.68)
Sotalol			0.88 (0.27, 2.27)

Note: Results are presented as agent in column vs. agent in row
"Control"=class 1c agent, rate control agent, or placebo
CI: Confidence interval

<u>Hospitalization</u>
There are no data directly comparing hospitalization rates between patients on amiodarone and patients on dronedarone. A single RCT in our sample found higher

annualized hospitalization rates among patients on amiodarone than those managed on a rate-control strategy (69% vs. 24%, p=.001). For dronedarone, hospitalization was assessed as a primary outcome in the ATHENA trial of dronedarone as well as in post hoc evaluations of stroke rates. The rate of cardiovascular hospitalization was significantly lower in the dronedarone group (29.3% vs. 36.9% for placebo, p<.001), a rate driven almost entirely by hospitalizations due to atrial fibrillation (14.6% vs. 21.9%, p<.001). Because of the differences in the amiodarone and dronedarone trials, no useful indirect comparison of hospitalization rates between amiodarone and dronedarone can be made.

Findings on hospitalization are presented in Appendix B, Table B5. Amiodarone's impact on hospitalization rates vs. a rate-control strategy was evaluated in a single RCT in our sample. In the PIAF trial, 252 patients were randomized to rhythm control with amiodarone vs. rate control with diltiazem and followed for 1 year. The percentage of patients hospitalized was significantly higher for amiodarone (69% vs. 24% for diltiazem, p=.001) (Hohnloser, 2000). However, the majority of admissions among patients on amiodarone were scheduled admissions for cardioversion. Findings from a separate amiodarone meta-analysis concluded no significant impact of amiodarone on all-cause hospitalization (OR=1.10; 95% CI=0.57, 2.13) (Doyle, 2009). A total of 5 studies were included in this analysis, including PIAF; however, 2 of the 4 other studies were for indications not in our scope (e.g., rheumatic AF, post-procedure AF), and an additional assumption was made for another study that all patients requiring cardioversion would be hospitalized.

Evidence for dronedarone comes from the ATHENA trial (Hohnloser, 2009). The rate of cardiovascular hospitalization was significantly lower in the dronedarone group (29.3% vs. 36.9% for placebo, p<.001), a rate driven almost entirely by hospitalizations due to atrial fibrillation (14.6% vs. 21.9%, p<.001). The observed effect did not appear to be due to cardioversion, which was primarily conducted in an outpatient setting, but rather to the consequences of AF for patients with comorbidity (e.g., angina, heart failure). As described previously, a post hoc analysis of data from ATHENA suggested no difference in the rate of stroke-related hospitalization (1.0% vs. 1.4% for dronedarone vs. placebo, p=.082).

The ATHENA trial also reports on the impact of dronedarone on the primary outcome (cardiovascular hospitalization or death) according to key subgroups. Significant reductions were observed in subgroups defined by age (<75 vs. ≥75 years), sex, and presence of CHF; however, no differential effects within each subgroup were observed (p>.65 for all comparisons).

No meta-analyses were conducted on the impact of AADs on hospitalization rates due to the variation and paucity of available data from our sample.

<u>Quality of Life</u>

Data are extremely limited on the impact of amiodarone or dronedarone on quality of life, and no direct comparative data exist. Amiodarone's impact on quality of life vs. rate-control has been evaluated in a single RCT; no significant improvement in quality of life

was observed. At present, there are no published quality of life data for patients on dronedarone.

Data on quality of life are presented in Appendix B, Table B6. Detailed information on amiodarone's quality-of-life impact comes from the previously-described PIAF trial vs. rate control with diltiazem (Hohnloser, 2000). Quality of life was assessed using multiple domains and summary scales of the SF-36. While significant improvement from baseline to 12 months was noted across all domains within both groups, differences between groups in this improvement were not statistically significant for any domain. At present, there are no published data on quality of life from any dronedarone trials.

While the findings demonstrating no significant improvement in quality of life on amiodarone may be surprising given the long-held belief that maintenance of sinus rhythm should improve quality of life, findings from the major trials of rhythm vs. rate control have also been equivocal in this regard. For example, in the AFFIRM trial, no significant differences between rhythm and rate control in quality of life or mental state were noted at any timepoint (AFFIRM Investigators, 2003; Wyse, 2002). In the CAFÉ-II study focusing on patients with AF and CHF, significant improvements on all QoL scales were only noted in a post-hoc analysis focusing on patients in NSR or with adequate rate control (Shelton, 2009).

The effects of amiodarone therapy on quality of life in key patient subgroups have not been recorded. Meta-analyses of quality of life data for AADs were not performed due to a paucity of relevant data.

3. Warfarin vs. dabigatran vs. WATCHMAN

Evidence on all outcomes for dabigatran and the WATCHMAN are limited in nature, given that there has been only one relevant published RCT to date for each intervention vs. warfarin. The key findings from each of these studies are described in detail below.

<u>Mortality</u>
Data from the 2 RCTs of dabigatran and the WATCHMAN indicate no difference in all-cause mortality relative to warfarin, although findings for the 150 mg dose of dabigatran are nearly statistically significant.

Findings for all-cause mortality are available in Appendix B, Table B2. In the RE-LY trial of dabigatran, the annual rates of all-cause mortality were 4.1%, 3.8%, and 3.6% for warfarin, 110 mg dabigatran, and 150 mg dabigatran (Connolly, 2009b). The difference in mortality between 110 mg dabigatran and warfarin was not statistically significant (RR=0.91; 95% CI=0.80, 1.03, p=.13), while the impact of 150 mg dabigatran was nearly so (RR=0.88; 95% CI=0.77, 1.00, p=.051). In addition, while the rate of vascular death did not differ between dabigatran 110 mg and warfarin (2.4% vs. 2.7%; RR=0.90; 95% CI=0.77, 1.06, p=0.21), this rate was significantly lower with dabigatran 150 mg (2.3% vs. 2.7%; RR=0.85; 95% CI=0.72, 0.99, p=.04). No further detail was provided on the causes of death or the possible reasons for lower mortality rates with higher-dose dabigatran.

In a subsequent analysis of RE-LY stratified by study site and time in therapeutic range (TTR) for warfarin patients (Wallentin, 2010), all-cause mortality was significantly reduced for both dabigatran 110 mg (HR=0.73; 95% CI=0.58, 0.92) and 150 mg (HR=0.67; 95% CI=0.53, 0.85) at sites with the lowest TTR levels (<57.1% of time in therapeutic range); on an overall basis, mortality rates were comparable for both doses of dabigatran vs. warfarin regardless of TTR level (p for interaction=0.066 and 0.052 respectively).
The rate of all-cause mortality also did not differ significantly between the WATCHMAN and warfarin (3.0 vs. 4.8 per 100 person-years; RR=0.62; 95% CrI=0.34, 1.24) in the PROTECT-AF study (Holmes, 2009). The observed difference in mortality was primarily due to reduced rates of death from stroke as well as unknown or other cardiovascular causes.

No data were presented in either of these trials on the impact of intervention on mortality in key patient subgroups. Meta-analyses of this outcome were not conducted due to a paucity of relevant data.

Stroke Rates
Data from the dabigatran trial suggests comparable or lower rates of total stroke relative to warfarin, and significantly lower rates of hemorrhagic stroke. Findings from the WATCHMAN trial also suggest a significantly lower rate of hemorrhagic stroke and an equivalent rate of total stroke in relation to warfarin.

Findings for stroke are available in Appendix B, Table B3. Annual rates of total stroke or systemic embolism in the RE-LY trial were 1.7%, 1.5%, and 1.1% for warfarin, dabigatran 110 mg, and dabigatran 150 mg respectively (Connolly, 2009b). These stroke rates did not differ between the lower dose of dabigatran and warfarin, but were significantly lower in the higher-dose comparison (RR=0.66; 95% CI=0.53, 0.82, p<.001). Annual rates of hemorrhagic stroke were higher in the warfarin group vs. both the 110 mg and the 150 mg dabigatran groups (0.38% vs. 0.12%, and 0.15%, respectively), a difference that was statistically significant for both comparisons (p<.001). Comparisons of ischemic stroke rates showed no difference in the rate for 110 mg dabigatran vs. warfarin (1.34% vs. 1.20% per year, p=.35), but a significantly lower rate was observed for 150 mg dabigatran (0.92% vs. 1.20% per year, p=.03).

Analyses of data stratified by study site and TTR levels (Wallentin, 2010) revealed comparable rates of total stroke, systemic embolism, and intracranial hemorrhage for both doses of dabigatran vs. warfarin irrespective of TTR levels (p for interaction=0.076-0.89).

In the PROTECT-AF trial of the WATCHMAN vs. warfarin, the primary efficacy endpoint was a composite of stroke, systemic embolism, or death due to cardiovascular or unexplained causes (Holmes, 2009). This rate did not differ between the WATCHMAN and warfarin arms (3.0 vs. 4.9 per 100 person-years; RR=0.62; 95% CrI=0.35, 1.25). The rate of hemorrhagic stroke was substantially lower in the WATCHMAN arm (0.1 vs. 1.6 per 100 person-years; RR=0.00, 0.45); however, the rate of ischemic stroke was higher, although not statistically significant (2.2 vs. 1.6 per 100 person-years; RR=1.34; 95% CI=0.60, 4.29). The

higher number of ischemic strokes was in part attributed to the risk of stroke during the procedure (5 of 463 patients).

For both RCTs, the impact of key subgroups was evaluated in relation to the primary outcome. In the RE-LY study of dabigatran vs. warfarin, no significant interactions with treatment were observed when stratified by sex, $CHADS_2$ score, presence of symptomatic CHF, or ethnic group (European/Arab vs. other). Most interactions were also nonsignificant in the PROTECT-AF trial of the WATCHMAN vs. warfarin; however, a significantly lower rate for the primary composite outcome was noted in males (HR=0.32; 95% CI=0.13, 0.77) and those with persistent vs. paroxysmal or permanent AF (HR=0.19; 95% CI=0.04, 0.98).

Meta-analyses on stroke rates were not conducted due to a paucity of available data.

Hospitalization

Data on hospitalization are available only from the RE-LY trial of dabigatran. The annual rate of all-cause hospitalization was significantly lower in the group receiving 110 mg dabigatran vs. warfarin; this rate did not differ in comparisons of 150 mg dabigatran vs. warfarin.

Hospitalization results are presented in Appendix B, Table B5. The annual rates of all-cause hospitalization were 20.8%, 19.4%, 20.2% for warfarin, dabigatran 110 mg, and dabigatran 150 mg respectively in the RE-LY trial (Connolly, 2009b). Differences were statistically significant in the lower-dose comparison (RR=0.92; 95% CI=0.87, 0.97, p=.003), and nonsignificant in the higher-dose comparison (RR=0.97; 95% CI=0.92, 1.03, p=.34). Hospitalization rates were not evaluated in the PROTECT-AF trial of the WATCHMAN.

No subgroup data were available with which to evaluate the differential impact of dabigatran on hospitalization rates across key subgroups. Meta-analyses of this outcome were not conducted due to a paucity of relevant data.

Quality of Life

To date, no assessments have been performed to assess the impact of dabigatran or the WATCHMAN on quality of life.

Potential Harms

The treatment strategies evaluated in this appraisal are associated with multiple harms, some of which are common to multiple strategies and others of which are unique to particular strategies. Relevant harms, as well as the range of reported rates in the set of studies evaluated for this appraisal, are listed for each strategy in Table 4 on page 107.

For both catheter ablation and TOP surgical ablation, we have categorized complications as major vs. minor: major complications were considered to be those that required a major procedure or intervention to correct (e.g., thoracotomy, dialysis, ICU admission), while minor complications represented those that required a minor procedure or intervention (e.g., pericardiocentesis, antibiotic therapy) or resolved on their own. Note that repeat catheter ablation and "retreatment" following TOP surgical ablation are also presented; while not technically patient harms, they nevertheless represent some clinical risk to the patient and are a key consideration in patient- and clinician decision-making.

Information on harms is presented separately for each treatment strategy in the sections that follow. Note that meta-analyses were not performed for any harm other than drug discontinuation due to adverse events, given (a) the lack of a comparator for intervention-specific harms; and (b) the paucity of high-quality data for harms that are common to multiple interventions.

Catheter Ablation

Peri-operative Death

There were no peri-operative deaths in catheter ablation RCTs that reported this measure; data from case series and cohort studies suggest that peri-operative death is extremely rare (0-0.7% across studies; mean: 0.1%).

Data on peri-operative death can be found in Appendix B, Table B9. Peri-operative death was measured in 4 RCTs of catheter ablation; no such deaths were observed in any of these studies. In catheter ablation case series and cohort studies reporting this measure, the rate of peri-operative mortality averaged 0.1% across studies (range: 0-0.7%).

Due to the rarity of peri-operative death, it was not possible to evaluate the impact of catheter ablation in important patient subgroups. Findings from the AHRQ review also indicate that the incidence of peri-operative death was low, identifying only 5 deaths (Ip, 2009).

Peri-operative Stroke

Similarly, peri-operative stroke appears to be rare among patients in catheter ablation studies; only 2 strokes were reported among 311 patients in 6 RCTs. Data from case series and cohort studies suggest that, while not as low a rate as peri-operative mortality, peri-operative stroke remains a rare event (0-1.5% across studies; mean: 0.4%).

Data on peri-operative stroke can be found in Appendix B, Table B9. Peri-operative stroke was reported in 6 RCTs of catheter ablation (n=311); a total of 2 strokes were recorded (0.6%). In catheter ablation case series and cohort studies, the rate of peri-operative stroke averaged 0.4%; the range was 0-1.5% across studies.

As with mortality, it was not feasible to evaluate the impact of catheter ablation on rates of peri-operative stroke across key patient subgroups due to the rarity of the event. The AHRQ review found the median rate of cerebrovascular events to be 0.9% across studies (range: 0-7%) (Ip, 2009); it is unclear, however, whether this measure is limited to peri-operative strokes alone or also includes strokes occurring during long-term follow-up.

Other Major Complications

Rates of major complications are highly variable across catheter ablation studies, and are affected by differences in definition and measurement. The most commonly reported major complications in RCTs and comparative cohort studies include major bleeding, cardiac tamponade, moderate-to-severe pulmonary stenosis, and worsening heart failure; rates range between 0-11% across studies.

While the rate of major catheter ablation-related complications appears to be relatively low, these rates vary widely across studies, and may be affected by differences in definition and measurement (for example, "major" bleeding or "moderate-to-severe" pulmonary stenosis). In many cases, little detail is provided on how complications are defined. Across all studies, the rate of overall complications averaged 1.3% (range: 0-11%).

The rate of major complications ranged between 0-6% in RCTs and comparative cohort studies. Complications reported most frequently included major bleeding (0-6%), cardiac tamponade requiring surgery or pericardiocentesis (0-6%), worsening heart failure (0-5%), and moderate-to-severe pulmonary stenosis (0-4%). Data were more variable in case series and cohort studies, ranging from 0-11% in most series. A high rate of moderate-to-severe pulmonary stenosis was reported in one study (24%) (Kanagaratnam, 2001); however, this estimate is based only on a subset of patients who received spiral CT post-procedure.

An important and often fatal complication of catheter ablation is atrioesophageal (AE) fistula, which typically manifests itself as a food embolism post-procedure (Stollberger, 2009). No instances of AE fistula were observed in any of the RCTs and comparative cohorts in our sample; in case series data, AE fistula remained a relatively rare event (0-2%). These findings correlate with those of a large, nationwide survey of nearly 600 physicians on the case histories of over 20,000 patients (Ghia, 2009); 6 cases of AE fistula were reported (0.03%).

Major complications also were assessed by patient age in a study stratifying those aged ≥80 vs. <80 years (Bunch, 2009). There were no significant differences in the rate of these complications, with the exception of deep vein thrombosis (2.8% vs. 0% for ≥80 and <80 years respectively, p=.05).

Findings from the AHRQ review drew similar conclusions to these, suggesting that the rate of major complications was less than 5% in most instances (Ip, 2009).

Minor Complications

The rate of minor complications was also highly variable across catheter ablation studies, but was generally higher than that for major complications (range: 0-30%; mean: 3.7%). Minor complications reported with the most frequency included mild pulmonary vein stenosis, pericardial effusion, and phrenic nerve injury.

Comparisons of the rate of minor complications across catheter ablation studies is made problematic by the lack of a common taxonomy for reporting as well as variability in the level of detail reported; for example, some series provide detailed information on the complications encountered, while others use an "other" category with no further detail provided. Nevertheless, some complication types do appear to be reported with more frequency than others. For example, the rate of mild pulmonary vein stenosis ranged from 0-24% in RCTs and comparative cohort studies, and also approached or exceeded the top of this range in multiple case series. Other common events included pericardial effusion (range: 0-3% in RCTs/comparative cohorts, 0-12% in case series) and phrenic nerve injury (0-2% in RCTs/comparative cohorts, 0-13% in case series). On an overall basis, the rate of minor complications was relatively low (3.7%), although this rate was subject to substantial variability (standard deviation: 6.7%; range: 0-30%).

Complications classified as "other" varied substantially by study. In one case series, for example, 27% of 530 patients suffered a groin hematoma from catheter insertion (Hunter, 2010). In another series, 5/40 patients (12.5%) reported dysphagia and coughing (Malmborg, 2008).

Differences in minor complications by sex were evaluated in a large series of over 3,000 patients (Patel, 2010). The only complications that differed significantly were both more frequent in females: hematoma (2.1% vs. 0.9% for females and males respectively, p=.026) and pseudoaneurysm (0.6% vs. 0.1%, p=.031).

The AHRQ review found a similar range of pulmonary vein stenosis (0-19%), but did not comment on any of the other above-described minor complications in detail (Ip, 2009).

Table 4. Reported ranges of harms, by treatment strategy.

Intervention/Harm	Mean (SD)	Reported Range
Catheter Ablation		
Peri-operative death	0.1% (0.2%)	0-0.7%
Peri-operative stroke	0.4% (0.5%)	0-1.5%
Major complications	1.3% (2.2%)	0-6%
Minor complications	3.7% (6.7%)	0-30%
TOP Surgical Ablation		
Peri-operative death	0.3% (0.6%)	0-2%
Peri-operative stroke	0.8% (1.2%)	0-3%
Major complications	3.8% (4.1%)	0-14%
Minor complications	8.2% (6.7%)	0-23%
AADs		
Pulmonary toxicity*		
Amiodarone	0.7% (0.7%)	0-1.6%
Dronedarone	0.1% (0.1%)	0-0.1%
Thyroid toxicity*		
Amiodarone	5.4% (4.4%)	0-12%
Dronedarone	5.5% (6.9%)	0-13%
Any AE leading to drug discontinuation*		
Amiodarone	14.8% (8.4%)	1.6-26.0%
Dronedarone	8.5% (6.0%)	0-17.9%
Stroke Prevention		
Major bleeding*		
Warfarin†	---	2-4%
Dabigatran	---	2.7-3.1%
WATCHMAN	---	3.5%
Procedure safety events*		
WATCHMAN	---	7.4%

NOTE: Means not reported for warfarin (no new evidence synthesized) or dabigatran/WATCHMAN (data from single trials only)
*Annualized rate
†Rate for warfarin inclusive of meta-analysis findings and observed rate in dabigatran and WATCHMAN trials
TOP: Thorascopic, off-pump; AADs: Antiarrhythmic drugs; AE: Adverse effect

Thorascopic, Off-Pump (TOP) Surgical Ablation

Peri-operative Death

Data from the limited case series information available suggests that, as with catheter ablation, the incidence of peri-operative death is a very rare event (mean: 0.3%; range: 0-2% across studies) as reported in TOP surgical ablation case series.

Peri-operative death was measured in a total of 11 case series; rates averaged 0.3% (range: 0-2%). As with catheter ablation, the rarity of this event and the limited evidence available for TOP surgical ablation preclude evaluation of TOP surgical ablation's impact in key patient subgroups. These rates are lower than 30-day mortality rates reported in a recent systematic review comparing "cut and sew" Maze procedures to ablation using various energy sources (2.1% vs. 4.2%) (Khargi, 2007), as well as meta-analyses of randomized and nonrandomized studies of surgical ablation as an adjunct to other cardiovascular procedures (3.7% vs. 2.8%) (Ad, 2010); it should be noted, however, that these reviews were not limited to studies of stand-alone AF surgery.

Peri-operative Stroke

Data on peri-operative stroke are even more limited in TOP surgical ablation series than information on peri-operative mortality; nonetheless, in the case series reporting on this event, rates also appeared to be quite low (mean: 0.8%; range: 0-3% across studies).

The incidence of peri-operative stroke averaged 0.8% across studies (range: 0-3%). As with mortality, the rarity of this event and the limited evidence available for TOP surgical ablation preclude evaluation of TOP surgical ablation's impact in key patient subgroups. In the above-described review by Khargi and colleagues, the pooled peri-operative stroke rate for "cut and sew" Maze procedures was similar to that observed in our analysis (0.5%), while the rate for energy-based procedures was somewhat higher (1.6%) (Khargi, 2007).

Other Major Complications

Limited data from TOP surgical ablation series suggest the incidence of major complications is also relatively infrequent (mean: 3.8%; range: 0-14%), although reporting is inconsistent across series. The most frequent major complications observed involved hemothorax or other major bleeding requiring thoracotomy or sternotomy.

Data from surgical series are often lacking in detail regarding the incidence and sequelae of major peri-operative complications. The incidence of major complications varies widely, ranging from 0-14% across studies (average: 3.8%). The most frequent complications observed were hemothorax or other major bleeding (0-7%) requiring thoracotomy or sternotomy. Single instances of pulmonary embolism, transient ischemic attack, and hypoventilation requiring mechanical ventilation were reported across all series. Pooled rates of major bleeding for cut-and-sew Maze and energy-based ablation were 4.9% and 4.4% respectively in a recent systematic review (Khargi, 2007).

The study reporting the highest rate of complications was a series of 43 patients undergoing thorascopic PVI and vagal denervation (Bagge, 2009). Six (14%) of these patients had

episodes of major bleeding, defined as hemorrhage requiring surgical intervention and/or transfusion and/or treatment cessation.

No data were presented in any TOP surgical ablation case series that evaluated the impact of the procedure on complication rates in key patient subgroups.

Minor Complications

Minor complications of TOP surgical ablation were reported across case series with rates ranging from 0-23% (mean: 8.2%). The most frequent such complication was requirement for permanent pacemaker implantation, which occurred in 0-10% of patients. Other minor complications included phrenic nerve injury (0-3%) and pericarditis (0-4%).

As with catheter ablation, evaluation of data on minor complications across surgical series is made difficult by a lack of common taxonomy as well as the level of detail in reporting. The overall rate of minor complications averaged 8.2% and ranged from 0-23% across series. Permanent pacemaker implantation was the most frequent minor complication observed, occurring in 4 of the 7 series reviewed. Percentages of patients requiring pacemakers ranged from 2-10% across these studies. The study reporting the highest rate of pacemaker implantation was a series of 30 patients undergoing PV antral ablation with an extended lesion set (Edgerton, 2009). Three patients received pacemakers, 2 for significant pause when converting spontaneously to sinus rhythm, and 1 for development of a slow junctional rhythm. Pacemaker implantation rates in the systematic review of cut-and-sew Maze (5.8%) and energy-based ablation (4.9%) (Khargi, 2007) were comparable to those seen in this analysis.

Other minor complications occurring with some frequency included phrenic nerve injury (reported in 3 series; range 1-3%) and pericarditis (reported in 2 series; range 1-4%). Other events included temporary respiratory distress (1 series; rate=4.4%), pleural effusion (1 series; rate=4.4%), and renal failure not requiring dialysis (1 series; rate=1.8%). Complications falling into the "other" category, when characterized, included disorders of cardiac rhythm, although no further detail was provided in series reports.

No data were presented in any TOP surgical ablation case series that evaluated the impact of the procedure on complication rates in key patient subgroups.

Amiodarone and Dronedarone

Pulmonary Toxicity

As measured in RCTs and comparative studies, the rate of pulmonary toxicity with amiodarone is relatively low, ranging from 0-1.6% (mean: 0.7%) on an annualized basis. Long-term follow-up studies and other evidence-based reviews have documented a much wider range of pulmonary toxicity (1-17%); however, many of the higher estimates were for amiodarone at maintenance dose levels ≥400 mg daily. Lower doses of amiodarone are now recommended in AF; rates of pulmonary toxicity observed from long-term studies in which amiodarone was used at these lower levels are in the lower range of 0-1.6%.

Acute pulmonary toxicity is considered the most serious adverse effect of long-term amiodarone therapy, as it is manifested as pulmonary fibrosis, which in some cases is irreversible even after drug discontinuation and can lead to death. Rates of pulmonary toxicity from earlier studies with maintenance dose levels of amiodarone ≥400 mg daily have ranged from 1-17% (Vassallo, 2007). However, maintenance dosing of amiodarone in AF is now recommended at 200 mg daily (Zimetbaum, 2007), which has resulted in much lower rates of 1.6-2% in meta-analyses and cohort studies at the lower dose (Goldschlager, 2007; Sunderji, 2000). Annualized rates in the studies that comprised our review were consistent with these findings, ranging from 0-1.6%.

Dronedarone has been touted as a safer alternative to amiodarone for long-term treatment. With regard to pulmonary toxicity, this appears to be true. Pulmonary toxicity events have only been reported in a single trial, ATHENA (Hohnloser, 2009). Five events were reported among 2,301 patients, or an annualized rate of 0.1%. However, mean follow-up in this study was 21 months, which may be too short to identify all cases of this event, as clinical symptoms may develop after several years on therapy (Wolkove, 2009). In the head-to-head DIONYSOS trial of amiodarone and dronedarone, no pulmonary events were detected in either arm over a median of 7 months of follow-up (Le Heuzey, 2010).

There is no information available with which to discern the impact of amiodarone or dronedarone on the rate of pulmonary toxicity within key patient subgroups.

Thyroid Toxicity

In the head-to-head DIONYSOS trial, rates of hypo- or hyperthyroidism were substantially higher with amiodarone (10.1% vs. 1.4% on an annualized basis), although the significance of this finding was not tested. Rates of thyroid toxicity (manifested either as hypo- or hyperthyroidism) range from 0-13% (mean: 5.5%) on an annualized basis in both amiodarone and dronedarone RCTs and comparative cohort studies; however, the dronedarone findings are skewed by results of the EURIDIS/ADONIS trials, which were based on laboratory findings from multiple tests. Exclusion of this study report would drop the average rate of thyroid toxicity with dronedarone to 1.6%.

Thyroid toxicity is a frequent consequence of long-term amiodarone therapy, and may manifest itself either as hypo- or hyperthyroidism. The latter is of particular concern, as it may exacerbate AF or precipitate ventricular tachyarrhythmias (Vassallo, 2007). As such, periodic thyroid function testing is recommended with amiodarone. In the head-to-head DIONYSOS trial (Le Heuzey, 2010), the annualized incidence of thyroid events (defined as clinical hypo- or hyperthyroidism as well as abnormal thyroid function testing requiring medical intervention) was 10.1% for amiodarone vs. 1.4% for dronedarone, although this difference was not specifically tested for statistical significance.

Reported rates of thyroid toxicity among the other amiodarone studies in our review have ranged from 0-12% (mean: 5.4%) on an annualized basis; a similar range of estimates was found for the dronedarone trials in our sample (0-13%) (mean: 5.5%). Variation in the rate of thyroid toxicity from these studies appears to be at least in part definitional in nature.

The highest reported rates come from studies that defined thyroid toxicity based on laboratory values alone, while lower rates were derived from studies that focused on clinical presentation. For example, the dronedarone study with the highest reported rate of thyroid toxicity (13.4%) was based on findings from 3 different laboratory tests in the EURIDIS and ADONIS trials (Singh, 2007); rates for dronedarone in these trials were in fact comparable to or significantly lower than placebo. With this study report excluded, the average annual rate of thyroid toxicity drops to 1.6%.

There is no information available with which to discern the impact of amiodarone or dronedarone on the rate of thyroid toxicity within key patient subgroups.

Other Adverse Effects

Other potential adverse effects with amiodarone include optic neuropathy/neuritis, skin discoloration, photosensitivity, liver toxicity, tremor, and ataxia. These have been reported with varying frequency in clinical study. Adverse effects occurring with more frequency than placebo in dronedarone trials include bradycardia, QT-interval prolongation, nausea, and diarrhea. The annualized rate of drug discontinuation due to any adverse effect has been reported over a similar range for amiodarone and dronedarone, although this rate is somewhat higher on average for amiodarone (15% vs. 8% for dronedarone) and also was higher in the head-to-head DIONYSOS trial. A mixed treatment comparison taking all amiodarone and dronedarone studies into account found no difference in the rate of discontinuation due to adverse effects.

Both amiodarone and dronedarone are associated with a variety of other adverse effects, as listed above. Most of these effects occur rarely or are not generally considered serious enough to consistently warrant drug discontinuation. A similar range of annual rates of *any* adverse effects leading to drug discontinuation has been reported in amiodarone (1.6-26.0%) and dronedarone (0-17.9%) trials respectively, although on average a higher rate was observed with amiodarone (14.8% vs. 8.5% for dronedarone).

In the DIONYSOS trial, the rate of drug discontinuation due to adverse events was 17.2% for dronedarone on an annualized basis compared to 22.9% for amiodarone; this difference was due primarily to reduced rates of thyroid, skin, ocular, and neurologic events, although the difference was not statistically significant (p=.23). Findings from our mixed treatment comparison of dronedarone to amiodarone suggests a likelihood of drug discontinuation in favor of amiodarone, although this difference was not significant (OR=2.02; 95% CI=0.14, 9.62). As shown in Table 5 on the following page (as well as in Appendix C, Table C2), differences were only significant in comparisons of amiodarone to control, although there is a very wide confidence interval around even those findings.

Table 5. Results of mixed treatment comparison of likelihood of drug discontinuation due to adverse effects, by agent and comparison.

	Amiodarone	Sotalol	Dronedarone
	Odds Ratio (95% CI)		
Control	5.82 (1.14, 20.01)	2.23 (0.13, 11.16)	8.89 (0.71, 43.41)
Amiodarone		0.46 (0.03, 2.20)	2.02 (0.14, 9.62)
Sotalol			12.86 (0.26, 74.58)

Note: Results are presented as agent in column vs. agent in row
"Control"=class 1c agent, rate control agent, or placebo
CI: Confidence interval

There is no information available on the impact of amiodarone or dronedarone on the rate of drug discontinuation due to adverse effects within key patient subgroups.

Warfarin, Dabigatran and the WATCHMAN

Warfarin

The incidence of major hemorrhage (other than hemorrhagic stroke) among patients receiving warfarin is estimated to be approximately 2% on an annual basis. Risks of hemorrhage are highly dependent on the success that patients and clinicians have in maintaining anticoagulation at a therapeutic level.

The primary risk of long-term warfarin treatment is that of major hemorrhage – both in terms of intracranial hemorrhage (i.e., hemorrhagic stroke) and major bleeding at other anatomic sites. Findings from a previous patient-level meta-analysis indicate an annual rate of major hemorrhage of 2.2%, exclusive of hemorrhagic stroke risk (0.5% annually) (van Walraven, 2002). Other complications of warfarin treatment include skin necrosis or gangrene (<0.1%), as well as the potential for warfarin to interact with many drugs and foods, which may in turn affect the balance between stroke prevention and major bleeding risks (Bristol Myers Squibb, 2010c).

Dabigatran

The single RCT of dabigatran demonstrated a lower rate of major bleeding for the 110 mg dose compared to warfarin* (2.7% vs. 3.4%, p=.003)*, and a comparable rate of bleeding at the higher 150 mg dose. The only other adverse effect of dabigatran that occurred at a higher rate than warfarin was dyspepsia. A higher rate of MI was observed with dabigatran relative to warfarin, a difference that was statistically significant for higher dose dabigatran.

In the RE-LY trial, the annual rate of major bleeding was comparable for the 150 mg dose of dabigatran relative to warfarin (3.1% vs. 3.4% per year, p=.31), and significantly lower for the 110 mg dose (2.7% vs. 3.4%, p=.003) (Connolly, 2009b); as reported previously, the rate

of hemorrhagic stroke was significantly lower for both doses relative to warfarin. The rate of bleeding with warfarin was higher than that reported in previous studies; the RE-LY authors speculate that this may be due to the use of an inclusive definition in this study (i.e., drop in hemoglobin of ≥20 g/l, transfusion of 2+ units of blood, or symptomatic bleeding in a critical area or organ).

Analyses of major bleeding rates according to study site and warfarin time in therapeutic range (TTR) (Wallentin, 2010) revealed comparable rates of major bleeding and total bleeding for dabigatran 110 mg vs. warfarin regardless of TTR level (p for interaction=0.50 and 0.076 for major and total bleeding respectively). Among patients receiving dabigatran 150 mg, however, a significant interaction was observed, with dabigatran associated with lower major bleeding rates than warfarin at centers with TTR levels <57%, and higher bleeding rates than warfarin at sites with TTR levels >65.5% (p for interaction=0.03); rates of total bleeding were comparable for dabigatran 150 mg vs. warfarin regardless of TTR level (p for interaction=0.15).

The only individual adverse effect occurring significantly more frequently with dabigatran than warfarin in the RE-LY trial was dyspepsia (11.3-11.8% vs. 5.8%, p<.001). However, the rate at which patients discontinued study therapy due to a serious adverse event also was significantly higher for dabigatran at both doses (2.7% vs. 1.7%, p<.001); no explanation is given for this difference.

Finally, while not technically recorded as an adverse effect, a higher annual rate of myocardial infarction was observed in RE-LY with dabigatran relative to warfarin (0.72% and 0.74% for 110 and 150 mg respectively vs. 0.53%); this difference was statistically significant for the higher-dose comparison (p=.048). The reason for this adverse finding is not immediately apparent. Although it could be a chance findings, the authors hypothesized that an increased relative risk for MI could be due not to a harmful effect of dabigatran but to warfarin's ability to confer relatively greater protection against ischemic events (Connolly, 2009b).

The RE-LY trial provided no data with which to determine dabigatran's impact on major bleeding or other harms in key patient subgroups.

WATCHMAN

Placement of the WATCHMAN device has been associated with a number of serious complications, most commonly serious pericardial effusion and major bleeding. In addition, peri-procedure stroke as reported appears to be more common with WATCHMAN implantation than with either catheter ablation or TOP surgical ablation. Further safety data on the WATCHMAN has been requested by the FDA, delaying the device's approval in the U.S.

In the PROTECT-AF trial, the rate of primary safety events was significantly higher with the WATCHMAN relative to warfarin control (7.4 vs. 4.4 per 100 patient-years; 95% CrI: 1.01, 3.19) (Holmes, 2009). Safety events in the WATCHMAN arm were most commonly serious pericardial effusion (i.e., requiring percutaneous or surgical drainage) (4.8%), and

major bleeding (3.5%). In comparison, the rate of major bleeding (other than hemorrhagic stroke) in the warfarin arm was 4.1%.

In addition, a total of 5 patients had a stroke associated with the procedure (1.1%). Less common were device emoblization (0.6%) and other event types (e.g., esophageal tear, arrhythmia, 0.4%). The authors hypothesize that the observed rates of complications are likely due to a procedure learning curve, but present no data on rates with increasing levels of experience. Due in all likelihood to safety concerns, the FDA has recently delayed the WATCHMAN's approval and asked for additional data (Atritech, 2010).

The PROTECT-AF trial provided no data with which to determine the WATCHMAN's impact on major bleeding or other harms in key patient subgroups.

8. Clinical and Economic Model

8.1 Overview

The objective of the decision analytic model was to compare the outcomes, costs, and cost-effectiveness of management strategies for patients with moderately to highly symptomatic atrial fibrillation, with a particular focus on those strategies identified through our appraisal process as of greatest interest to patients, clinicians, and policymakers.

Each strategy in the model has a cardiovascular component for managing the heart rhythm or rate and a stroke prevention component. The cardiovascular components of the management strategies under study include left atrial catheter ablation (LACA) as an initial approach; LACA following the failure of rhythm control; and thorascopic, off-pump (TOP) surgical ablation; rhythm control using amiodarone; rhythm control using dronedarone; rhythm control with initial dronedarone and amiodarone for failure of dronedarone; and rate control. The stroke prevention components of the management strategies include standard treatment with warfarin or aspirin; dabigatran at 110 mg and 150 mg; and a strategy with catheter placement of a left atrial appendage exclusion device (the WATCHMAN).

The analysis presented here will provide a summary of the clinical outcomes and medical care costs resulting from each management strategy in hypothetical cohorts of patients with symptomatic atrial fibrillation. The clinical course of patients' atrial fibrillation management by clinical disease state is summarized in graphs of clinical states over time and in tables of summary measures of quality adjusted life years and medical care costs. Detailed tables provide lists of the clinical services, outcomes and costs as well as key clinical events to facilitate comparisons.

The presentation of results will focus on five major clinical comparison areas: (1) The use of LACA as an initial treatment or after failure of amiodarone for rhythm control ("AAD failure") ; (2) TOP surgical ablation compared to LACA as options following AAD failure; (3) Rhythm control with amiodarone compared to dronedarone alone and to dronedarone with amiodarone used second-line following dronedarone failure; (4) stroke prevention with dabigatran compared to adjusted dose warfarin or aspirin; and (5) stroke prevention with the WATCHMAN procedure (as a potential archetype for LAA exclusion) compared to adjusted dose warfarin or aspirin.

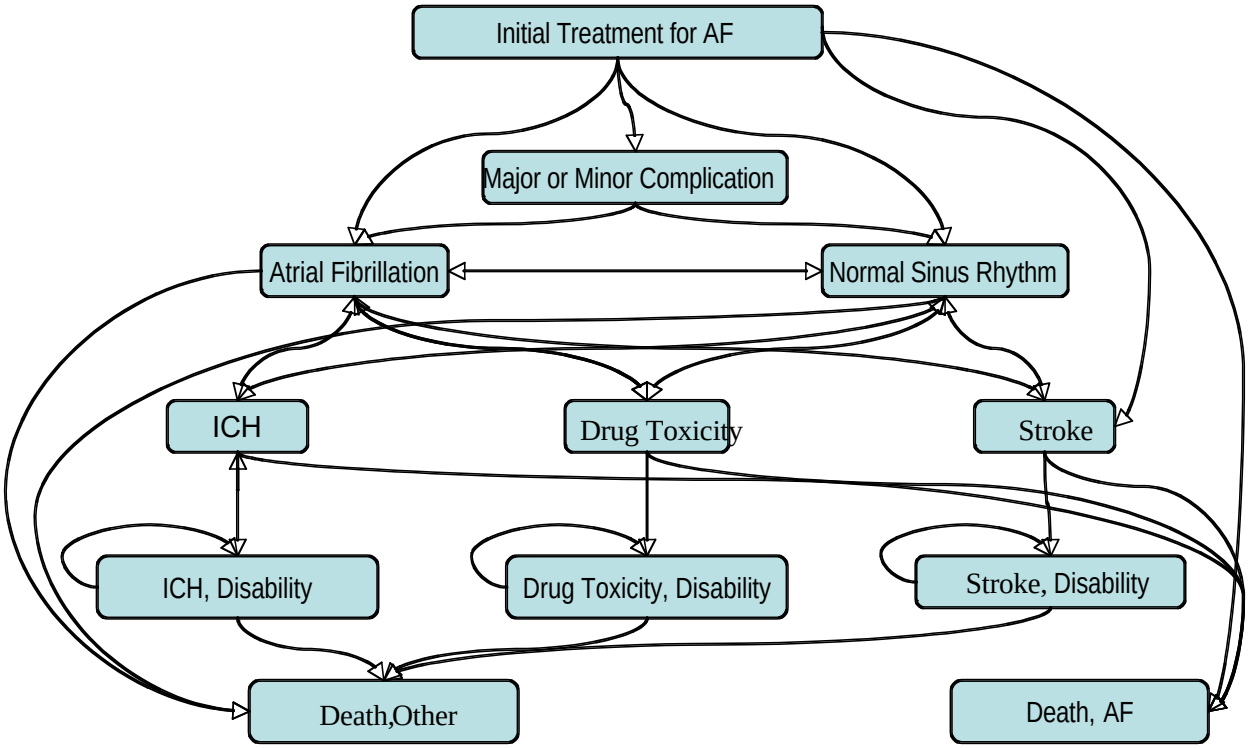
8.2 Methods

Approach

The decision analytic model is a discrete state, discrete time, state transition model (Markov model). In the Markov model, patients' clinical status in each time interval is classified into discrete, mutually exclusive states; time intervals are 3 months in duration. The disease states describe important clinical status such as AF, NSR, disability due to stroke, disability due to hemorrhage, or death. In the model, patients transition between clinical states over

their lifetime from the onset of initial AF management through death. The transitions between states include clinical services such as procedures and medications, as well as clinical events such as strokes, intracranial hemorrhage, complications from procedures, and adverse drug events. The decision analytic model is modeled as a decision tree, a graphic summary of the sequence of events that occur in the transitions between states. The Markov Disease State Diagram in Figure 1 below shows the disease states and the possible transitions between disease states. In general, patients enter the model in an initial treatment state such as a catheter ablation or AAD therapy, and may experience major or minor complications (including drug adverse events), stroke or death. Patients may than move from a NSR or AF state over time. Patients in AF or NSR may experience an ischemic stroke, an intracranial hemorrhage, or drug toxicity, or may die of other causes. Patients who experience an ischemic stroke, an intracranial hemorrhage or drug toxicity may have reversible morbidity, permanent disability, or may die of as a result of these AF related adverse events.

Figure 1. AF Markov Disease State Diagram



The model builds upon an extensive number of prior studies that have used decision analytic models to evaluate new drugs, devices, and procedures for the management of atrial fibrillation (Beck, 1983; Naglie, 1992; Disch, 1994; Eckman, 1995; Eckman, 1998; Gage, 1995; Gage, 1998; Lightowlers, 1998; Catherwood, 1999; O'Brien, 2005; Chan, 2006; Lamotte, 2007; McKenna, 2009; Quenneville, 2009; Reynolds, 2009).

Perspective
We followed most recommendations of the Panel on Cost-Effectiveness in Health and Medicine (Gold, 1996) but since we were not addressing societal questions of the full return on investment for various treatment strategies, we adopted a public payer perspective for the base case which includes capital expenditures in its reimbursement framework. Medicare payment rates were used to estimate direct medical care costs. We did not take patient time in therapy or patient productivity into account in this model given what we perceived to be serious limitations in our ability to estimate these elements. For example, while symptomatic AF is known to impact worker productivity, these effects may be highly individualized, making development of a population-level estimate problematic.

Time Horizon
A lifetime horizon was adopted as the primary approach to summarize clinical outcomes, health related quality of life, and costs. In addition, short-term summaries using a 5-year time horizon after initial treatment are also reported.

Outcome Measures
The analysis summarizes clinical events including procedures and complications, adverse drug events, stroke and stroke outcomes, intracranial hemorrhages and intracranial hemorrhage outcomes, and deaths. Costs include those of procedures and complications, medications and adverse drug events, stroke and stroke related disability, and intracranial hemorrhage and disability. Summary clinical measures include total life-years, "AF time," and quality-adjusted life years. The "AF time" measure is calculated as total time (in years) during which an episode of atrial fibrillation occurs in a 3-month model interval over the total course of the time horizon. This measure is a model analogue of the clinical concept of "AF burden," and along with total life-years, provides an indicator of the proportion of years in AF. Life-years and AF time are *not* discounted (see below) in order to provide useful clinical comparison measures for clinicians and patients.

Cost-Utility Analysis
Cost-utility analyses were conducted comparing AF management strategies within relevant sets of alternative approaches for each set of comparisons. The primary outcomes were costs and quality-adjusted life years, both discounted at a 3% annual rate. The analysis was conducted using TreeAge Pro 2009 (TreeAge Software, Williamstown, MA). The life-years, AF-years, quality adjusted life years, and total costs and components of costs were calculated in a Markov cohort analyses of each strategy. The analysis of the number of clinical procedures and adverse outcomes was implemented in a microsimulation using tracker variables. The summary measures of these outcomes shown in the appendices have inherent variation due to sampling and should be interpreted cautiously when differences in these outcomes between strategies are small.

Deterministic and Probabilistic Sensitivity Analyses
Multiple one-way sensitivity analyses were performed to identify important model parameters that had an impact on quality adjusted life-years, costs, and optimal strategy. Probabilistic (Monte Carlo) sensitivity analyses were conducted to identify the joint impact of uncertainty in model parameters on quality adjusted life-years, costs and incremental

cost-effectiveness ratios. Second order Monte Carlo simulations with 10,000 samples from distributions for 42 model parameters were performed. Incremental quality adjusted life years, incremental costs, and incremental ICER and their 95% confidence intervals are reported in the text and scatterplots of the ICERs; the $100,000 per quality adjusted life year willingness-to pay line and 95% confidence ellipse are shown for each of the major comparisons. Acceptability curves are used to summarize the proportion of simulations that are below a willingness-to-pay threshold as that threshold is varied; these are shown in Appendix E. The acceptability curves are pairwise comparisons of each intervention strategy with the referent or comparison strategy and are grouped on a single figure for each set of comparisons.

Patient Population

The eligible population is adult patients with atrial fibrillation who were assumed to have moderately severe impact of AF on their quality of life (-0.065 quality-adjusted life years) (Reynolds, 20009). Our base case selected men for the patient scenarios, as men have higher age-specific mortality and lower life expectancy. Our model is based on the $CHADS_2$ clinical classification to predict stroke which has been previously validated (Gage, 2001) and is widely used in practice and described in the ACC/AHA/ESC Guidelines. The stroke predictions from this model are not sex specific, and accordingly sex-specific analyses are not presented here. The clinical course is modeled from initiation of each management strategy through to the end of the patient's lifetime, or alternatively, 5 years. At the outset patients are assumed not to have valvular heart disease concomitant to their atrial fibrillation, to be clinically stable, and to be "eligible" for each treatment strategy. Patients with heart failure, coronary heart disease, hypertension, and other (non-structural) heart disease are included within the scope of the patient population. Indeed, management decisions for atrial fibrillation patients with these associated comorbid conditions are relevant because of the associated risk of stroke and intracranial hemorrhage.

Our analysis, guided by input from the ERG, focused on three patient scenarios for the comparison of the management strategies:

- *60 year old male patient with paroxysmal AF:*
    - This scenario describes a younger patient with paroxysmal atrial fibrillation and no comorbidity ($CHADS_2$ score = 0) at low risk of stroke.
    - Guidelines recommend aspirin for stroke patients with $CHADS_2 = 0$.

- *65 year old male patient with long-standing persistent AF and heart failure:*
    - This scenario describes a patient with a single comorbid condition, heart failure, at an intermediate risk of stroke ($CHADS_2 = 1$).
    - Heart failure is mild/moderate and controlled (to allow for dronedarone use)
    - Guidelines recommend aspirin or warfarin; aspirin is used in our analyses for patients with $CHADS_2 = 1$ if age is less than 75.

- *75 year old male patient with hypertension and diabetes mellitus and persistent AF:*
    - This scenario describes an older patient with substantial comorbidity at high risk of stroke ($CHADS_2 = 3$).
    - Guidelines recommend adjusted dose warfarin for stroke prevention.

8.3 Model Structure & Key Assumptions

The model follows hypothetical cohorts of simulated male patients transitioning between disease states at fixed time intervals from the onset of their initial management with each strategy through the course of their lifetime.

Key Strategy Comparison Sets
Each management strategy has a cardiovascular component for management of heart rhythm or rate and a stroke prevention component. The decision analytic model evaluated 5 key sets of alternative strategies for management of atrial fibrillation:

1. *LA Catheter Ablation (LACA) strategies*
    a. Primary LACA as initial therapeutic intervention
    b. Rhythm control with amiodarone followed by LACA (secondary LACA) for AAD failure
    c. Rhythm control with amiodarone

2. *Thorascopic, off-pump (TOP) surgical ablation for patients with AF not otherwise requiring cardiac surgery for structural heart disease*
    As described in earlier sections of this appraisal, the published evidence on the clinical effectiveness of TOP surgical ablation is extremely limited. The best evidence has been obtained via case series of patients who have largely been referred for surgery after multiple failed LACA attempts. However, there is increasing interest in the possibility of using TOP ablation approaches in lieu of initial attempts at LACA for patients who fail AAD therapy. To explore these questions we compared TOP surgical ablation to LACA for patients with AAD failure, but we wish to emphasize that the model findings should be viewed as highly exploratory. We will frame the results as an attempt to evaluate a hypothetical clinical and policy question: how much more effective than LACA in returning patients to NSR would TOP surgical ablation need to be in order to provide additional QALY benefits at an incremental cost-effectiveness ratio of $100,000.
    a. Rhythm control with amiodarone with secondary LACA for AAD failure
    b. Rhythm control with amiodarone with thorascopic, off-pump (TOP) surgical ablation for AAD failure. The TOP procedure is assumed to include left atrial appendage excision for stroke prevention.

3. *Dronedarone vs. amiodarone for rhythm control.* Our study selected rhythm control strategies with amiodarone as our base case for comparison with the catheter ablation and surgical ablation strategies. Our goal was not to explore individual rhythm strategies with sequential choices for AAD. A rhythm control strategy with

dronedarone, a new AAD of the same class as amiodarone, was compared to a rhythm control strategy with amiodarone. The preliminary results were reviewed by our AF ERG who advised us to consider a strategy with dronedarone as an initial AAD with amiodarone for recurrent AF based on the findings from the DIONYSOS study and current clinical practice.

   a. Rhythm control with amiodarone
   b. Rhythm control with dronedarone
   c. Rhythm control with dronedarone as the initial agent with amiodarone as a second agent for persistent or recurrent AF.

4. *Dabigatran or guideline based anti-coagulation (warfarin or aspirin) for stroke prevention*
   a. Dabigatran 110 mg for stroke prevention within an amiodarone rhythm control strategy
   b. Dabigatran 150 mg for stroke prevention within an amiodarone rhythm control strategy
   c. Guideline-based anti-coagulation (warfarin or aspirin) within an amiodarone rhythm control strategy

5. *WATCHMAN device or guideline-based anti-coagulation (warfarin or aspirin) for stroke prevention*
   a. WATCHMAN device within a rate control strategy
   b. Guideline-based anti-coagulation (warfarin or aspirin) within a rate control strategy

Decision Analytic Model Assumptions

Major assumptions of the model as well as relevant sources and justification are presented in the Tables on the following pages. Our model was based on the work of previously published decision analysis models of management of AF and recent well-documented, comprehensive models of radiofrequency ablation for AF that provided a framework for evaluating the effectiveness and cost-effectiveness of LA catheter ablation in reducing stroke risk for the design of future clinical trials (Chan, 2006; Reynolds, 2009). Key assumptions were subject to testing in sensitivity analyses.

Although there are many important assumptions that were made as part of the model, during the creation of the model 4 assumptions stood out as potentially of greatest impact and controversy, especially for the comparisons of LACA strategies with rhythm control on amiodarone. These four assumptions involved (1) the impact of AF on quality of life; (2) the relative decrease (if any) in stroke risk following conversion of AF to NSR, whether by drugs or ablation; (3) whether warfarin anti-coagulation would be discontinued following successful conversion of AF to NSR, particularly by ablation techniques; and (4) the impact of chronic warfarin use on quality of life. Our rationale for base case assumptions is presented on the following pages for the overall disease process and by treatment strategy, but these four assumptions provided the basis for *a priori* alternative scenarios that we decided to run as part of the sensitivity analyses performed for this review.

1. Impact of AF on Quality of Life

Atrial fibrillation is associated with decreased quality of life, particularly for symptomatic AF (Dorian, 2000; Hagens, 2004), but rhythm control has not demonstrated improvement in quality of life relative to rate control (Hagens, 2004; Rienstra, 2006) (2003). Catheter ablation has been shown to improve quality of life in some clinical trials, cohort studies, and meta-analyses (Wazni, 2005) (Oral, 2006b) (Wood, 2000) (Wokhlu, 2010). The impact of AF on quality of life varies widely among AF patients, and so this sensitivity analysis was performed to assess how changes in quality-of-life impact from AF affect the relative effectiveness and cost-effectiveness of various approaches to restore NSR in our model.

2. Stroke Risk Following Conversion of AF to NSR

Three uncontrolled follow-up studies report low risk of stroke following catheter ablation for patients in NSR in whom oral anticoagulation was either stopped at 3-6 months or continued (Oral, 2006a; Themistoclakis, 2010; Nademanee, 2008). The rate of stroke in one study was similar to the rate expected for patients in normal sinus rhythm from the Framingham cohort (Oral, 2006a). A sensitivity analysis was performed by varying the stroke risk for LA catheter ablation patients who were in NSR. This analysis assumed lower risk only for patients in NSR after LA catheter ablation.

3. Warfarin Use Following Conversion of AF to NSR

Warfarin is effective in preventing stroke in AF patients, and current guidelines recommend anticoagulation with aspirin or warfarin based on stroke risk using the $CHADS_2$ risk factors. Some studies (Themistoclakis, 2010; Nademanee, 2008) report discontinuation of oral anticoagulation at 3-6 months for selected patients in NSR independent of $CHADS_2$ score. Our base case assumed patients were managed with guideline-based anticoagulation; in an alternate scenario aspirin alone was used for anticoagulation after LACA independent of the $CHADS_2$ score..

4. Impact of Chronic Warfarin Use on Quality of Life

Warfarin requires frequent monitoring and changes in dose, and has risks of hemorrhage and stroke. Studies of AF patients have reported a wide range of decreased quality of life with warfarin (Gage, 1996). A survey of patients participating in a randomized, controlled trial of warfarin for the prevention of stroke in AF did not find overall differences in health perceptions overall, but did report QoL decreases in patients who had a bleeding episode (Lancaster, 1991). We estimated a modest reduction in quality of life for patients taking warfarin and performed a sensitivity analysis on this estimate.

Key Assumptions – Atrial Fibrillation Disease Course

Assumptions	Rationale & Source
Atrial Fibrillation Disease Course	
• Patients' heart rhythm may be NSR or AF and AF patients in NSR may have recurrent episodes of AF.	ACC/AHA/ESC 2006 Guidelines (Fuster, 2006)
• Decreased quality of life while in AF compared to quality of life in NSR.	(Chan, 2006; Gage, 1995; Gage, 1998; Catherwood, 1999; O'Brien, 2005; Reynolds, 2009) ("Prior CEAs") ERG review
AF and Stroke	
• AF patients have an increased risk of stroke. Stroke risk varies by CHADS2 score for AF patients.	(Beyth, 2002; Singer, 2009; Wang, 2003; Wolf, 1991)
• Stroke risk has decreased in recent years. Assume secular trend in stroke risk using ATRIA study.	ERG review (Singer, 2009)
• Stroke outcomes include no disability, mild disability, moderate/severe disability and death	Prior CEAs
• Patients with stroke have increased risk of subsequent stroke	Prior CEAs
• Stroke risk may be lower for AF patients with NSR induced by LA catheter ablation than in AF patients with recurrent AF after LA catheter ablation. Base case will not assume lower risk for post LA catheter ablation patients with NSR.	(Nademanee, 2008; Oral, 2006a; Themistoclakis, 2010)
• Stroke risk is reduced for patients undergoing thorascopic, off-pump surgical ablation as a consequence of LAA excision.	(Blackshear, 1996)
AF and Stroke Prevention	
• Stroke prevention follows the ACC/AHA/ESC guidelines for management of patients with AF	ACC/AHA/ESC 2006 Guidelines (Fuster, 2006)
• Stroke prevention treatment with warfarin, aspirin, dabigatran, and WATCHMAN procedure reduce risk of stroke	(Hart, 1999; Holmes, 2009; van Walraven, 2002)
Stroke Prevention and Hemorrhage	
• Warfarin, aspirin, and dabigatran are associated with an increased risk of hemorrhage	(Connolly, 2009b; Hart, 1999; van Walraven, 2002)
• Hemorrhage may be intracranial (ICH) or non-intracranial	(Hart, 1999; van Walraven, 2002)
• Intracranial hemorrhage outcomes include no disability, mild disability, moderate/severe disability and death	Prior CEAs
AF and Death	
• AF patients have elevated risk of non-stroke and non-hemorrhagic probability of death	Prior CEAs
• AF patients treated with warfarin or aspirin have reduced risk of cardiovascular, non-stroke death that differs for warfarin and aspirin	Prior CEAs
• AF patients with stroke- or ICH-associated disability have increased risk of death	Prior CEAs
• Patients with mild or moderate/severe disability following stroke or intracranial hemorrhage have increased risk of death that varies by severity of disability	Prior CEAs

Key Assumptions: LA Catheter Ablation Strategy

Assumptions	Rationale & Source
Primary LA Catheter Ablation Strategy	
• Initial LA catheter ablation with PVI or other lines or targets of ablation is highly successful in returning patients to NSR	HRS/EHRA/ECAS Expert Consensus Statement (Calkins, 2007)
• Probability of recurrent AF requiring a repeat LA catheter ablation is constant during the first year and is estimated from the proportion of patients who are in NSR at 1 year.	Assumption. There is a 3-month "blanking period" with high rates of recurrent AF and Aflutter. There are limited data on repeat LA catheter procedures during the blanking period.
• Patients with recurrent AF after initial LA catheter ablation with PVI will have a repeat LA catheter ablation with other lines or targets of ablation, which is successful in returning patients to NSR. Patients may have 2 repeat LA catheter ablation procedures after the initial LA catheter ablation (3 total). Patients with recurrent AF after the second repeat LA catheter ablation are managed with a rate control strategy.	ERG advice
• The rate of recurrent AF following LA catheter ablation after the first year may differ from the 1-year recurrence rate.	ICER systematic review
• LA catheter ablation has potential risks of major complications and minor complications, stroke and death	ICER systematic review HRS/EHRA/ECAS Expert Consensus Statement (Calkins, 2007)
• AADs are stopped after LA catheter ablation.	ERG advice
• Anticoagulation with warfarin is continued for 3 months; then stroke prevention with anticoagulation is managed by guideline based on $CHADS_2$.	Assumption based on HRS/EHRA/ECAS Expert Consensus Statement (Calkins, 2007)

Secondary LA Catheter Ablation	
• Initial treatment with rhythm control strategy with amiodarone	Current practice for many AF patients ACC/AHA/ESC guidelines (Fuster, 2006); while amiodarone is a 2nd-line agent for more patients, it is widely regarded as the most effective AAD at maintaining NSR, and is therefore more likely to be used in highly symptomatic patients ERG advice
• First failure (recurrent AF) is the criterion for LA catheter ablation	ERG advice
• Patient management and outcomes after secondary LA catheter ablation are the same as primary LA catheter ablation strategy	Current practice and published literature describe failure of prior rhythm or rate control management due to symptoms or drug toxicity as criteria for LA catheter ablation

Key Assumptions: Thorascopic, Off-Pump Surgical Ablation Strategy

Assumptions	Rationale & Source
Rhythm Control -> Thorascopic, Off-Pump Surgical Ablation (TOP) Strategy	
• Initial management with rhythm control. First failure (recurrence of AF) is indication for thorascopic, off-pump (TOP) surgical ablation with PVI and other possible ablation targets as well as LA excision or exclusion	ICER systematic review ERG advice
• TOP surgical ablation has risk of major complications, minor complications, stroke, or death.	ICER systematic review
• Patients in NSR have AADs and anticoagulation discontinued within 3 months.	ICER systematic review ERG advice
• Patients have risk of recurrent AF after TOP surgical ablation. The risk is estimated from the probability of NSR at 1 year.	ICER systematic review
• The rate of AF recurrence after 1 year differs from the 1-year recurrence rate	ICER systematic review
• Patients with recurrent AF after the 3-month blanking period are treated with LA catheter ablation with other lines or targets of ablation. Patients may have up to 2 LA catheter ablations after TOP surgical ablation (3 total ablation procedures).	ICER systematic review ERG advice
• Patients with recurrent AF after all ablation attempts are treated with a rate control strategy.	ERG advice
• Stroke risk after TOP surgical ablation is reduced due to LA excision (reduction of 60%)	(Blackshear, 1996)
• Stroke risk after TOP surgical ablation does not vary by NSR or AF	Conservative assumption parallel to that for LACA and in keeping with ACC/AHA/ESC guidelines

Key Assumptions: Rhythm Control Strategies with Dronedarone, Amiodarone, and Dronedarone followed by Amiodarone; Rate Control Strategy with Digoxin/Atenolol

Assumptions	Rationale & Source
Amiodarone	
• Patients managed with rhythm control initially treated with amiodarone	ACC/AHA/ESC 2006 Guidelines (Fuster, 2006); while amiodarone is a 2nd-line agent for many patients, it is widely regarded as the most effective AAD at maintaining NSR, and is therefore more likely to be used in highly symptomatic patients
• Majority of patients on rhythm control initially convert to NSR with pharmacologic or DC electrical cardioversion, but have high rate of recurrent AF	ACC/AHA/ESC 2006 Guidelines (Fuster, 2006)
• Patients treated with amiodarone have a risk of reversible toxicity (thyroid toxicity), permanent toxicity (pulmonary toxicity) or death.	ACC/AHA/ESC 2006 Guidelines (Fuster, 2006)
• Anticoagulation managed according to guidelines based on $CHADS_2$ score.	ACC/AHA/ESC 2006 Guidelines (Fuster, 2006)
Dronedarone	
• Dronedarone may decrease hospitalizations or deaths from cardiovascular causes compared to amiodarone, but this will not be included as a base case assumption.	Comparisons of hospitalization rates across strategies are problematic due to differences in health systems and/or treatment goals.
• Dronedarone may have reduced risk of all-cause mortality compared to amiodarone but this will not be included in the model as a base case assumption.	ICER systematic review Findings on mortality from indirect treatment comparison were not significant. A sensitivity analysis will examine a presumed mortality benefit for dronedarone vs. amiodarone.
• Increased risk of AF recurrence vs. amiodarone	(Le Heuzey, 2010)
• Dronedarone has lower risks of both reversible (thyroid) and permanent (pulmonary) drug toxicity	ICER systematic review (Le Heuzey, 2010)
• Dronedarone may reduce stroke risk, but this will NOT be included in the model.	Based only on post-hoc analysis of ATHENA data (Connolly, 2009a); no primary data available
Dronedarone followed by Amiodarone for AF Recurrence	
• Response of AF to amiodarone after dronedarone failure is midpoint between AF response to amiodarone as first agent and the difference between amiodarone and dronedarone efficacy in DIONYSOS study.	ERG advice; no primary data available (Le Heuzey, 2010)
Rate Control Strategy	
• Many patients with rate control initially convert to NSR with pharmacologic or DC electrical cardioversion.	Prior CEAs
• Patients with rate control have high rate of recurrent AF	(Van Gelder, 2002)
• Patients treated with atenolol or digoxin have a small risk of reversible toxicity	Prior CEAs
• Anticoagulation follows guidelines based on stroke risk	ACC/AHA/ESC 2006 Guidelines (Fuster, 2006)

Key Assumptions: Dabigatran for Stroke Prevention

Assumptions	Rationale & Source
Stroke prevention with dabigatran	
• Dabigatran is effective in lowering risk of stroke, and the effectiveness varies by dose (110 mg vs. 150 mg).	(Connolly, 2009b)
• Dabigatran is assumed to have smaller disutility than warfarin and is assumed to have the same disutility as taking aspirin.	Assumption; based on no need for monitoring or dietary restrictions as with warfarin
• Dabigatran lowers the risk of major hemorrhage and intracranial hemorrhage compared to warfarin, but risk varies by dose.	(Connolly, 2009b)
• There is a potential increased risk of MI with dabigatran, but this is not included as a base case assumption. A sensitivity analysis will examine an increased risk of MI deaths or ischemic heart disease relative to warfarin.	(Connolly, 2009b) ERG advice
• Dabigatran is assumed to reduce (non-stroke and non-ICH) cardiovascular death similar to the general cardiovascular benefits of warfarin. In a sensitivity analysis the impact of loss of cardioprotective effect is modeled as a possible mechanism for the increased risk of MI seen in trial data.	Connolly, 2009b ERG advice

Key Assumptions: WATCHMAN Device for Stroke Prevention

Assumptions	Rationale & Source
WATCHMAN Device for Stroke Prevention	
• Implantation and LAA exclusion will be included in the model	The WATCHMAN trial reported successful implantation in 91% of patients and successful LAA exclusion was documented in 86% of patients (Holmes, 2009)
• WATCHMAN procedure has major complications, minor complications, risk of stroke and death.	(Holmes, 2009)
• Anticoagulation is required during the initial implantation period but is discontinued within 3 months for patients with successful LAA exclusion	(Holmes, 2009)
• WATCHMAN procedure reduces risk of total stroke	(Holmes, 2009); hypothesized based on point estimates from trial

Model Outcome Measures

Clinical Outcomes
The clinical outcomes measures used to evaluate each strategy are total life years from onset of treatment through death, AF life years, total number of procedures (for LACA, TOP, and WATCHMAN procedure), complications (major complications, minor complications, peri-procedure strokes, and peri-procedure deaths), drug toxicity episodes, total strokes, intracranial hemorrhages, death due to the adverse events of AF or AF treatment (strokes, hemorrhages, and drug toxicity) and deaths due to other (non-AF-related) causes. Quality adjusted life years (QALYs) were used a summary measure for clinical outcomes.

Economic Outcomes
The cost measures used to evaluate each strategy are payments for direct medical care estimated from Medicare fee schedules and expressed in 2010 US dollars. The costs were further categorized as procedure costs (LACA, TOP, WATCHMAN), complication costs (including costs of peri-procedural stroke), drug costs (including costs of drug toxicity), and adverse event costs (strokes, intracranial hemorrhage, and major [non-intracranial] hemorrhage costs). Total costs are used as a summary measure for economic outcomes.

Model Inputs
All variable inputs for the model are shown in Tables A, B, and C at the end of this section. Some of the key parameter inputs are described in the paragraphs below.

Patient Population
The patient population variables include patient age, sex, the classification of atrial fibrillation as paroxysmal or as long-standing persistent, and the presence of specific comorbidities (heart failure, hypertension, diabetes mellitus, previous stroke or TIA) which are summarized in the $CHADS_2$ score to predict the probability of stroke.

Probabilities of Clinical Outcomes
Probabilities of clinical outcomes used in the model are shown in Table A. These inputs were derived from the ICER systematic review, peer-reviewed publications, US life tables, US vital statistics, and input from the ERG. The probabilities of death due to AF treatment or death due to adverse outcomes such as stroke or intracranial hemorrhage were obtained from published peer-reviewed studies. US vital statistics and life tables were used to calculate the probabilities of death due other causes. Transition probabilities between disease states are converted to 3-month probabilities for the 3-month cycle time of the Markov model. All rates were converted to probabilities.

Quality of Life
The quality of life variables are listed in Table B. The health related quality of life for patients with moderate-to-severe symptoms of AF was based on a study that included data from a registry of AF patients receiving AADs, patients enrolled in the a drug trial, and patients referred for ablation (Reynolds, 2009) and were below the mean and median values for national quality of life estimates for patients with cardiac dysrhythmias (Sullivan, 2006). The quality of life for the comorbid conditions in the $CHADS_2$ clinical classification for

stroke prediction was obtained from the Medical Expenditure Panel Survey (MEPS), a national survey of the US non-institutionalized population, using the EuroQoL (EQ-5D) measure with US population norms for scoring. The MEPS provides representative age and sex specific quality of life measures for the population. Condition-specific analyses of the independent impact of chronic conditions after adjusting for age, sex, race/ethnicity, education and family income (Sullivan, 2006) were used to estimate the QoL impact of disability due to stroke, intracranial hemorrhage, non-intracranial hemorrhage, and amiodarone pulmonary toxicity. Additional estimates were obtained from previous clinical and economic models of AF management.

Short term morbidity associated with procedures, complications, and adverse events was estimated by using the allowed Medicare Severity (MS)-DRG length of stay in days for the duration of morbidity and assumed a short term disutility of 0.5 during those days.

Costs

The cost variables are provided in Table C. Costs of direct medical services were estimated using the 2010 Medicare fee schedule for payments for hospital care for procedures based on CMS 2010 MS-DRGs with additional payments for physician, anesthesia, and surgeon fees for procedures. The cost estimates for *uncomplicated* major procedures included: (1) LACA = $11,231; (2) TOP surgical ablation = $26,818; (3) WATCHMAN = $11,340 (the device is not yet reimbursed in the US, so the costs for closure of an atrial septal defect were used as a reasonable proxy). Drug costs were estimated from the AHFS Drug monographs and drugstore.com. Annual costs of treatment were estimated at $434 for amiodarone and $3,120 for dronedarone; costs for the former included those of quarterly thyroid function testing. The annual cost of warfarin was estimated to be $440 vs. $4,734 for dabigatran 110 mg or 150 mg; costs for the former included those of monthly INR testing ($6 per test) and quarterly physician office visits ($51 per visit). Because dabigatran is not yet on the U.S. market, costs were estimated based on published prices from a Canadian online pharmacy (CanadaDrugs.com). Costs for chronic disability due to stroke, various complications, adverse events, and toxicities were obtained from previously published studies and adjusted to 2010 US dollars using the Consumer Price Index.

8.4 Results

Detailed summaries of lifetime clinical outcomes for all cardiovascular management and stroke prevention strategies are presented in Appendix D in Tables D1 and D2 respectively. Lifetime costs are presented in Tables D3 and D4 for these strategies. Corresponding results for the 5-year analyses are available in Tables D5-D8.

Comparison Set #1: Amiodarone with Secondary Rate Control for AAD failure, Amiodarone with Secondary LACA for AAD failure, and Primary LACA

This section summarizes the findings for two strategies with LA catheter ablation individually compared to a rhythm control strategy with amiodarone. Note that while a primary rate control strategy is not summarized below due to the analytic focus on patients with moderate-to-severe AF symptoms, findings for this strategy are presented in the Appendix; not surprisingly, the rhythm control strategies evaluated in the model produce more QALYs than a rate control in the symptomatic patient (Table D1).

The primary and secondary LACA strategies resulted in a large reduction in AF time and drug toxicity compared to rhythm control with amiodarone. The primary LACA strategy has a lower risk of drug toxicity than the amiodarone-rate control strategy or the secondary LACA strategy. Both the primary and secondary LACA strategies have a modest increase in the risk of stroke compared to rhythm control in our base case analysis, which did not assume a reduction in stroke after LA catheter ablation for patients in NSR (but does include peri-procedure strokes from ablation). Patients also experienced a small risk of other peri-procedure complications and death.

Amiodarone with Secondary Rate Control vs. Amiodarone with Secondary LACA
Secondary LACA -- LACA following failure of rhythm control on amiodarone--- produced higher total QALYs than a strategy of switching to rate control after recurrence of AF for all three patient cohorts with modest incremental costs. Incremental cost-effectiveness ratios increased with age and comorbidity but were less than $100,000 per QALY for all three cohorts (see Table 1 on the following page as well as Table D10 in the Appendix).

Table 1. Costs and effectiveness of amiodarone with secondary rate control for AAD failure vs. amiodarone with LACA for AAD failure, by patient cohort.

Strategy	Cost	Incremental Cost	Effectiveness (QALYs)	Incremental Effectiveness (QALYs)	ICER ($/QALYs)
60 M Paroxysmal AF					
Amiodarone-> 2° Rate Control	$20,265		11.12		
Amiodarone -> 2° LA Catheter Ablation	$35,038	$14,773	11.51	0.39	$37,808
65 M CHF and Persistent AF					
Amiodarone-> 2° Rate Control	$20,332		8.67		
Amiodarone -> 2° LA Catheter Ablation	$37,522	$17,190	8.90	0.23	$73,947
75 M DM HTN and Persistent AF					
Amiodarone-> 2° Rate Control	$17,759		5.80		
Amiodarone -> 2° LA Catheter Ablation	$32,081	$14,322	5.94	0.15	$96,846

NOTE: Findings rounding to hundredths
QALY: Quality-adjusted life year; ICER: Incremental cost-effectiveness ratio; AF: Atrial fibrillation
CHF: Congestive heart failure; DM: Diabetes mellitus; HTN: Hypertension

Primary LA Catheter Ablation vs. Amiodarone

Primary LACA compared to rhythm control with amiodarone also produced higher QALYs for all patient cohorts at a marginal cost that produced incremental cost-effectiveness ratios less than $100,000 per QALY (see Table 2 below as well as Table D11 in Appendix D).

Table 2. Costs and effectiveness of primary LA catheter ablation vs. rhythm control with amiodarone, by patient cohort.

Strategy	Cost	Incremental Cost	Effectiveness (QALYs)	Incremental Effectiveness (QALYs)	ICER ($/QALYs)
60 M Paroxysmal AF					
Amiodarone -> 2° Rate Control	$20,265		11.12		
Primary LA Catheter Ablation	$34,044	$13,779	11.63	0.51	$26,869
65 M CHF and Persistent AF					
Amiodarone -> 2° Rate Control	$20,332		8.67		
Primary LA Catheter Ablation	$38,245	$17,913	8.96	0.30	$60,804
75 M DM HTN and Persistent AF					
Amiodarone -> 2° Rate Control	$17,759		5.80		
Primary LA Catheter Ablation	$34,410	$16,651	6.00	0.21	$80,615

NOTE: Findings rounded to hundredths
QALY: Quality-adjusted life year; ICER: Incremental cost-effectiveness ratio; AF: Atrial fibrillation
CHF: Congestive heart failure; DM: Diabetes mellitus; HTN: Hypertension

Alternative Assumption Scenarios for Comparison Set #1

As described earlier, during the creation of the model 4 assumptions stood out as potentially of greatest impact and controversy in the comparisons of LACA strategies to rhythm control with amiodarone. These four assumptions involved (1) the impact of AF on quality of life; (2) the relative decrease (if any) in stroke risk following conversion of AF to NSR, whether by drugs or ablation; (3) whether warfarin anticoagulation would be discontinued following successful conversion of AF to NSR, particularly by ablation techniques; and (4) the impact of chronic warfarin use on quality of life. We ran alternative scenarios to examine the potential impact of each of these key assumptions on our model findings, and the results are described below.

Quality of Life in AF

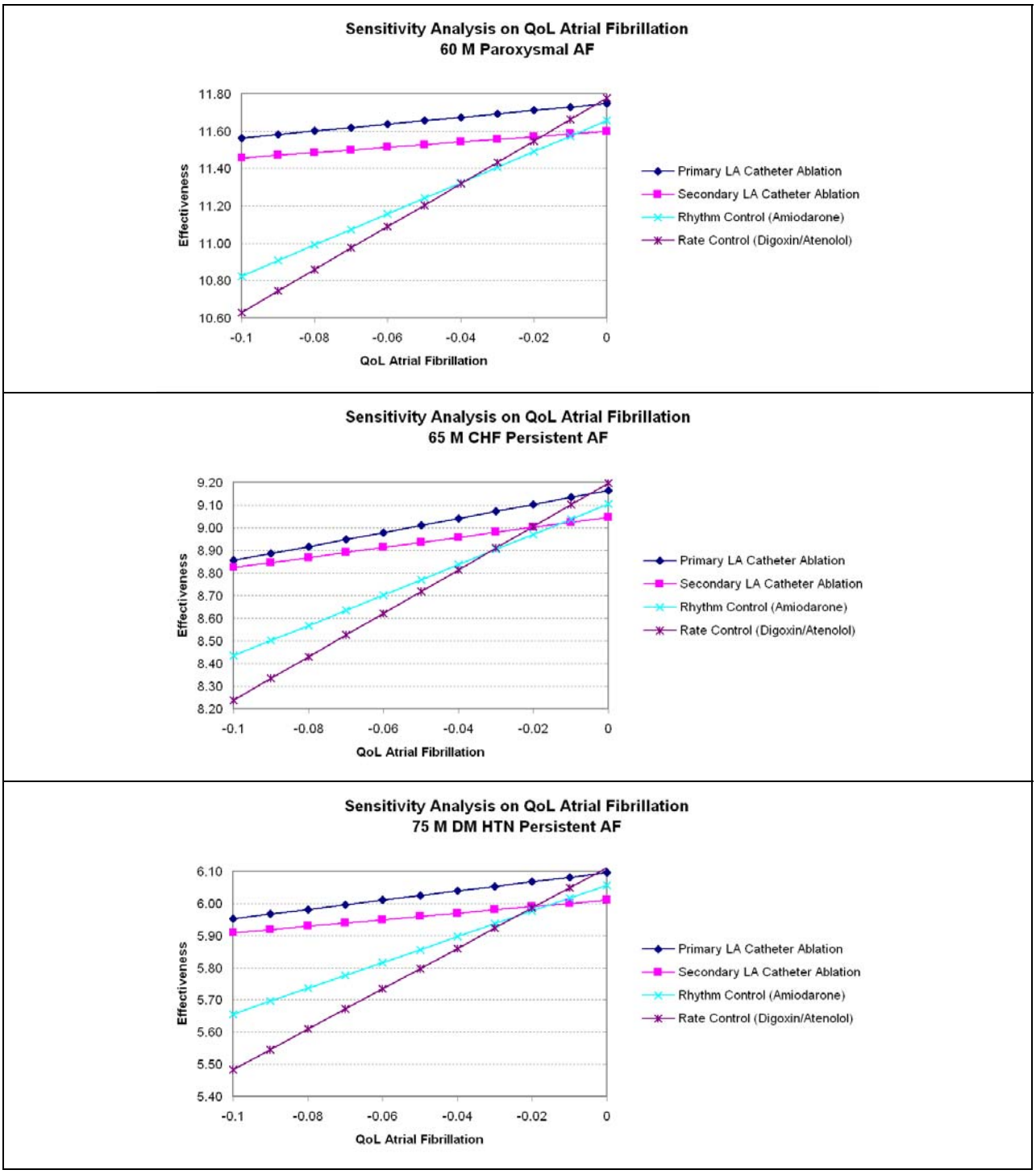
Sensitivity analyses were performed to determine the impact of altering the base case assumption of this model that the negative impact of AF on quality of life among patients with "moderate to highly symptomatic" atrial fibrillation would be represented by a utility decrement of -0.065 QALYs.

As can be seen in Figure 2 on the following page, at one extreme, when there is no decrement in quality of life from AF, all strategies provide nearly identical total QALYs; in fact, a pure rate control strategy is the most effective. However, as the quality of life associated with AF decreases, strategies such as primary and secondary LACA, which produce higher rates of return to normal sinus rhythm, provide relatively greater effectiveness. For the cohort of 65 year-old males with CHF and persistent AF, both primary and secondary LACA strategies start to open up a widening advantage in QALYs over the amiodarone rhythm control strategy as the decrement in quality of life from AF exceeds -0.02. The impact of quality of life in AF and the thresholds are similar for all three patient cohorts. This finding emphasizes that the expected effectiveness of various management strategies for AF will vary notably depending upon the severity of symptoms experienced by an individual patient when in AF.

Stroke Risk following Conversion of AF to NSR

The base case assumed no difference in stroke risk for patients who return to NSR following any of the rhythm control strategies. However, data from recent observational studies suggests very low stroke risk following ablation in certain patients. In analyses that approximated the magnitude of stroke risk reduction (an 85% reduction in stroke risk for patients with a $CHADS_2$ score=1 who were successfully converted to NSR) in a large multicenter cohort study of AF patients in NSR and who had warfarin discontinued (Themistoclakis, 2010), the incremental QALY advantages of secondary and primary LACA strategies are augmented, and the corresponding incremental cost-effectiveness ratios are lower than in the base case findings. For example, in the cohort of 65-year-old men with persistent AF and CHF, there would be an increase in lifetime incremental QALYs associated with the primary and secondary LACA strategies of approximately 0.16 and 0.11 QALYs, respectively, and the incremental cost-effectiveness ratios for these strategies compared to rhythm control with amiodarone are reduced to $30,759 and $42,565.

Figure 2. Sensitivity Analysis: Effectiveness (in QALYs) of primary and secondary LA catheter ablation, rhythm control, and rate control as a function of the decrement in quality of life for patients in AF



Warfarin Use Following Conversion of AF to NSR
The base case assumed that even when patients convert to NSR following LACA, they remain on warfarin or aspirin according to guideline recommendations. Under an alternative assumption that patients converted to NSR have an 85% reduction in the risk of stroke and are all managed on aspirin alone, there would be a small overall reduction in lifetime QALYs of 0.01 to 0.02 for the LACA strategies across all three patient cohorts, reflecting the absence of the protective effect of warfarin in reducing stroke.

Impact of Chronic Warfarin Use on Quality of Life
The base case assumed a decrease in quality of life of -0.013 related to warfarin use based on the burden of frequent blood tests and periodic dosage changes, with the attendant inconvenience and anxiety associated with each (Gage, 1993; Lancaster, 1991). In alternative scenarios, further decreases in the quality of life on chronic warfarin produce no changes in any patient cohort in the ranking by total QALYs of the LACA strategies vs. amiodarone.

Comparison Set #2: Secondary LACA for AAD failure vs. Secondary Thorascopic, Off-Pump (TOP) Surgical Ablation for AAD Failure

Base Case Results
The base case assumed similar probabilities of NSR at 1 year and similar rates of recurrent AF for LACA and TOP surgical ablation. In Table 3 on the following page (Table D12 in Appendix D) we show that for all three patient cohorts -- 60 year-old paroxysmal AF, 65 year-old CHF, and 75 year-old multiple comorbidities – our model found that a secondary TOP ablation strategy was more expensive and produced total lifetime QALYs slightly lower than a secondary LACA strategy.

The TOP surgical ablation strategy results in more major complications, minor complications, and peri-procedural strokes than LACA. The TOP strategy does result in a reduction in total strokes, however, consistent with the benefits conveyed by left atrial appendage excision. The TOP ablation strategy is also associated with a reduction in intracranial hemorrhage due to the fact that the model assumes discontinuation of warfarin three months following the surgery for all patients successfully converted to NSR. It is important to note again that these findings are considered highly speculative given the sparse data available on TOP surgical ablation outcomes and the complete lack of direct head-to-head trials.

Table 3. Costs and effectiveness of thorascopic, off-pump surgical ablation vs. secondary LA catheter ablation, by patient cohort.

Strategy	Cost	Incremental Cost	Effectiveness (QALYs)	Incremental Effectiveness (QALYs)	ICER ($/QALYs)
60 M Paroxysmal AF					
Amiodarone -> 2° LA Catheter Ablation	$35.038		11.51		
Amiodarone -> 2° TOP Surgical Ablation	$43,976	$8,937	11.46	-0.04	Dominated
65 M CHF and Persistent AF					
Amiodarone -> 2° LA Catheter Ablation	$37,522		8.90		
Amiodarone -> 2° TOP Surgical Ablation	$46,163	$8,641	8.89	-0.02	Dominated
75 M DM HTN and Persistent AF					
Amiodarone -> 2° LA Catheter Ablation	$32,081		5.94		
Amiodarone -> 2° TOP Surgical Ablation	$39,744	$7,663	5.83	-0.12	Dominated

NOTE: Findings rounded to hundredths
QALY: Quality-adjusted life year; ICER: Incremental cost-effectiveness ratio; AF: Atrial fibrillation
CHF: Congestive heart failure; DM: Diabetes mellitus; HTN: Hypertension

Threshold Analysis of TOP Surgical Ablation Effectiveness at Conversion to NSR
The base case assumption of the model was that the success rate of conversion from AF to NSR following TOP surgical ablation was identical to that following an initial LACA (82% and 70% for paroxysmal and persistent AF respectively). In an analysis that varied the probability of NSR in persistent AF after TOP surgical ablation from the baseline assumption (70%) up to perfect effectiveness (100%), the TOP ablation strategy produced higher QALYs only when the probability of NSR was higher than 87%. Even at 100% success, however, the marginal QALY advantage of TOP ablation was so small that incremental cost-effectiveness ratios remained well above $100,000.

Threshold Analysis of TOP Surgical Ablation Stroke Risk Reduction due to Excision of LA Appendage
The base case assumed a 60% reduction in stroke risk due to LA appendage excision based studies suggesting that approximately 60 percent to 90 percent of strokes in AF may be due to thrombi that originate in the LA appendage. TOP surgical ablation would have incremental QALYs compared to secondary LACA when the reduction in risk of stroke due to LA appendage excision exceeds 68%.

Comparison Set #3: Dronedarone, Amiodarone, and Dronedarone followed by Amiodarone for Recurrent AF

Base Case Results
As shown in Table 4 on the following page (Table D13 in Appendix D), the dronedarone with second-line amiodarone strategy produced the highest total lifetime QALYs in all three of the patient cohorts. The QALY differences were not large, however. The

dronedarone alone strategy is dominated (albeit by very small QALY margins) by the other strategies despite the lower drug toxicity of dronedarone because it is less effective at keeping patients out of AF, and the cumulative decrement in quality of life in AF outweighs the benefits of reduced drug toxicity (Table D1). The dronedarone followed by amiodarone strategy has the lowest time in AF and correspondingly, the highest QALYs. Although this strategy produces more drug toxicity episodes than rhythm control with amiodarone because patients with recurrent AF on initial dronedarone are subsequently exposed to amiodarone, the dronedarone followed by amiodarone strategy still produces higher QALYs than rhythm control with amiodarone. In an analysis of time free from AF recurrence, drug toxicity, or death , the median time to recurrent AF, drug toxicity, or death was 5.6 years for the dronedarone followed by amiodarone strategy, 3.7 years for amiodarone, and 2.0 years for the dronedarone alone strategy, confirming the summary QALY benefits observed.

Table 4. Costs and effectiveness of amiodarone, dronedarone alone, and dronedarone first with amiodarone for recurrent AF, by patient cohort.

Strategy	Cost	Incremental Cost	Effectiveness (QALYs)	Incremental Effectiveness (QALYs)	ICER ($/QALYs)
60 M Paroxysmal AF					
Amiodarone	$ 20,265		11.12		
Dronedarone alone	$27,749	$7,484	11.02	-0.09	Dominated
Dronedarone -> amiodarone	$30,700	$10,435	11.22	0.10	$103,892
65 M CHF and Persistent AF					
Amiodarone	$20,332		8.67		
Dronedarone alone	$27,829	$7,497	8.59	-0.09	Dominated
Dronedarone -> amiodarone	$30,536	$10,204	8.76	0.09	$110,440
75 M DM HTN and Persistent AF					
Amiodarone	$17,759		5.80		
Dronedarone alone	$24,334	$6,575	5.73	-0.06	Dominated
Dronedarone -> amiodarone	$26,560	$8,801	5.87	0.07	$120,398

Dronedarone strategies compared to amiodarone
NOTE: Findings rounded to hundredths
QALY: Quality-adjusted life year; ICER: Incremental cost-effectiveness ratio; AF: Atrial fibrillation
CHF: Congestive heart failure; DM: Diabetes mellitus; HTN: Hypertension

The amiodarone strategy had higher total QALYs and lower costs than the dronedarone alone strategy for all three patient cohorts. The dronedarone followed by amiodarone strategy had higher costs than the amiodarone strategy, with incremental cost-effectiveness ratios in the $100,000 to $120,000 range for all for three patient scenarios.

It should be noted that the dronedarone followed by amiodarone strategy was created to explore the potential impact of sequential use of these agents in clinical practice, and was not based on any published data. Additionally, our study did not systematically analyze

strategies with sequential use of other AADs, which may also compare favorably with single-drug strategies.

Alternative Assumption Scenarios for Comparison Set #3

Risk of Recurrence of AF and of Drug Toxicity with Dronedarone
Sensitivity analyses on the relative risk of atrial fibrillation recurrence and the relative risk of drug toxicity across the three strategies were performed to determine if varying these parameters across the ranges of the 95% confidence intervals reported in the DIONYSOS trial would be likely to affect the ranking of total QALYs. The QALYs produced by the dronedarone alone strategy remained less than those in the amiodarone strategy over the full range of the sensitivity analyses for all three patient scenarios. Similarly, the QALYs associated with the dronedarone followed by amiodarone strategy remained higher than the amiodarone strategy for all three patient scenarios across the full range of sensitivity analyses.

Risk of All-Cause Mortality with Dronedarone
The ICER systematic review explored through an indirect treatment comparison a potential reduction in all-cause mortality associated with dronedarone compared to amiodarone. Our indirect meta-analysis found a non-significant increased relative risk of all-cause mortality of amiodarone compared to dronedarone of 1.80 (95% CI 0.68, 4.78). We performed a sensitivity analysis using this point estimate. The ICER clinical and economic review assessed the impact of this potential reduced risk of all cause mortality of dronedarone compared to amiodarone in the dronedarone strategy and the dronedarone followed by amiodarone strategy compared to amiodarone strategy. For the 65 year-old cohort with CHF and persistent AF, this alternative assumption would increase the lifetime QALYs of the dronedarone followed by amiodarone strategy and the dronedarone strategy in relation to the amiodarone strategy by approximately 0.3 QALYs. For this cohort, the dronedarone alone strategy would have higher QALYs than the amiodarone strategy if the relative risk of all-cause mortality for amiodarone compared to dronedarone was greater than 1.16.

Comparison Set #4: Dabigatran vs. Guideline-directed Warfarin or Aspirin

Base Case Results
Both the dabigatran and warfarin/aspirin strategies were evaluated as components of a rhythm control strategy using amiodarone. Two separate dabigatran strategies were modeled based on data regarding two potential doses: 110 mg and 150 mg. As can be seen in Table 5 on the following page (Table D14 in Appendix D), both dabigatran strategies were associated with higher QALYs compared to a guideline-directed warfarin/aspirin strategy across all three patient scenarios due to the reduction in strokes and intracranial hemorrhages associated with dabigatran (see Table D2 in Appendix D). The cost for both dabigatran strategies was substantially higher, however, producing incremental cost-effectiveness ratios that were in the $175,000 to $250,000 per QALY range across the three patient cohorts.

Table 5. Costs and effectiveness of dabigatran (110 mg and 150 mg doses) vs. warfarin, by patient cohort.

Strategy	Cost	Incremental Cost	Effectiveness (QALYs)	Incremental Effectiveness (QALYs)	ICER ($/QALYs)
60 M Paroxysmal AF					
Warfarin/Aspirin	$ 20,265		11.12		
Dabigatran 150 mg	$82,780	$62,514	11.42	0.30	$207,760
Dabigatran 110 mg	$83,015	$62,750	11.40	0.29	$220,212
65 M CHF and Persistent AF					
Warfarin/Aspirin	$20,332		8.67		
Dabigatran 150 mg	$72,451	$52,119	8.96	0.29	$178,483
Dabigatran 110 mg	$72,795	$52,463	8.94	0.27	$197,321
75 M DM HTN and Persistent AF					
Warfarin/Aspirin	$17,759		5.80		
Dabigatran 150 mg	$50,944	$33,184	5.97	0.17	$191,757
Dabigatran 110 mg	$51,351	$33,592	5.93	0.14	$244,121

All strategies use amiodarone for rhythm control
NOTE: Findings rounded to hundredths
QALY: Quality-adjusted life year; ICER: Incremental cost-effectiveness ratio; AF: Atrial fibrillation
CHF: Congestive heart failure; DM: Diabetes mellitus; HTN: Hypertension

Alternative Assumption Analyses for Comparison Set #4

Risk of MI with Dabigatran

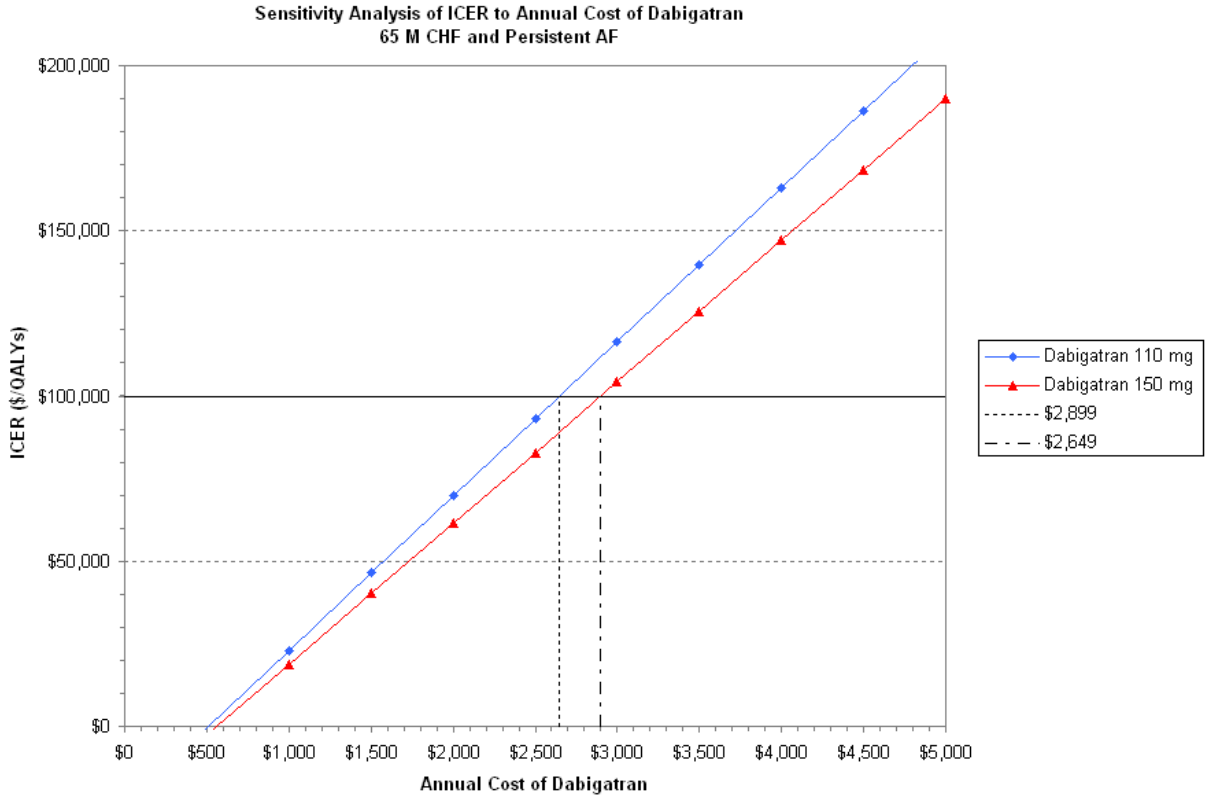
The RE-LY randomized trial of dabigatran compared to warfarin in patients with AF (Connolly, 2009b) found a statistically significant increase in the risk of myocardial infarction (MI) at the 150 mg dose (RR= 1.38, 95% CI=1.00, 1.91, p=0.048). The increased risk for MI with the 110 mg dose neared but did not reach statistical significance (RR=1.35, 95% CI 0.98 to 1.87, p=0.07). Our decision analytic model was not designed to include MI or ischemic heart disease rates as direct parameter inputs. However, we were able to evaluate the impact of a potential increased risk of MI with dabigatran through a potential increase in deaths from MI or an increase in all ischemic heart disease deaths. The impact of an increased risk in ischemic heart disease deaths would be greater because of a higher proportion of deaths are due to ischemic heart disease than are due to MI.

For the cohort of men age 65 with CHF and persistent AF, if the relative risk of *MI* deaths were 1.38 based on the point estimate from the trial, both of the dabigatran strategies would still produce higher total lifetime QALYs than the warfarin strategy over the range of the 95% confidence interval around this risk. If the relative risk of *ischemic heart disease* deaths was 1.38, then the dabigatran 150 mg strategy would have higher QALYs than the warfarin rhythm control strategy if the relative risk were less than 1.78, and the dabigatran 110 mg strategy would have higher QALYs if the relative risk was less than 1.72. These findings emphasize the importance of judgments about the unexpected trial finding of an increased risk of MI with dabigatran.

Relative risk of Hemorrhage, Intracranial Hemorrhage and Stroke
Sensitivity analyses were conducted for the key findings of the RE-LY study about the relative risk of hemorrhage, intracranial hemorrhage, and stroke for the two doses of dabigatran across all patient scenarios. The dabigatran strategies had substantially higher QALYS than the warfarin rhythm control strategy. For all three variables at both doses across all three patient scenarios, the QALYs of the dabigatran strategies were higher than the rhythm control with adjusted dose warfarin strategy, and there were no thresholds with lower QALYs.

Cost of Dabigatran
A sensitivity analysis was conducted to determine the sensitivity of the incremental cost-effectiveness ratios of the dabigatran strategies to the assumed cost of dabigatran. For the cohort of men age 65 with CHF and persistent AF, the incremental cost-effectiveness ratios of the dabigatran 150 mg and dabigatran 110 mg doses would be less than $100,000 per QALY gained if the annual cost of dabigatran was less than $2,899 ($242 per month) and $2,649 ($221 per month), respectively (Figure 3 below), which is approximately 6-7 times the estimated annual cost of warfarin ($440). Incremental cost-effectiveness would drop below $50,000 per QALY gained at an annual cost of approximately 3 times that of warfarin ($1,500).

Figure 3. Sensitivity Analysis of ICER to Cost of Dabigatran



Ischemic Stroke & ICH Outcomes from the ATRIA Study

The base case for the ICER clinical and economic model used probabilities of disability and death from ischemic stroke and intracranial hemorrhage based on data from previous cost-effectiveness analyses (Naglie, 1992; Catherwood, 1999; Disch, 1994; Gage, 1995; OBrien, 2005; Chan, 2006), cohort studies (Dennis, 1993), randomized controlled trials (SPAF III, 1998; Petersen, 1989; Connolly, 1991; Ezekowitz, 1992; SPAF II, 1994), analyses of pooled data from RCTs (Atrial Fibrillation Investigators, 1994) and systematic reviews (Antiplatelet Trialists Collaboration, 1994). While the estimates are derived from many studies and settings, the lower incidence of stroke and changes in the treatment of ischemic stroke and intracranial hemorrhage in AF patients have resulted in different outcomes in recent years. The ATRIA cohort is a large cohort of 13,559 adult patients with nonvalvular AF who were identified from community practices for which ischemic stroke outcomes (Hylek, 2003) and hemorrhagic stroke outcomes have been reported (Fang, 2007). In a alternate analysis using the ATRIA cohort ischemic stroke and intracranial hemorrhage outcomes we found that dabigatran 150 mg strategy incremental QALYS would increase slightly from our base case estimate of 0.29 to 0.31 and the ICER would decrease from $178,483 to $161,457 per QALY. The incremental QALYS of the dabigatran 110mg strategy would increase from our base case estimate of 0.27 to 0.29 and the incremental cost-effectiveness ratio would decrease from $197,321 to $173,857 per QALY.

Comparison Set #5: WATCHMAN Device vs. Guideline-directed Warfarin or Aspirin

Base Case Results

Both of these stroke prevention strategies were assumed to be used within a rate control strategy with atenolol or digoxin. As can be seen in Table 6 on the following page (Table D15 in Appendix D), in all three patient cohorts the WATCHMAN procedure was associated with substantially higher costs and slightly lower effectiveness as measured by lifetime QALYs.

In the greater detail available in Appendix D, Table D2, the results of the model showed that the WATCHMAN procedure reduced numbers of total strokes and intracranial hemorrhages across all three patient cohorts relative to warfarin/aspirin; differences were mitigated with increasing age and comorbidity, however, given the presence of other major stroke risk factors. In addition, the incidence of peri-procedure strokes and major/minor complications further reduced QALYs, leading to the WATCHMAN's domination by warfarin/aspirin for all three patient cohorts.

Table 6. Costs and effectiveness of WATCHMAN vs. warfarin, by patient cohort.

Strategy	Cost	Incremental Cost	Effectiveness (QALYs)	Incremental Effectiveness (QALYs)	ICER ($/QALYs)
60 M Paroxysmal AF					
Warfarin/Aspirin	$15,299		11.03		
WATCHMAN	$23,053	$7,754	11.01	-0.02	Dominated
65 M CHF and Persistent AF					
Warfarin/Aspirin	$15,721		8.57		
WATCHMAN	$22,659	$6,938	8.56	-0.01	Dominated
75 M CHF and Persistent AF					
Warfarin/Aspirin	$13,792		5.70		
WATCHMAN	$20,625	$6,833	5.60	-0.10	Dominated

All strategies use digoxin/atenolol for rate control
NOTE: Findings rounded to hundredths
QALY: Quality-adjusted life year; ICER: Incremental cost-effectiveness ratio; AF: Atrial fibrillation
CHF: Congestive heart failure; DM: Diabetes mellitus; HTN: Hypertension

Alternative Assumption Analyses for Comparison Set #5

Sensitivity analyses were performed to evaluate alternative assumptions for the relative risk of stroke after WATCHMAN when this risk was varied over the 95% confidence interval from the study, as well as whether the probability of successful WATCHMAN procedure implantation, successful left atrial appendage (LAA) exclusion, and the probability of peri-procedure stroke associated with WATCHMAN implantation might produce scenarios in which the WATCHMAN had higher QALYs than warfarin/aspirin. For the cohort of men age 65 with CHF and persistent AF, the WATCHMAN procedure would have higher QALYs if the relative risk of stroke were less than 0.60, a value below the relative risk of 0.71 (95% CI=0.35, 1.64) reported in the trial (Holmes, 2009). The WATCHMAN would have higher QALYS if the probability of peri-procedure stroke were less than 0.6%, also below the 1.1% probability reported in the trial. The WATCHMAN would not have higher QALYS even with 100% LAA exclusion or 100% successful implantation in our analysis. The WATCHMAN procedure strategy would produce higher QALYS for patients for whom the disutility of quality of life on warfarin is less than -0.016, a value only slightly lower than our base case estimate of -0.013.

8.5 Model Results With a Five-Year Horizon

The primary analysis was a lifetime analysis that began with initial treatment of AF and followed patients through to death. Because some stakeholders wish to gain insight into model findings by evaluating shorter time horizons, we performed analyses looking at five-year QALY and cost outcomes. The five-year outcomes represent a shorter time for costs and the benefits to accrue and differ most strikingly from the lifetime analysis when costs of strategies and the benefits in terms of QALYs occur over different time periods. This is most evident in the LACA and TOP surgical ablation strategies where the initial costs and

adverse events associated with procedures occur early in a patient's clinical course over the five years while the benefits of future reduction in disease-related events such as strokes and intracranial hemorrhages after the initial five years are not reflected in the analysis. Full outcome and cost summaries over a five-year time horizon are presented in Appendix D (Tables D5-D8). Cost-effectiveness findings for each comparison set over a five-year time horizon are presented in Tables D16-D22.

The contrast between the lifetime and 5-year analyses for LACA strategies vs. amiodarone is shown below in Table 7, which summarizes the previously reported lifetime analysis from Table 2 and the 5-year analysis for secondary LACA compared to rhythm control. As can be seen, the QALY advantages of LACA strategies seen in the lifetime analysis are greatly reduced in the shorter 5-year time frame. Although LACA strategies remain more effective, their incremental cost-effectiveness ratios are significantly higher, reflecting the fixed up-front costs of the procedures and the diminished marginal effectiveness as measured by QALYs.

Table 7. Lifetime and 5-year costs and effectiveness of secondary LA catheter ablation vs. rhythm control on amiodarone with secondary rate control, by patient cohort.

Strategy	Cost	Incremental Cost	Effectiveness (QALYs)	Incremental Effectiveness (QALYs)	ICER ($/QALYs)
Lifetime Analysis					
60 M Paroxysmal AF					
Amiodarone	$20,265		11.12		
Secondary LA Catheter Ablation	$35,038	$14,773	11.51	0.39	$37,808
65 M CHF and Persistent AF					
Amiodarone	$20,332		8.67		
Secondary LA Catheter Ablation	$37,522	$17,190	8.90	0.23	$73,947
75 M DM HTN and Persistent AF					
Amiodarone	$17,759		5.80		
Secondary LA Catheter Ablation	$32,081	$14,322	5.94	0.15	$96,846
5-Year Analysis					
60 M Paroxysmal AF					
Amiodarone	$6,062		3.63		
Secondary LA Catheter Ablation	$15,337	$9,275	3.68	0.05	$193,272
65 M CHF and Persistent AF					
Amiodarone	$6,464		3.29		
Secondary LA Catheter Ablation	$17,340	$10,876	3.33	0.04	$267,261
75 M DM HTN and Persistent AF					
Amiodarone	$8,710		2.90		
Secondary LA Catheter Ablation	$18,988	$10,278	2.93	0.04	$294,599

NOTE: Findings rounded to hundredths
QALY: Quality-adjusted life year; ICER: Incremental cost-effectiveness ratio; AF: Atrial fibrillation
CHF: Congestive heart failure; DM: Diabetes mellitus; HTN

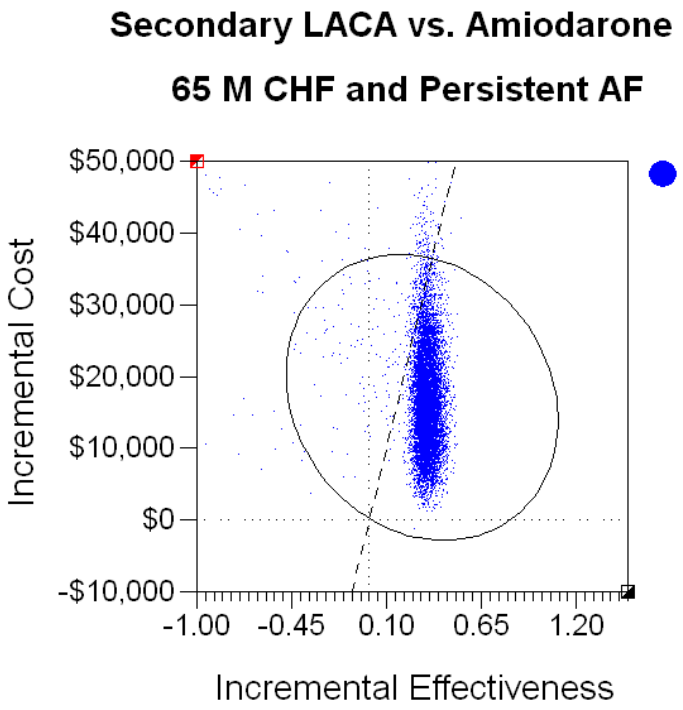
8.6 Probabilistic Sensitivity Analyses

Comparison set #1: Secondary LACA, Primary LACA, and Amiodarone Strategies

Effectiveness and Costs of Primary LACA, Secondary LACA, and Amiodarone Strategies
The secondary LACA strategy produces 8.94 QALYs (95% CI 8.72 to 9.06), and has a cost of $37,772 (95% CI $25,792 to $55,487). The primary LACA strategy produces 8.97 QALYs (95% CI 8.74 to 9.12) and costs $38,482 (95% CI $22,777 to $61,874). The amiodarone strategy produces 8.64 QALYs (95% CI 8.44 to 8.78) and has a cost of $20,632 (95% CI $17,935 to $23,896).

Secondary LACA compared to Amiodarone
The secondary LACA strategy in comparison with the amiodarone strategy has 0.31 incremental QALYs (95% CI 0.17 to 0.44) with an incremental cost of $17,089 (95% CI $5,306 to $34,705) and has an ICER of $46,211 (95% CI $9,420 to $106,205). The mean ICER is similar to the median ICER ($46,211). A scatter plot of the ICERs from the probabilistic sensitivity analysis with the $100,000 per QALY line and the 95% confidence ellipse is shown in Figure 4 below. Overall 98% of the simulations had positive incremental QALYs and 94.6% of the simulations had an ICER below $100,000 per QALY.

Figure 4. Scatterplot of ICERs for secondary LACA compared to amiodarone.

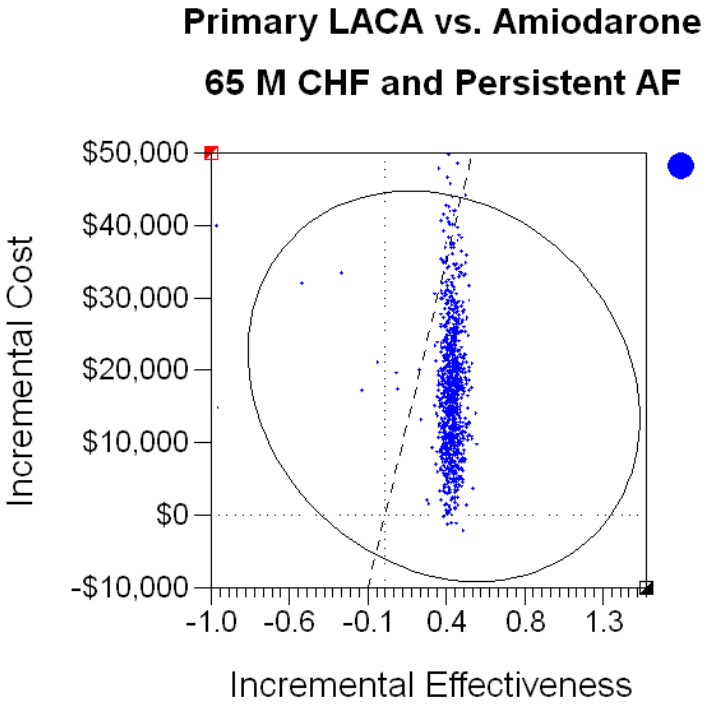


The Figure displays a sample of 1000 ICERs from the 10,000 samples and the axes are restricted to the range encompassing the 95% confidence ellipse. The 95% confidence ellipse includes 95% of the 10,000 ICERs and its shape is influenced by ICERs that are beyond the range in the figure. Dashed line represents willingness to pay at $100,000 per QALY gained.

Primary LACA compared to Amiodarone

The primary LACA strategy in comparison with the amiodarone strategy has 0.34 incremental QALYs (95% CI 0.15 to 0.47) with an incremental cost of $17,849 (95% CI $2,099 to $41,408) and has a mean ICER of $77,991 (95% CI -$806 to $106,186). The mean ICER was larger than the median ICER ($41,411). A scatter plot of the ICERs from the probabilistic sensitivity analysis with the $100,000 per QALY line and the 95% confidence ellipse is shown in Figure 5 below. Overall 97.9% of the simulations had positive incremental QALYs and 95.1% of the simulations had an ICER below $100,000 per QALY.

Figure 5. Scatterplot of ICERs for primary LACA compared to amiodarone.



The Figure displays a sample of 1000 ICERs from the 10,000 samples and the axes are restricted to the range encompassing the 95% confidence ellipse. The 95% confidence ellipse includes 95% of the 10,000 ICERs and its shape is influenced by ICERs that are beyond the range in the figure. Dashed line represents willingness to pay at $100,000 per QALY gained.

Comparison Set #2: TOP Surgical Ablation and Secondary LACA

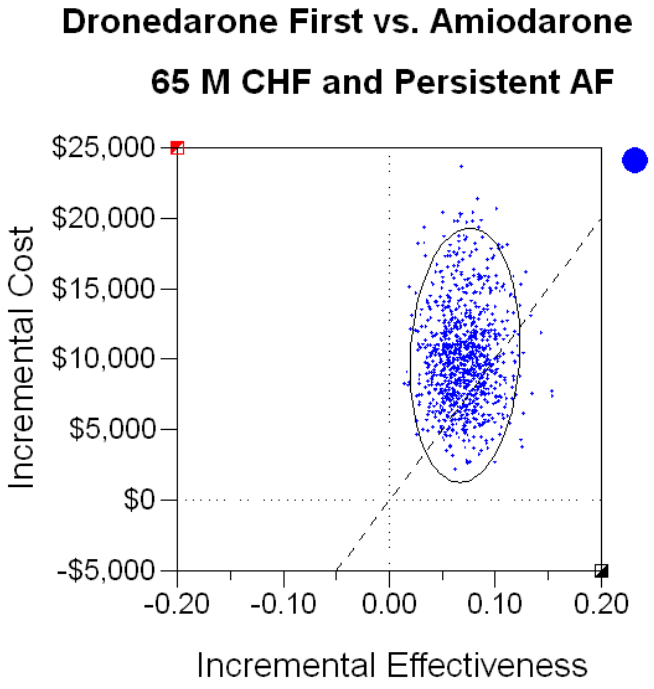
TOP surgical ablation was assumed to have rates of return to sinus rhythm identical to those of secondary LACA, given the low level of evidence currently available for TOP techniques. Probabilistic sensitivity analyses were therefore not conducted, as there are no available data with which to judge any potential differences in effectiveness.

Comparison set #3: Dronedarone First, Dronedarone Only, and Amiodarone

Effectiveness and Costs of Dronedarone First, Dronedarone Only, and Amiodarone Strategies
The dronedarone first strategy produces 8.71 QALYs (95% CI 8.52 to 8.84 QALYs) and has a cost of $30,921. The dronedarone only strategy produces 8.55 QALYs (95% CI 8.33 to 8.72 QALYs) and has a cost of $28,212 (95% CI $21,866 to $36,916). The amiodarone strategy results in 8.64 QALYs (95% CI 8.44 QALYs to 8.78 QALYs) and costs $20,632 (95% CI $17,935 to $23,896).

"Dronedarone First" compared to Amiodarone
The "dronedarone first" strategy in comparison with the amiodarone strategy results in greater incremental QALYs, 0.07 QALYS (95% CI 0.03 to 0.12) and has incremental costs of $10,289 (95 % CI $4,574 to $18,621) and a mean ICER of $157,625 (95% CI $56,572 to $345,583). The mean ICER is higher than the median ICER ($141,751). A scatter plot of the ICERs from the probabilistic sensitivity analysis with the $100,000 per QALY line and the 95% confidence ellipse is shown in Figure 6 below. Overall all of the simulations had positive incremental QALYs, but only 22.1% of the simulations had an ICER below $100,000 per QALY.

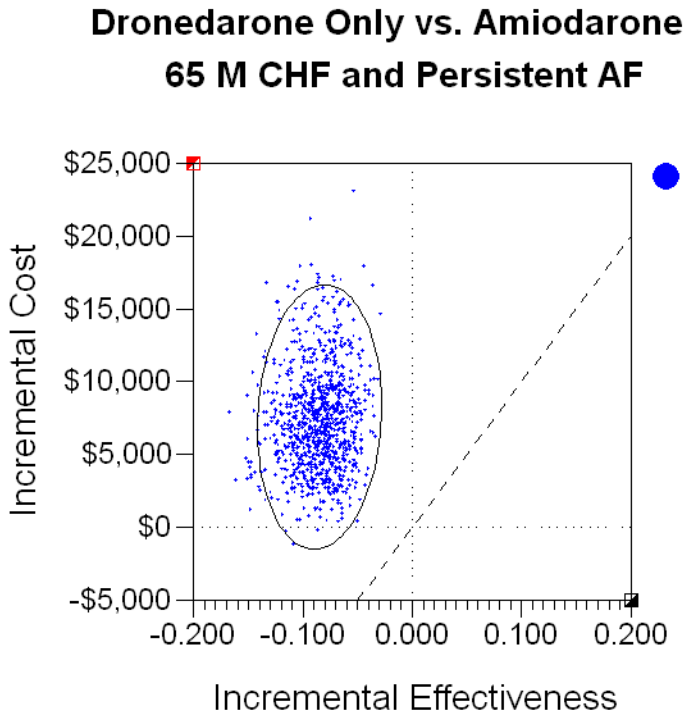
Figure 6. Scatterplot of ICERs for "dronedarone first" compared to amiodarone.



The Figure displays a sample of 1000 ICERs from the 10,000 samples and the axes are restricted to the range encompassing the 95% confidence ellipse. The 95% confidence ellipse includes 95% of the 10,000 ICERs and its shape is influenced by ICERs that are beyond the range in the figure. Dashed line represents willingness to pay at $100,000 per QALY gained.

"Dronedarone Only" compared to Amiodarone
The "dronedarone only" strategy in comparison with the amiodarone strategy results in lower incremental QALYs, -0.08 QALYS (95% CI -0.14 to -0.04) and greater incremental costs of $7,580 (95 % CI $1,754 to $15,953). A scatter plot of the ICERs from the probabilistic sensitivity analysis with the $100,000 per QALY line and the 95% confidence ellipse is shown in Figure 7 below. Overall all of the simulations had negative incremental QALYs, and 99.8% of the simulations had greater costs.

Figure 7. Scatterplot of ICERs for "dronedarone only" compared to amiodarone.



The Figure displays a sample of 1000 ICERs from the 10,000 samples and the axes are restricted to the range encompassing the 95% confidence ellipse. The 95% confidence ellipse includes 95% of the 10,000 ICERs and its shape is influenced by ICERs that are beyond the range in the figure. Dashed line represents willingness to pay at $100,000 per QALY gained.

Comparison set #4: Dabigatran compared Guideline-directed Warfarin or Aspirin

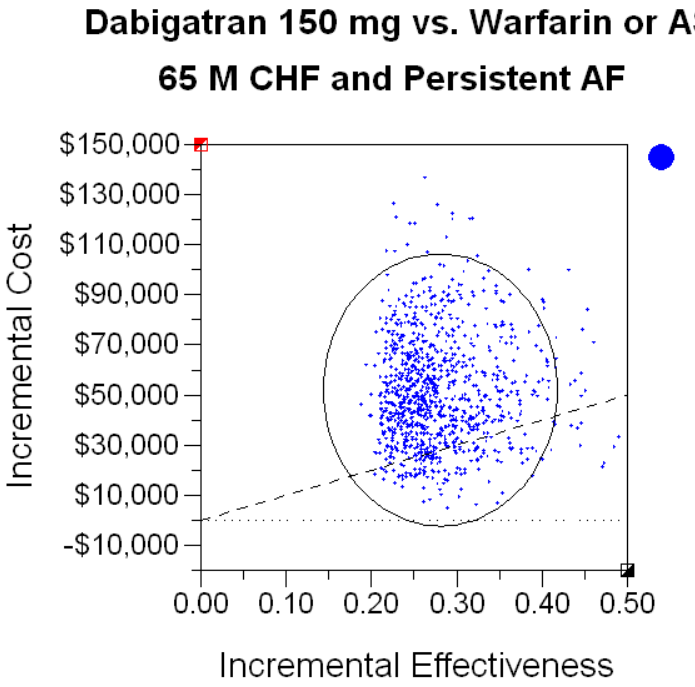
Findings from probabilistic sensitivity analyses were very similar for the 150 mg and 110 mg doses of dabigatran. For simplicity, the probabilistic sensitivity analysis results are presented only for the 150 mg dose.

Effectiveness and Costs of Dabigatran and Guideline-directed Warfarin or Aspirin Strategies
The dabigatran 150 mg strategy results in 8.92 QALYs (95% CI 8.76 to 9.05) and costs $72,600 (95% CI $37,681 to $122,846). The dabigatran 110 mg strategy results in 8.88 QALYs (95% CI 8.73 to 9.02) and costs $73,027 (95% CI $38,306 to $122,859). The dabigatran strategies were compared to guideline-directed warfarin or aspirin within a rhythm control

strategy with amiodarone; as noted above, this strategy results in 8.64 QALYs (95% CI 8.44 to 8.78) and costs $20,632 ($17,935 to $23,896).

The dabigatran 150 mg strategy in comparison with the guideline-directed warfarin or aspirin strategy results in greater incremental QALYS, 0.28 QALYs (95% CI 0.21 to 0.42) and has greater incremental costs $51,968 (95% CI $17,006 to $101,800) and has an ICER of $191,306 (95% CI $57,047 to $401,061). The mean ICER is higher than the median ICER ($177,686). A scatter plot of the ICERs from the probabilistic sensitivity analysis with the $100,000 per QALY line and the 95% confidence ellipse is shown in Figure 8 below. Overall all of the simulations had positive incremental QALYs, but only 13.4% of the simulations had an ICER below $100,000 per QALY.

Figure 8. Scatterplot of ICERs for dabigatran 150 mg compared to guideline-directed warfarin or aspirin.



The Figure displays a sample of 1000 ICERs from the 10,000 samples and the axes are restricted to the range encompassing the 95% confidence ellipse. The 95% confidence ellipse includes 95% of the 10,000 ICERs and its shape is influenced by ICERs that are beyond the range in the figure. Dashed line represents willingness to pay at $100,000 per QALY gained.

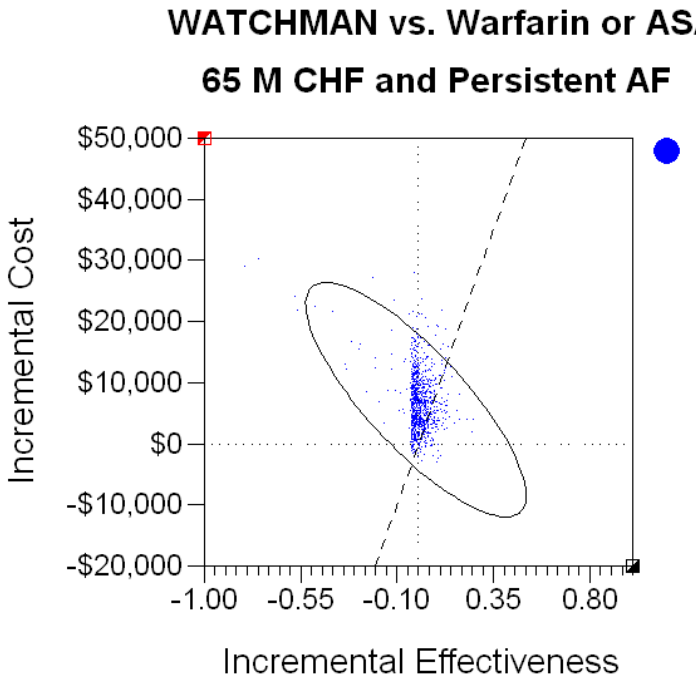
Comparison set #5: WATCHMAN Device compared to guideline-directed Warfarin or Aspirin

Effectiveness and Costs of WATCHMAN Device and Guideline-directed Warfarin or Aspirin Strategies

The WATCHMAN device strategy results in 8.56 QALYS (95% CI 8.27 to 8.77) and costs $23,204 (95% CI $14,903 to $36,678). The WATCHMAN device strategies were compared to guideline-directed warfarin or aspirin within a rate control strategy with digoxin and atenolol, and results in 8.57 QALYs (95% CI 8.33 to 8.77) and costs $16,020 ($13,365 to $19,413).

The WATCHMAN device strategy compared to guideline-directed warfarin or aspirin results in lower incremental QALYs, -0.01 QALYs (95% CI -0.24 to 0.13) and has higher incremental costs of $7,183 (95% CI -$697 to $20,468). A scatter plot of the ICERs from the probabilistic sensitivity analysis with the $100,000 per QALY line and the 95% confidence ellipse is shown in Figure 9 below. Overall 53.9% of the simulations had positive incremental QALYs, and 20.2% of the simulations had an ICER below $100,000 per QALY.

Figure 9. Scatterplot of ICERs for WATCHMAN device compared to guideline-directed warfarin or aspirin.



The Figure displays a sample of 1000 ICERs from the 10,000 samples and the axes are restricted to the range encompassing the 95% confidence ellipse. The 95% confidence ellipse includes 95% of the 10,000 ICERs and its shape is influenced by ICERs that are beyond the range in the figure. Dashed line represents willingness to pay at $100,000 per QALY gained.

8.7 Comparison of Results to Prior Health Economic Evaluations

The recognition of stroke risk associated with AF as well as the introduction of new medications, procedures and devices in cardiovascular management and stroke prevention have quickly been followed by decision analyses and economic models to assist in decisions about AF management. We briefly focus on our findings and highlight selected relevant studies for comparison.

Catheter Ablation Studies

Our study found that secondary LACA was more effective but more costly than rhythm control with amiodarone. A cost-effectiveness analysis of catheter ablation examined the magnitude of stroke reduction that would be required for patients if LACA had an 80% NSR success rate at one year for various cost-effectiveness ratios. The study analysis was stratified based on $CHADS_2$ stroke risk (Chan, 2006). This well-documented study identified risk of stroke in AF, reversion to AF following catheter ablation, discontinuation of warfarin therapy, risk of hemorrhage with warfarin, and the efficacy of rate control as factors affecting incremental cost-effectiveness ratios. A potential limitation of this study was the assumption that normal sinus rhythm post-catheter ablation reduced stroke risk in AF patients to the level seen in the general population without AF.

A more recent CEA study examined radiofrequency ablation (RFA) for AF compared to antiarrhythmic drugs (AAD) for 60 year-old men over a 5-year time frame (Reynolds, 2009). The strategy assumes a trial of AAD for failure of RFA before repeat RFA and modeled response to different AADs. The study estimated higher costs for the RFA and for the AAD strategies than our study but found lower incremental costs than in our 5-year analysis. This study estimated lower overall QALYs for RFA and AADs, but with higher incremental QALYs than in our 5-year analysis. The study estimated an ICER of $51,431 per QALY for RFA compared to AADs, in contrast to our 5-year estimate of $193,272 per QALY and $37,808 in our lifetime analysis.

A similar analysis was recently completed for an assessment of catheter ablation conducted by the Canadian Agency for Drugs and Technologies in Health (CADTH) (Assasi, 2010). This analysis also assumed a 5-year time horizon and secondary use of RFA after AAD failure in a 65 year-old with intermediate stroke risk ($CHADS_2$=2); in contrast to our analysis, however, a reduction in stroke risk as a result of return to NSR was assumed in the base case. The base case ICER was $59,194 per QALY gained; if no difference in stroke risk was assumed, the ICER rose to nearly $90,000 per QALY gained.

ICERs for all of these analyses were sensitive to the time horizon for the analysis, the quality of life with successful ablation (NSR) and while on AADs, and the cost of ablation. Although these models differ from ours in the structure of the strategies analyzed and there are some differences in the parameter estimates, many of these study findings are consistent with ours.

Thorascopic, Off-Pump Surgical Ablation
We evaluated TOP surgical ablation for patients who would not otherwise require cardiac surgery. To our knowledge, no other economic study has addressed TOP surgical ablation for this group of patients. Prior studies have found that surgical ablation at the time of cardiac surgery is cost-effective in comparison to either surgery alone (Quenneville, 2009) or to the classic open "cut and sew" Maze procedure, percutaneous ablation with concomitant cardiac surgery, or drug therapy (Lamotte, 2007).

Dronedarone
Dronedarone has been evaluated as part of a technology assessment process in the U.K. (NICE, 2010). Economic model findings submitted by dronedarone's manufacturer suggested that the drug was more effective at relatively low marginal costs compared to amiodarone or sotalol as first-line agents (NICE, 2009). However, the main driver of incremental cost-effectiveness was a mortality benefit attributed to dronedarone based on the findings of the ATHENA trial (Hohnloser, 2009); when the mortality benefit was removed, dronedarone ceased to be more effective than amiodarone, a comparable finding to our own results.

Dabigatran
Our study found that dabigatran would be substantially more effective than guideline-directed warfarin or aspirin and markedly more expensive, assuming equivalent cardioprotective effects to those of warfarin and aspirin reductions in the risk of stroke and intracranial hemorrhage. Dabigatran has previously been modeled for prophylaxis against venous thromboembolism, but to date there have been no published reports of dabigatran's potential cost-effectiveness in AF.

WATCHMAN
Our study found small net decrease in QALYS for patients receiving the WATCHMAN, with anticipated high associated costs. We were not able to identify any published economic studies of the WATCHMAN device or similar interventions.

TABLE A
Model Probabilities

Description	Value *	Rationale and Source
Procedures		
LA Catheter Ablation (LACA)		
Complications		
Probability of Minor Complication after LACA	0.037	ICER Systematic Review
Probability of Major Complication after LACA	0.013	ICER Systematic Review
Probability of Stroke - LACA Procedure	0.004	ICER Systematic Review
Probability of Death with LACA	0.001	ICER Systematic Review
Stroke & Stroke Outcomes		
Probability of No Disability after Stroke	0.110	Chan, 2006
Probability of Mild Disability with Stroke	0.411	Chan, 2006
Proability of Moderate/Severe Disability with Stroke	0.300	Chan, 2006
Probability of Death due to Stroke	0.179	Chan, 2006
Cardiac Rhythm Outcomes		
Probability of NSR after LACA at 1 year, paroxysmal	0.821	ICER Systematic Review
Probability of NSR after LACA at 1 year, persistent AF	0.698	ICER Systematic Review
Rate of Recurrent AF, per year, paroxysmal AF	0.085	ICER Systematic Review; Wokhlu, 2010 Chan, 2006
Rate of Recurrent AF, per year, persistent AF	0.149	ICER Systematic Review; Wokhlu, 2010 Chan, 2007
RR Stroke After LACA if NSR	1.000	RR=0.15 in alternate scenario: Oral, 2006, Themistoklakis, 2010 & Nademanee, 2008
Thorascopic Off-Pump Surgical Ablation (TOP)		
Complications		
Probability of Minor Complication - MISA	0.082	ICER Systematic Review
Probability of Major Complication - MISA	0.038	ICER Systematic Review
Probability of Stroke after MISA	0.008	ICER Systematic Review
Probability of Death - MISA	0.003	ICER Systematic review
Cardiac rhythm outcomes		
Probability of NSR after TOP at 1 year, paroxysmal AF	0.821	ICER Systematic Review
Probability of NSR after TOP at 1 year, persistent AF	0.698	ICER Systematic Review
Rate of Recurrent AF, per year, paroxysmal AF	0.085	ICER Systematic Review; Wokhlu, 2010 Chan, 2006
Rate of Recurrent AF, per year, persistent AF	0.149	ICER Systematic Review; Wokhlu, 2010 Chan, 2007
Relative Risk Reduction for Stroke after LAA exclusion	0.600	Blackshear, 1996
WATCHMAN		
Procedure Outcomes & Complications		
Probability of Successful Implantation	0.910	Holmes, 2009
Probability of LAA Exclusion	0.860	Holmes, 2009
Probability of Minor Complicaion	0.058	Holmes, 2009
Probability of Major Complication	0.035	Holmes, 2009
Probability of Stroke	0.010	Holmes, 2009
Stroke Outcomes		
Realtive Risk of Stroke after WATCHMAN	0.710	Holmes, 2009
Cardioversion		
Rate control (atenolol & digoxin)		
Probability of NSR (cardioversion)	0.380	Chan, 2006
Rate of digitalis toxicity	0.011	Chan, 2006
Rate of beta blocker toxicity per yr	0.002	Chan, 2006
Rate of recurrent AF	0.097	AFFIRM Substudy Investigatators, 2003; Chan, 2006
Amiodarone		
Probability of death with cardioversion from	0.010	Chan, 2006
Probability of NSR (Cardioversion)	0.833	LeHeuzey, 2010 DIONYSOS Study
Probability of NSR after dronedarone (Cardioversion)	0.777	ICER ERG advice (midpoint amiodarone as iniital agent & dronedarone as initial agent)
Rate of AF recurrence	0.097	AFFIRM Substudy Investigators, 2006
Amiodarone Toxicity		
Rate of reversible amiodarone toxicity	0.104	Le Heuzey, 2010 DIONYSOS Trial
Rate of permanent disability from toxicity	0.011	Chan, 2006
Rate of fatal amiodarone pulmonary toxicity	0.000	Chan, 2006
Dronedarone		
Probability of NSR (cardioversion)	0.731	Le Heuzey, 2010 DIONYSOS Trial
RR of recurrent AF with droneadarone vs amiodarone	1.590	Le Heuzey, 2010 DIONYSOS Trial
RR of drug toxicity with dronedarone vs amiiodarone	0.800	Le Heuzey, 2010 DIONYSOS Trial
Rate of reversible dronedarone toxicity	0.104	Le Heuzey, 2010 DIONYSOS Trial
Rate of permanent disability after toxicity	0.011	Chan, 2006
Rate of death after toxicity	0.000	Chan, 2006

Description	Value *	Rationale and Source
Dabigatran		
RR of hemorrhage dabigatran 110 mg vs Warfain	0.800	Connolly, 2009
RR of hemorrhage dabigatran 150 mg vs Warfarin	0.930	Connolly, 2009
RR of ICH dabigatran 110 mg vs warfarin	0.310	Connolly, 2009
RR of ICH dabigatran 150 vs warfarin	0.400	Connolly, 2009
RR of stroke with dabigatran 110 mg vs warfarin	0.920	Connolly, 2009
RR of stroke dabigatran 150 mg	0.640	Connolly, 2009
RR of MI Death	1.000	Connolly, 2009, ICER ERG (base case 1.0; alternate scenarios 1.3 for MI or ischemic heart disease
ASA		
RRR for Stroke with ASA	0.210	Singer, 2008
RRR Vascular Deaths due to ASA	0.170	Chan, 2006 Catherwood, 1999 Gage, 1995 Pooled data, Arch Intern Med, 1994
Warfarin		
RRR for Stroke with Warfarin	0.680	Singer, 2008
RRR of Vascular Death due to Warfarin	0.330	Chan, 2006 Catherwood, 1999 Gage, 1995 Pooled data, Arch Intern Med, 1994
Hemorrhage & Intracranial Hemorrhage		
Rate of Major Hemorrhage (No Rx)	0.006	Hart, 1999
Rate of Major Hemorrhage with ASA	0.012	Hart, 1999; van Walraven, 2002
Rate of Major Hemorrhage with Warfarin	0.018	Hart, 1999; van Walraven, 2002
Outcomes		
Probability of Mild Disability after ICH	0.670	Chan, 2006
Probability of Moderate Disability after ICH	0.170	Chan, 2006
Probability of Death after ICH	0.200	Chan, 2006
Strokes		
Incidence		
Annual incidence rate	0.019	(CHADS2=0) Rates vary by CHADS2 score. Gage, 2001
RR Stroke, Secuar Trend	0.315	Reduced risk of stroke (secular trends in incidence, NRAF vs ATRIA). Singer, 2009; Gage, 2001
Outcomes		
Probability of No Disability after Stroke	0.110	Chan, 2006
Probability of Mild Disability with Stroke	0.411	Chan, 2006
Proability of Moderate/Severe Disability with Stroke	0.300	Chan, 2006
Probability of Death due to Stroke	0.179	Chan, 2006
Prognosis		
RR of Death with Mild Disability	1.300	Chan, 2006
RR Death with Moderate/Severe Disability	2.300	Chan, 2006
RR Reduction in Stroke - Secular Trends	0.315	Singer, 2009 and Gage, 2001

* Note: Valyues are probabilites, unless othewise

TABLE B
Model Cost Estimates

Description	Value	Rationale and Source
Procedures and Complications		
Cardioversion	$2,823	MS-DRG 312 Chest Pain
LA Catheter Ablation		
Annual Cost of Disability after LACA	$2,990	Chan, 2006 adjusted to 2010 US$
Cost of LA Catheter Ablation	$11,231	CMS MS-DRG 251 Percutaneous cardiovascular procedure w/o coronary artery stent w/o major comorbidity or complication CPT 93651
Cost of LA Catheter Ablation with Major Complicaiton	$17,024	CMS MS-DRG 250 Percutaneous cardiovascular procedure w/o coronary artery stent w/ major comorbidity or complication
Thorascopic, Off-Pump Surgical Ablation		
TOP surgical ablation	$26,818	MS-DRG 230, CMS 2010 Average National Payment Rates MS-DRG 230 Other cardiovasculr procedure w/o complication or comorbidity CPT 33265
TOP Surgical ablation w/minor complication	$32,270	MS-DRG 229 Other Cardiovascualr procedures w/complication or comorbidity (minor)
TOP surgical ablation with major complication or comorbidity	$46,358	MS-DRG 228 Other cardiovascular procedures with major comorbidity or complication CPT 33265
Annual Cost of disability after TOP	$2,990	Chan, 2006 adjusted to 2010 US$
WATCHMAN		
WATCHMAN implantation procedure	$11,340	MS-DRG 251 Percutaneous Cardiology procedure without cardiac stent w/o major comorbidity or complication
WATCHMAN with comorbidity or complications	$17,133	MS-DRG 250 Percutanus cardilogy procedure w/o stent with comorbidity or complications, assume similar to CPT 93580 transcatheter closure of ASD
Annual Drug Costs		
ASA	$23	AHFS Drug Monographs, 2010 (Pricing from drugstore.com)
Amiodarone 200 mg	$434	AHFS Drug Monographs, 2010 (Pricing from drugstore.com)
Atenolol	$80	AHFS Drug Monographs, 2010 (Pricing from drugstore.com)
Clopidogril	$3,192	AHFS Drug Monographs, 2010 (Pricing from drugstore.com)
Dabigatran	$4,734	AHFS Drug Monographs, 2010 (Pricing from CanadaDrugs.com)
Digoxin	$263	AHFS Drug Monographs, 2010 (Pricing from drugstore.com)
Dronedarone	$3,120	AHFS Drug Monographs, 2010 (Pricing from drugstore.com)
Warfarin	$440	AHFS Drug Monographs, 2010 (Pricing from drugstore.com) inludes monthly INR & quarterly physician visit ($50.87)
Dug Toxicity		
Reversible Drug Toxicity Visit	$100	Estimate (ambulatory visit)
Acute Amiodarone Pulmonary Toxicity	$4,250	MS-DRG 198 Interstitial Lung Disease w/o CC or MC
Chronic Amiodarone Pulmonary Toxicity	$4,025	Chan, 2006 adjusted to 2010 US$
Hemorhage & Intracranial Hemorrhage		
Cost of Hemorrhage, Not ICH	$3,750	MS DRG 379
Acute Costs (Hospital Care)		
ICH - No Disability	$4,295	MS-DRG 66 Intracranial Hemorrhage w/ cc/MCC
ICH - Mild Disability	$6,048	MS-DRG 65 Intracranial Hemorrhage with CC
ICH - Moderate/severe disability	$9,536	MS-DRG 64 Intracranial Hemorrhage with MCC
Annual Costs		
Mild disabiity	$2,990	Chan, 2006 adjusted to 2010 US$
Moderate/severe disability	$26,450	Chan, 2006 adjusted to 2010 US$
Stroke		
Acute Costs (Hospital Care)		
Acute Costs of Stroke - No disability	$7,932	MS-DRG 63
Acute costs of Stroke with Mild Disability	$10,075	MS-DRG 62
Acute Costs of Stroke with Moderate/Severe Disability	$15,235	MS-DRG 61
Annual Costs		
Annual Cost of Stroke - Mild Disability	$2,990	Chan, 2006 adjusted to 2010 US$
Annual Costs of Stroke with Moderate/Severre Disability	$26,450	Chan, 2006 adjusted to 2010 US$

TABLE C
Model Utility Estimates

Description	Value	Rationale and Source
Quality of Life		
QoL Well in NSR	0.827	Male, age 60, varies by age & sex, Sullivan, 2006
Atrial Fibrillation		
Atrial Fibrillation	-0.065	Reynolds, 2009; Sullivan, 2006; ICD-9 427 Cardac Dysrhythmias
Comordity		
Heart Failure	-0.0635	Sullivan, 2006
Diabetes Mellitus	-0.0351	Sullivan, 2006
Hypertension	-0.0250	Sullivan, 2007
Previous Stroke or TIA	-0.0524	Sullivan, 2006 Mild stoke = mean disutility for stroke
QoL (Short-Term) Morbidity	0.5000	Chan, 2006
Procedures and Complications		
All procedures		
Quality of Life		
Disutility, procedure, acute	-0.5	Assumption
Cardioversion		
Quality of Life		
QoL Disutility of Cardioversion	-0.016	Chan, 2006
Morbidity, days		
Duration of Cardioversion or Telemetry (days)	3	MS-DRG 312
LA Catheter Ablation (LACA)		
Quality of Life		
Disutility of LA Catheter Ablation	-0.004	Short term morbidity adjustment for LACA
Disutility of LA Catheter Ablation with Major Complication	-0.010	Assumption
Morbidity, days		
Duration of LACA Morbidity	2.7	MS-DRG 251
Duration of LACA Morbiditywith Minor Complication	4.7	Assume 2 additional days of morbidity
Quality of life, permanent disability		
QoL Disability following LACA	-0.049	Estimated from Sullivan, 2006 Cardiac (ICD-9 429 Ill defined Heart disease) use -0.0492
Thorascopic, Off-pump Surgical Ablation (TOP)		
Quality of life		
Disutility for TOP with Minor Complication	-0.008	QoL Hospital Morbidity Day * Days of Morbidity
Disutility for TOP with Minor Complication	-0.012	QoL Hospital Morbidity Day * Days of Morbidity
Disutility of TOP with Major Complication	-0.019	QoL Hospital Morbidity Day * Days of Morbidity
Quality of life, permanent disability		
QoL Disability from TOP	-0.049	Estimated from Sullivan, 2006 if Cardiac (ICD-9 429 Ill defined Heart disease)
Morbidity, days		
Duration of Morbidity - TOP with Major Complication (days)	14.2	MS-DRG 228
Duration of Morbidity - TOP with Minor Complication (days)	8.5	MS-DRG 229
WATCHMAN		
Quality of Life		
Disutility of WATCHMAN Placement	-0.004	QoL Hospital Morbidity Day * Days of Morbidity
Disutility for WATCHMAN with Major Complication	-0.010	QoL Hospital Morbidity Day * Days of Morbidity
Morbidity, days		
WATCHMAN Morbidity (days)	2.7	MS-DRG 251
WATCHMAN with Major Comorbidity (days)	7	MS-DRG 250
Drugs		
Amiodarone Therapy	-0.002	Chan, 2006
ASA	-0.002	Gage, 1996; Chan, 2006
Dabigatran	-0.010	Assumption
Digoxin/Atenolol	-0.002	Assumption
Dronedarone	-0.002	Assume same as amiodarone
Warfarin	-0.013	Gage, 1995; Chan, 2006
Drug Toxicity		
Quality of Life		
Disutility, Drug Toxicity, acute	-0.400	Assumption
Morbidity, Days		
Amiodarone Pulmonary Toxicity	3	Chan, 2006
Quality of life, permanent disability		
Amiodarone Pulmonary Toxicity	-0.043	Sullivan, ICD-9 518 Other lung disease disutiliy adjusted -0.0428
Hemorrhage and Intracranial Hemorrhage		
Quality of life, permanent disability		
QoL ICH with Mild Disability	-0.052	Sullivan, 2006 Mild disutility reflects disutility of CVA ICD-9 436
QoL ICH with Moderate/Severe Disability	-0.305	Sullivan, 2006 Moderate/severe ICH disutility relects 25th percentile for CVA patients ICD-9 436
Morbidity, days		
Duration of Hemorrhage (Non-ICH)	3	Chan, 2006
Duration ICH, No Disability	7	Chan, 2006
Duration of ICH, Mild Disability	10	Chan, 2006
Duration of ICH, Moderate/Severe Disability	14	Chan, 2006
Strokes		
Quality of life, permanent disability		
Stroke Mild Disability	-0.052	Sullivan, 2006 Mild stoke = mean disutility for stroke
Stroke Moderate/Severe Disability	-0.305	Sullivan, 2006 Moderate/severe stroke disutility results in stroke utility at 25th percentile
Morbidity, Days		
Duration of Acute Morbidity of Stroke with No Disability	7	MS-DRG 63
Duration of Morbidity of Stroke with Mild Disability	10	MS-DRG 62
Duration of Acute Morbidity of Stroke with Moderate/Severe Disability	14	MS-DRG 61

9. Recommendations for Future Research

As documented in this appraisal report, despite the high prevalence and importance of atrial fibrillation, syntheses of the available medical literature, even when complemented with decision analytic modeling, reveal many notable areas of uncertainty that cloud judgments of the comparative clinical effectiveness and comparative value of the major management options for atrial fibrillation. In part the need for further research is driven by the impressive and ongoing innovation in pharmaceutical, device, and procedural interventions. Rapid innovation creates difficulties for evidence review because published data may lag clinical developments by a year or more.

Other evidence gaps, however, arise from a variety of structural and historical features of the U.S. health care system. Among these we would highlight the following:

1) The lack of patient input into framing research questions and clinical outcome measures
2) The lack of a requirement of active comparator trials for FDA marketing approval of new pharmaceuticals
3) The low evidence thresholds traditionally required for FDA approval of devices
4) The lack of early collaboration among clinical investigators, manufacturers, payers, and patients to create standards for definitions of patient characteristics and clinical outcome measures that will allow robust comparisons across studies of different types of interventions for the management of atrial fibrillation
5) The lack of inclusion of patient-reported quality of life measures in many studies
6) The lack of inclusion of cost and health-system impact measures in many studies

While our appraisal has provided insight into many specific areas of uncertainty, these high-level issues must be recognized as the most influential barriers to developing an improved body of evidence in the future.

Summary of Evidence Quality

As noted earlier, the most abundant data identified for our review were for catheter ablation (79 studies), followed by AADs (33) and thorascopic, off-pump (TOP) surgical ablation (12). Of the 79 catheter ablation studies, 12 were from a previous AHRQ review of catheter ablation (Ip, 2009) and 67 were newly-abstracted as part of this appraisal. Single RCTs were identified examining dabigatran (Connolly, 2009b) and devices for LAA exclusion (the WATCHMAN; Holmes, 2009). While nearly 40% of the studies identified for this review were RCTs, these varied substantially in study quality, as fewer than half were rated as "good" quality studies. Evidence for TOP surgical ablation was particularly scant; no RCTs were identified, and the remaining case series and cohort studies varied significantly in patient selection, technical approach, outcome measurement, and level of reporting detail.

Research Recommendations by Comparison Set:
Rhythm control with left atrial catheter ablation (LACA) vs. anti-arrhythmic drugs

Important evidence gaps or deficiencies include:

1) No evidence on long-term outcomes of mortality and stroke
2) Limited evidence on rate of recurrence of AF beyond one year
3) Lack of uniformity in definitions of patient clinical variables, measures of AF recurrence, and other key outcomes
4) Limited evidence on under what conditions return to NSR improves quality of life
5) Limited evidence on whether return to NSR with ablation reduces future stroke risk
6) Limited evidence on safety of warfarin discontinuation following successful ablation
7) Limited evidence on how many patients require repeat ablations, and the pattern of these repeated ablations over the longer term
8) Limited evidence with which to weigh risks and benefits of alternative treatment options for patients with particular clinical characteristics, including women, age >65, type of AF, heart failure, and presence of multiple comorbidities

Recurrence of AF is an admittedly weak surrogate outcome measure for more meaningful outcomes such as quality of life, stroke risk, and overall mortality. Nonetheless, measuring recurrence of AF will remain an important outcome measure in clinical research because stroke risk and mortality are outcomes that could only be measured in extremely long-term studies. It is helpful that standards for measurement and reporting of treatment success have been promulgated by the Heart Rhythm Society (HRS) in conjunction with the ACC, AHA, STS, and other cardiology-based medical societies (Calkins, 2007). However, there is substantial variation in how frequently or intensively these standards have been applied, even in recent studies. For example, the HRS guidelines describe an episode of AF as an ECG-documented episode lasting a minimum of 30 seconds, yet episode duration thresholds in recent ablation trials have ranged from 14 seconds to 3 minutes. In addition, as described earlier in this report, treatment success may be a very patient-specific formula, as some patients will consider a substantial reduction in symptoms a success, while others may only tolerate complete elimination of AF.

Data from the ongoing CABANA trial should address some of the uncertainties described above. This study will randomize approximately 3,000 individuals with AF, aged ≥65 years or <65 years with at least one stroke risk factor, to receive left atrial catheter ablation or drug therapy with AADs and/or rate control medications (specific agents used will be left to the discretion of the treating physician). Patients will be followed for 2 years or longer; the primary outcome of interest is the impact of these treatment strategies on all-cause mortality, but one of the strengths of this study is the broad scope of its secondary outcomes, including heart failure mortality; disabling stroke; serious bleeding; and cardiac arrest; cardiovascular hospitalization; arrhythmic mortality; freedom from recurrent AF; medical costs, resource utilization, and cost-effectiveness; quality of life; and adverse events.

Data from CABANA will not be available until at least 2015. Given the evidence gaps and deficiencies listed above, ICER makes the following recommendations for future studies that might provide additional or complementary information to assist in clinical decision-making and policy-setting.

General recommendations:

1. The clinical research community should work with patients, manufacturers, and payers to develop a uniform system of defining patient clinical characteristics at entry into trials so that patient populations can be more easily compared (e.g., prevalence of CHF by NYHA class, number of prior AF episodes within a given timeframe prior to study entry). In addition, uniform definitions should be adopted for the various types of AF, procedural variations of catheter ablation.
2. Similarly, heightened collaborative efforts are needed to standardize the measurement of AF recurrence so that results of different studies can be compared more directly. Although there is no perfect definition, ICER supports universal acceptance of the HRS/ACC/AHA/STS standard of an ECG-documented episode lasting a minimum of 30 seconds. To enhance the usefulness of a standardized definition, ICER recommends that researchers adopt a standard mechanism for monitoring for AF recurrence. Again, there are tradeoffs involved in any single approach, but ICER suggests as a starting point that the research community consider use of a single 24-hour Holter monitor measurement every 3 months.
3. Given the controversy regarding the effects of return to NSR on quality of life, the impact of catheter ablation on quality of life should be evaluated as a standard component of every randomized controlled trial. Evaluation should occur at multiple timepoints during follow-up, and should employ standardized and validated instruments.
4. Studies should be designed with follow-up durations longer than the typical 6 to 12 months observed in the current literature. A minimum of two years is recommended.
5. Efforts should be made to study a broader range of patients, including the very elderly, sicker patients who have been under-represented in previous research.
6. Measurement of the pattern of repeat ablations should be standardized and included in the evidence reported from every study of ablation.

Specific study recommendations:

1. *Multi-center, long-term prospective cohort study.* While disease-based cohorts such as ATRIA and large patient series such as those reported on by Pappone and Wokhlu exist, to the best of our knowledge, none has compared certain outcomes of interest across treatment options over the long term. Such a cohort could be used to assess, for example, patterns of late AF recurrence and repeat ablation and/or retreatment could be compared for patients undergoing catheter vs. surgical ablation. In addition, such a study design would be ideal to examine the impact of cessation of anticoagulation following successful ablation on stroke rates as well as the likelihood of restarting anticoagulation due to AF recurrence or changes in stroke risk. Patient assessments could also be completed at multiple timepoints to measure other important outcomes such as rehospitalization, quality of life, and treatment

complications as well as side effects. Analyses could be stratified by important potential confounding factors such as type of AF, level of stroke risk, etc.

2. *Retrospective database analysis.* Although a retrospective health care claims database would lack the clinical detail to measure many of the outcomes described above, such an analysis would still be important because of the ability to (a) generate sufficient sample sizes quickly for analysis; and (b) evaluate outcomes of interest in a setting reflective of community practice. At a minimum, the study could compare outcomes for all treatment options that would be associated with utilization of health care services, including hospitalization by reason (e.g., stroke, CHF, arrhythmia), cardioversion, repeat procedures, and services rendered for treatment complications or side effects. Component and total costs (AF-related and unrelated) could also be compared between treatment groups. While selection bias is always a concern in quasi-experimental designs such as this, levels of bias could be mitigated through design adjustments such as propensity matching or use of instrumental variables as well as regression-based or stratified analyses.

Research Recommendations by Comparison Set:
Rhythm control with LACA vs. thorascopic, off-pump (TOP) surgical ablation

Thorascopic, off-pump surgical ablation is an emerging surgical technique, as there are many variations in how the procedure is performed, there is no evidence on longer term outcomes, and what evidence is available on intermediate or surrogate outcomes is limited to a few surgical case series. The available evidence suffers from all the shortcomings already detailed for comparisons of catheter ablation and AADs, but in addition there are several additional features of note. The ICER ERG provided patient input that the most important unanswered question for many patients was what to do after one or more "failed" catheter ablations; was it better to continue with further catheter ablations or try a surgical approach.

Key evidence gaps or deficiencies are listed below:

1) No comparative data to guide decisions for patients having failed one or more catheter ablations who are deciding between further catheter ablation and a surgical option
2) No evidence on long-term outcomes of mortality and stroke
3) Limited evidence on rate of recurrence of AF beyond one year
4) Lack of uniformity in definitions of patient clinical variables, measures of AF recurrence, and other key outcomes
5) Limited evidence on under what conditions return to NSR improves quality of life
6) Limited evidence on whether return to NSR with ablation or TOP surgical ablation reduces future stroke risk
7) Limited evidence on safety of warfarin discontinuation following successful ablation or TOP surgical ablation

8) Limited evidence on how many patients require repeat ablations or continued AAD therapy following initial catheter ablation or TOP surgical ablation, and the pattern of these repeated ablations over the longer term
9) Limited evidence with which to weigh risks and benefits of alternative treatment options for patients with particular clinical characteristics, including women, age >65, type of AF, heart failure, and presence of multiple comorbidities

Given these evidence gaps and deficiencies, ICER makes the following recommendations regarding future studies:

General recommendations:

1. The clinical research community should work with patients, manufacturers, and payers to develop a uniform system of defining patient clinical characteristics at entry into trials so that patient populations can be more easily compared. In addition, uniform definitions should be adopted for the various types of AF, procedural variations of catheter ablation and TOP surgical ablation, how AF recurrence is measured, and how the impact of AF on quality of life is assessed
2. Studies should be designed with follow-up durations longer than the typical 6 to 12 months observed in the current literature. A minimum of two years is recommended.
3. Despite published data suggesting better AF monitoring accuracy with implantable devices, these are only feasibly employed in a surgical setting. Studies of surgical and catheter ablation should therefore use a single accepted external monitoring technique -- ICER suggests 24-hour Holter at 3-month intervals -- to enable comparisons of outcomes across techniques.
4. Efforts should be made to study a broader range of patients, including the very elderly, sicker patients who have been under-represented in previous research.
5. Measurement of the pattern of repeat ablations and other ancillary treatments should be standardized and included in the evidence reported from every study of catheter ablation and TOP surgical ablation.
6. Data on the learning curve or standards for practitioner experience should be included as part of all studies of catheter ablation and of TOP surgical ablation

Specific study recommendations:

The evolution of TOP surgical ablation is probably at too early a stage to contemplate an RCT. Needed first is further work to standardize the procedure and more rigorous data on short (and hopefully long) term outcomes. In the near term, however, small single-center RCTs may have an important role in addressing the choice that patients face after an initial "failed" catheter ablation. While surgical ablation has been accepted as a reasonable approach for patients who have failed multiple catheter ablation attempts and are highly symptomatic when in AF, it is likely that greater interest in the future will focus on comparisons of TOP surgical ablation and catheter ablation for patients who require further treatment after an initial failed catheter ablation.

With these considerations in mind, ICER makes the following specific study recommendations:

1. *Multi-center cohort trial of TOP surgical ablation.* A multi-center study that could recruit larger patient populations and provide more rigorous prospective data on short-term outcomes such as adverse events, freedom from AF at 6-12 months, and early retreatment, would be very helpful in guiding clinical practice and policy. Inclusion of organizations such as the Heart Rhythm Society and the International Society of Minimally Invasive Cardiothoracic Surgery in the design phase would ensure that standard definitions and outcome measures would be used.

Randomized controlled trial of TOP surgical ablation vs. catheter ablation for highly symptomatic patients having failed an initial catheter ablation. As mentioned earlier, one or more single-center RCTs comparing TOP surgical ablation and further catheter ablation for these patients would help meet a critical current evidence gap. Single-center RCTs would be unlikely to have enough patients to provide more than early, suggestive evidence, but without randomization the selection bias inherent in surgical case or cohort series would continue to make comparisons between catheter ablation outcomes and surgical ablation outcomes nearly meaningless.

Research Recommendations by Comparison Set:
Rhythm control with amiodarone vs. dronedarone

As noted in our appraisal, even though there have been multiple RCTs of dronedarone vs. placebo and amiodarone vs. placebo, there has been but a single RCT of dronedarone vs. amiodarone, and there are still significant evidence gaps that remain. Some of the issues surrounding definitions of patient variables, measurement of AF, etc., that plague comparisons of catheter ablation to AADs are still germane to the evidence base for amiodarone vs. dronedarone. There are head-to-head data from the single short-term RCT, the DIONYSOS trial, with which to judge the differential impact on all-cause mortality for amiodarone vs. dronedarone. All-cause mortality was 3.4% for amiodarone vs. 1.4% for dronedarone on an annualized basis, but this difference was not statistically significant, and therefore further head-to-head research is needed to address this critical question. Similar questions remain regarding the comparative effectiveness of the two drugs on longer-term outcomes such as stroke rates, cardiovascular death, and quality of life.

The clinical role of dronedarone in comparison to amiodarone is generally viewed as that of a less effective agent that has a better side effect profile, particularly important for patients who may require treatment with AADs for many years. For this reason, the inconsistent measurement of side effects, and the wide variation in study findings, presents particular challenges for comparisons of clinical benefit between the two agents, and is a clear target for future research. In addition, the finding from placebo-controlled trials that dronedarone reduces hospitalization raises interesting questions about its relative benefits on this outcome compared to amiodarone, questions that will require head-to-head studies to evaluate.

Our decision analytic model produced interesting findings showing that a strategy of dronedarone first, followed by amiodarone for patients who have recurrence of AF on dronedarone, may produce greater net health benefits at a reasonable cost compared to either amiodarone or dronedarone as single treatment strategies. Further research is needed to evaluate the experience of patients who begin on amiodarone and are then switched to amiodarone or another AAD.

Key evidence gaps or deficiencies are listed below:

1) Limited evidence on long-term outcomes of mortality and stroke
2) Limited evidence on long-term rates of AF recurrence
3) Lack of direct head-to-head data on impact on hospitalization
4) Limited data on the impact on quality of life. Amiodarone's impact on quality of life has been evaluated in a single RCT; no significant improvement in quality of life was observed relative to rate control. At present, there are no published quality of life data for patients on dronedarone.
5) No evidence on the clinical or economic outcomes of patients who begin on dronedarone and are then switched to another AAD only if AF recurs.
6) Limited evidence with which to weigh risks and benefits of alternative treatment options for patients with particular clinical characteristics, including women, age >65, type of AF, heart failure, and presence of multiple comorbidities

With these considerations in mind, ICER makes the following specific study recommendations:

1. *RCT of dronedarone-first strategy vs. amiodarone-first strategy*. Although some of the specific questions about comparative side effect rates would be best answered in a simple head-to-head RCT, these drugs are used as part of care strategies that often involve switching to another drug if effective reduction in symptoms is not achieved and/or side effects arise. For this reason we suggest an RCT be designed to follow patients on explicit two-stage treatment strategies in order to compare clinical and economic outcomes over a longer term.

2. *Prospective observational analysis*. It is possible that some of the evidence gaps could be addressed with analyses from a prospective patient registry of patients on dronedarone and amiodarone. Despite the lack of randomization, such an analysis would still be important because of the ability to (a) generate sufficient sample sizes quickly for analysis; and (b) evaluate outcomes of interest in a setting reflective of community practice. Bias could be mitigated through design adjustments such as propensity matching or use of instrumental variables as well as regression-based or stratified analyses.

Research Recommendations by Comparison Set:
Stroke prevention with warfarin/aspirin vs. dabigatran

Data on dabigatran is limited to a single RCT and therefore the evidence remains insufficient to make strong conclusions on its comparative effectiveness against guideline-directed warfarin and aspirin. Data from the RE-LY RCT indicate no significant differences in the rate of all-cause mortality between dabigatran at 110 mg or 150 mg and warfarin. However, the difference in mortality between the 150 mg dose of dabigatran was nearly statistically significant (3.6% vs. 4.1% per year for warfarin, p=.051) (Connolly, 2009b); the rate of vascular mortality was significantly lower with higher dose dabigatran (2.3% vs. 2.7% with warfarin, p=.04). No reasons were given as to the possible reasons for reduced mortality with dabigatran.

The most intriguing findings from the RE-LY study were the significant reductions in the risk of hemorrhagic stroke relative to warfarin (0.10-0.12% vs. 0.38% per year, p<.001 for both comparisons). And yet in this study dabigatran was also associated with a higher rate of myocardial infarction, (0.72-0.74% vs. 0.53% for warfarin); this difference was statistically significant for the higher-dose comparison (p=.048). The reason for this adverse finding is not immediately apparent. Although it could be a chance finding, the authors hypothesized that an increased relative risk for MI could be due not to a harmful effect of dabigatran but to warfarin's ability to confer relatively greater protection against ischemic events (Connolly, 2009b). Among the most important questions to address in future research, therefore, is dabigatran's long-term impact on cardiovascular outcomes

Key evidence gaps or deficiencies are listed below:

1) Comparative data from more than a single RCT
2) Limited evidence on long-term outcomes of MI, other cardiovascular outcomes, stroke, and overall mortality
3) Impact of dabigatran on quality of life compared to warfarin
4) Impact of dabigatran on hospitalization and all other economic outcomes

With these considerations in mind, ICER makes the following specific study recommendations:

1. *Additional RCTs of dabigatran vs. guideline-directed warfarin*. Inclusion of broader patient populations, including very elderly and patients with multiple comorbidities would help provide some information on potential subpopulations for whom the relative risks and benefits of dabigatran vary significantly

Research Recommendations by Comparison Set:
Stroke prevention with warfarin/aspirin vs. left atrial appendage (LAA) exclusion devices

The only extant RCT of a left atrial appendage device is the PROTECT-AF trial of the WATCHMAN device (Holmes, 2009). The risk of mortality did not differ in PROTECT-AF, but it was observed that lower numbers of deaths due to stroke as well as cardiovascular or unexplained causes occurred in the WATCHMAN arm. The rate of hemorrhagic stroke in PROTECT-AF also was lower in the WATCHMAN arm relative to warfarin (0.1% vs. 1.6% per year), while the rate of ischemic stroke was higher (2.2% vs. 1.6% respectively); neither comparison was statistically significant. Placement of the WATCHMAN device was associated with a number of serious complications, most commonly serious pericardial effusion (4.8%) and major bleeding (3.5%). In addition, peri-procedure stroke as reported appears to be more common with WATCHMAN implantation (1.1%) than with either catheter ablation or TOP surgical ablation. The question of peri-procedural and longer-term adverse events was important enough to lead the FDA to delay consideration of marketing approval until further studies were performed.

Key evidence gaps or deficiencies are listed below:

1) Comparative data from more than a single RCT
2) Questions about peri-procedural safety and longer-term adverse events
3) No evidence on long-term outcomes of mortality and stroke
4) No evidence on impact on quality of life
5) No evidence on economic outcomes such as hospitalization
6) Limited evidence with which to weigh risks and benefits of alternative treatment options for patients with particular clinical characteristics, including women, age >65, type of AF, heart failure, and presence of multiple comorbidities

With these considerations in mind, ICER makes the following specific study recommendations:

1. *Additional RCTs of left atrial appendage exclusion devices vs. guideline-directed warfarin*. Inclusion of broader patient populations, including very elderly and patients with multiple comorbidities would help provide some information on potential subpopulations for whom the relative risks and benefits of this procedure vary significantly. Standardized approaches to defining training and experience thresholds for practitioners would be useful.

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APPENDIX A

LITERATURE SEARCH STRATEGY

The search strategy for catheter ablation was:

Databases:

- Ovid Medline(R) 1996 to Present with Daily Update
- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations

Search:

1. atrial fibrillation.mp OR exp atrial fibrillation/
2. atrial flutter.mp OR exp atrial flutter/
3. (atrial adj (arrhythmia or tachycardia)).mp
4. OR/1-3
5. limit 4 to (english language AND humans AND yr=2000-2010)
6. limit 5 to (addresses OR bibliography OR biography OR case reports OR comment OR editorial OR lectures OR legal cases OR letter OR news OR newspaper article)
7. 5 NOT 6
8. exp catheter ablation/
9. pulmonary vein$.mp OR exp pulmonary veins/
10. catheter ADJ2 ablat$.mp
11. (transcatheter OR trans-catheter) ADJ2 ablat$.mp
12. OR/8-11
13. 7 AND 12
14. remove duplicates from 13

Database:

- EMBASE

Search:

1. 'heart atrium fibrillation'/exp
2. 'atrial flutter'/exp
3. atrial NEXT/1 (tachycardia OR arrhythmia)
4. #1 OR #2 OR #3
5. #4 AND [humans]/lim AND [english]/lim AND [2000-2010]/py
6. #5 NOT (editorial:it OR letter:it OR note:it)
7. 'catheter ablation'/exp
8. 'pulmonary veins'/exp
9. catheter NEXT/2 ablat*
10. (transcatheter OR trans-catheter) NEXT/2 ablat*
11. #7 OR #8 OR #9 OR #10
12. #6 AND #11 AND [embase]/lim NOT[medline]/lim

Databases:

- EBM Reviews - Cochrane Database of Systematic Reviews 2005 to May 2010
- EBM Reviews - Database of Abstracts of Reviews of Effects 2nd Quarter 2010
- EBM Reviews - Health Technology Assessment 2nd Quarter 2010

- EBM Reviews - Cochrane Central Register of Controlled Trials 2nd Quarter 2010

Search:

1. atrial fibrillation.mp
2. atrial flutter.mp
3. (atrial adj (arrhythmia or tachycardia)).mp.
4. OR/1-3
5. limit 4 to (english language AND humans AND yr=2000-2010)
6. 'catheter ablation'.mp
7. pulmonary vein$.mp
8. catheter ADJ2 ablat$.mp
9. (transcatheter adj2 ablat$).mp
10. (trans-catheter adj2 ablat$).mp
11. OR/6-10
12. 5 AND 11
13. remove duplicates from 12

The search strategy for thorascopic, off-pump surgical ablation was:

Databases:

- Ovid Medline(R) 1996 to Present with Daily Update
- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations

Search:

1. atrial fibrillation.mp OR exp atrial fibrillation/
2. atrial flutter.mp OR exp atrial flutter/
3. (atrial adj (arrhythmia or tachycardia)).mp
4. OR/1-3
5. limit 4 to (english language AND humans AND yr=2000-2010)
6. limit 5 to (addresses OR bibliography OR biography OR case reports OR comment OR editorial OR lectures OR legal cases OR letter OR news OR newspaper article)
7. 5 NOT 6
8. surgical ADJ2 ablation.mp
9. (minimaze OR mini-maze OR mini maze).mp
10. minimally ADJ invasive ADJ surg$.mp OR exp Surgical Procedures, Minimally Invasive/
11. (intraoperative OR intra-operative) ADJ2 ablat$.mp
12. pulmonary vein$.mp OR exp pulmonary veins/
13. OR/8-12
14. (Cox-Maze OR Cox-Maze III OR Maze III).mp
15. 13 NOT 14
16. 7 AND 15
17. remove duplicates from 16

Database:

- EMBASE

Search:

1. 'heart atrium fibrillation'/exp
2. 'atrial flutter'/exp
3. atrial NEXT/1 (tachycardia OR arrhythmia)
4. #1 OR #2 OR #3
5. #4 AND [humans]/lim AND [english]/lim AND [2000-2010]/py
6. #5 NOT (editorial:it OR letter:it OR note:it)
7. surgical NEXT/2 ablation
8. minimaze OR 'mini maze'
9. 'minimally invasive surgery'/exp
10. (intraoperative OR intra-operative) NEXT/2 ablat*
11. #7 OR #8 OR #9 OR #10
12. Cox-Maze OR 'Cox-Maze III' OR 'Maze III'
13. #11 NOT #12
14. #6 AND #13 AND [embase]/lim NOT [medline]/lim

Databases:

- EBM Reviews - Cochrane Database of Systematic Reviews 2005 to May 2010
- EBM Reviews - Database of Abstracts of Reviews of Effects 2nd Quarter 2010
- EBM Reviews - Health Technology Assessment 2nd Quarter 2010
- EBM Reviews - Cochrane Central Register of Controlled Trials 2nd Quarter 2010

Search:

1. atrial fibrillation.mp
2. atrial flutter.mp
3. (atrial adj (arrhythmia or tachycardia)).mp.
4. OR/1-3
5. limit 4 to (english language AND humans AND yr=2000-2010)
6. surgical ADJ2 ablation.mp
7. (minimaze OR mini-maze OR mini maze).mp
8. minimally ADJ invasive ADJ surg$.mp
9. (intraoperative OR intra-operative) ADJ2 ablat$.mp
10. OR/6-9
11. (Cox-Maze OR Cox-Maze III OR Maze III).mp
12. 10 NOT 11
13. 5 AND 12
14. remove duplicates from 13

The search strategy for antiarrhythmic agents was:

Databases:

- Ovid Medline(R) 1996 to Present with Daily Update
- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations

1. atrial fibrillation.mp OR exp atrial fibrillation/
2. atrial flutter.mp OR exp atrial flutter/
3. (atrial adj (arrhythmia or tachycardia)).mp
4. OR/1-3
5. limit 4 to (english language AND humans AND yr=2000-2010)
6. limit 5 to (addresses OR bibliography OR biography OR case reports OR comment OR editorial OR lectures OR legal cases OR letter OR news OR newspaper article)
7. 5 NOT 6
8. amiodarone/ OR amiodarone.mp
9. dofetilide/ OR dofetilide.mp
10. sotalol/ OR sotalol.mp
11. flecainide/ OR flecainide.mp
12. propafenone/ OR propafenone.mp
13. dronedarone/ OR dronedarone.mp
14. OR/8-13
15. 7 AND 14
16. remove duplicates from 15

Database:

- EMBASE

1. 'heart atrium fibrillation'/exp
2. 'atrial flutter'/exp
3. atrial NEXT/1 (tachycardia OR arrhythmia)
4. #1 OR #2 OR #3
5. #4 AND [humans]/lim AND [english]/lim AND [2000-2010]/py
6. #5 NOT (editorial:it OR letter:it OR note:it)
7. amiodarone:dd OR pacerone:tn OR cordarone:tn
8. dofetilide:dd OR tikosyn:tn
9. sotalol:dd OR betapace:tn
10. flecainide:dd OR tambocor:tn
11. propafenone:dd OR rythmol:tn
12. dronedarone:dd OR multaq:tn
13. #7 OR #8 OR #9 OR #10 OR #11 OR #12
14. #6 AND #13 AND [embase]/lim NOT[medline]/lim

Databases:

- EBM Reviews - Cochrane Database of Systematic Reviews 2005 to May 2010
- EBM Reviews - Database of Abstracts of Reviews of Effects 2nd Quarter 2010

- EBM Reviews - Health Technology Assessment 2nd Quarter 2010
- EBM Reviews - Cochrane Central Register of Controlled Trials 2nd Quarter 2010

Search:

1. atrial fibrillation.mp
2. atrial flutter.mp
3. (atrial adj (arrhythmia or tachycardia)).mp.
4. OR/1-3
5. limit 4 to (english language AND humans AND yr=2000-2010)
6. amiodarone.mp
7. dofetilide.mp
8. sotalol.mp
9. flecainide.mp
10. propafenone.mp
11. dronedarone.mp
12. OR/6-11
13. 5 AND 12
14. remove duplicates from 13

APPENDIX B

SYSTEMATIC REVIEW EVIDENCE TABLES

Table B1. Study Characteristics

Author	Year	Study Design	Study N	AF monitoring method	% PAF	% PmAF	% PeAF	Mean Age	% Male	Study specific parameters	
				Catheter ablation						**Ancillary ablation sets, procedures, and/or populations**	**Non-catheter ablation comparators**
Arentz	2003	Case Series	55	ECG, 24-hour Holter monitor	67.3	0	32.7	53	72.7	SVC, tricuspid annulus/IVC isthmus ablation	NA
Arentz	2003	Case Series	47	24-hour Holter monitor	76.6	0	23.4	55	78.1	RA, SVC, LA	NA
Atienza	2009	Case Series	50	ECG	64	0	36	52	74	CPVI + dominant frequency sites	NA
Baman	2009	Case Series	93	ECG, event monitor	56	0	44	60	77	CFAEs in LA and CS	NA
Berkowitsch	2009	Prospective Cohort Study	215	Symptoms report, 7-day Holter ECG	69.3	NR	NR	57	71.6	CFAEs, with RFCA	NA
			105		90.5	NR	NR	58	57.1	CFAEs, with cryoballoon ablation	NA
Bertaglia	2009	Prospective Cohort Study	240	24-hour ECG Holter or a 7-day ECG recording	NR	NR	NR	57	72.3	Segmental PV ostia isolation	NA
			107		NR	NR	NR	54.5	84.1	CPVI guided by 3D electroanatomical mapping	NA
			226		NR	NR	NR	57	77.3	CPVI guided by electroanatomical mapping integrated with MR/CT images of the left atrium	NA
Bunch	2010	Prospective Cohort Study	717	Event monitor	54.1	17.7	28.2	64.1	59.3	WACA, LA linear ablation, CTI; ablation in <80 year olds	NA

Author	Year	Study Design	Study N	AF monitoring method	% PAF	% PmAF	% PeAF	Mean Age	% Male	Study specific parameters	
			35		45.7	20.1	34.3	82.1	45.7	WACA, LA linear ablation, CTI; ablation in ≥80 year olds	NA
Calvo	2010	Prospective Cohort Study	33	24- or 48-hour Holter monitor, ECG	64	NR	NR	52.1	79	LA roof and LA posterior wall, mitral isthmus	NA
			42		74	NR	NR	48.5	93	LA roof and LA posterior wall, mitral isthmus; patients with lone AF who are also athletes	NA
			107		74	NR	NR	47.3	77	LA roof and LA posterior wall, mitral isthmus; patients with lone AF	NA
Cheema	2006	Case Series	64	ECG, 7-day Holter monitor, event monitor	45	25	29	59	73	CPVI	NA
Corrado	2009	RCT	160	ECG, 48-hour Holter monitor	46	28	26	57	73.4	PVI only	NA
			134		46	29	25	55	73.9	SVC	NA
Deisenhofer	2003	Case Series	75	7-day Holter monitor	92	0	8	58	73.3	PVI only	NA
Deisenhofer	2009	RCT	48	7-day Holter ECG	NR	NR	NR	58	69	PVI only	NA
			50		NR	NR	NR	55	82	CFAEs	NA
Della Bella	2009	RCT	145	7-day Holter, 24-hour ECG Holter monitor	73	0	27	56	75.8	CartoMerge™	NA
			145		70	0	30	55	69	Conventional RFCA procedure	NA
Di Biase	2009	Prospective Cohort Study	193	7-day Holter monitor	66	2	28	63	75	Posterior LA wall, CFAEs, mitral annular/LA roof lesions, CS isolation, and RA ablation; manual approach	NA

Author	Year	Study Design	Study N	AF monitoring method	% PAF	% PmAF	% PeAF	Mean Age	% Male	Study specific parameters	
			197		69	3	28	61	74	Posterior left atrial wall, CFAEs, mitral annular/LA roof lesions, CS isolation, and RA ablation; robotic approach	NA
Di Biase	2009	RCT	35	48-hour Holter monitor, event recorder	100	0	0	57	83	PVI only	NA
			34		100	0	0	59.9	76	CFAEs ablation only	NA
			34		100	0	0	58.4	88	CFAEs	NA
Essebag	2005	Case Series	85	24-hour Holter monitor, 2-week event recorder, or continuous mobile outpatient cardiac telemetry	100	0	0	53	66	Mitral isthmus line and/or posterior LA line	NA
Forleo	2009	RCT	35	ECG Holter monitor	45.7	0	0	63.2	57.1	CTI, roofline connecting superior PVs, isthmus between mitral annulus and left inferior PV	NA
			35		37.1	0	0	64.8	65.7	NA	ADT (Oral flecainide, oral propafenone, oral sotalol, or oral amiodarone according to recommended guidelines)
Helms	2009	Case Series	73	Holter or event monitor	66	0	34	56	82	CPVI (Linear ablation - LA roof line plus a line connecting the left inferior PV to the mitral annulus)	NA
Hocini	2005	RCT	45	ECG	100	0	0	55	76	PVI only	NA

Author	Year	Study Design	Study N	AF monitoring method	% PAF	% PmAF	% PeAF	Mean Age	% Male	Study specific parameters	
			45		100	0	0	54	82	Linear ablation joining the 2 superior PVs (roofline) + CTI	NA
Hof	2009	Case Series	146	ECG with event monitoring and reporting of symptoms	55	27	18	57	83	WACA	NA
Hsieh	2005	Prospective Cohort Study	37	ECG	100	0	0	72	92	SVC, non-PV foci, and CTI	NA
			32		100	0	0	73	81	NA	AVN ablation
Hunter	2010	Case series	285	Ambulatory monitor	53	0	47	57	75	WACA; for persistent AF: linear ablation and CFAEs	NA
Husser	2004	Case Series	79	ECG, Holter monitor, or event monitor	68	0	32	55	65	RA isthmus	NA
Jais	2008	RCT	53	ECG, 24-hour Holter monitor	100	0	0	49.7	84.9	Allowed at discretion of investigator; CTI, linear lesions (LA roof), mitral isthmus	NA
			59		100	0	0	52.4	83.1	NA	ADT (Amiodarone, quinidine, disopyramide, flecainide, propafenone, cibenzoline, dofetilide, and sotalol). No specific regimen was mandated
Joshi	2009	Case Series	72	ECG, Holter monitor, event monitor, loop recorder for AF	67	0	33	59.8	69	Linear ablation (mitral isthmus and LA roof)	NA

Author	Year	Study Design	Study N	AF monitoring method	% PAF	% PmAF	% PeAF	Mean Age	% Male	Study specific parameters	
				burden							
Kanagaratnam	2001	Case Series	71	48-hour Holter monitor, loop recorder	0	0	100	57	73.2	PVI only	NA
Khaykin	2009	RCT	30	ECG, 24-hour Holter monitor	83	0	17	54	80	PVI only	NA
			30		77	0	23	57	77	CPVI, CFAE (30%), mitral isthmus and LA roof lines (77%)	NA
Kim	2010	Prospective Cohort Study	49	ECG or 24-hour Holter monitor	NR	NR	NR	52.3	77.6	CPVI with ablation of residual potentials	NA
			53		NR	NR	NR	54.2	83	CPVI alone	NA
Klemm	2006	Case Series	80	Transtelephonic ECG, Holter ECG	NR	NR	NR	59	73	Segmental PVI, RA isthmus ablation	NA
Knecht	2010	Prospective Cohort Study	47	Ambulatory monitor	43.2	0	56.2	58	NR	LA and RA appendages, CFAEs, CTI using 3DATG imaging	NA
			44		32	0	68.1	57	NR	LA and RA appendages, CFAEs, CTI using Carto imaging	NA
Kriatselis	2009	Case series	44	24-hour Holter ECG	63.6	0	36.4	57	NR	PVI only	NA
Kumagai	2005	Prospective Cohort Study	50	ECG, 24-hour Holter monitor	100	0	0	58	80	Circular catheter-guided ablation	NA
			50		100	0	0	57	70	Basket catheter-guided ablation	NA
Kusumoto	2009	Case Series	240	24-hour ambulatory ECG monitor, 30-day event recorder, or 21-day mobile cellular outpatient	58.7	41.3	0	66.4	72.08	Stepwise ablation: after PVI, linear ablation, CFAEs	NA

Author	Year	Study Design	Study N	AF monitoring method	% PAF	% PmAF	% PeAF	Mean Age	% Male	Study specific parameters	
				telemetry							
Lakkireddy	2005	Prospective Cohort Study	86	Rhythm transmitter, 48-hour Holter monitor	59	28	13	60	60	PVI in patients with pacemakers or ICD	NA
			86		61	29	10	60	60	PVI in patients without pacemakers or ICD	NA
Lin	2009	Prospective Cohort Study	30	24-hour Holter monitor and/or cardiac event monitor	0	NR	NR	49	86.7	Linear ablation (roof line and lateral mitral line)	NA
			30		0	NR	NR	49	80	Linear ablation (roof line and lateral mitral line) + CFAEs	NA
Lo	2009	Prospective Cohort Study	49	24-hour Holter monitor and/or cardiac event monitor	0	0	100	55	79.6	Linear ablation, CFAEs; LA diameter of < 45mm	NA
			37		0	0	100	51	89.2	Linear ablation, CFAEs; LA diameter of ≥45mm	NA
Macle	2002	Case Series	136	Telephone interview	90	0	10	52	80	Bidirectional CTI block, linear ablation, lateral mitral isthmus line	NA
Macle	2007	Case Series	64	ECG, Holter monitor	76.6	0	23.4	52	79.7	Posterior LA	NA
Malmborg	2003	Case Series	40	24-hour Holter ECG	80	0	20	56.3	90	PVI only	NA

Author	Year	Study Design	Study N	AF monitoring method	% PAF	% PmAF	% PeAF	Mean Age	% Male	Study specific parameters	
Mangrum	2002	Case Series	64	ECG, Holter monitor; 24-hour Holter monitor or 30-day event recorder	100	0	0	52	71.4	CPVI; additional ablation for AFL or right AFL: tricuspid annulus/IVC linear lesion(s) and ectopy-initiating AF outside the PV	NA
Marrouche	2007	RCT	26	24-hour Holter monitor	61.5	38.5	0	53	73.1	Open-Irrigation	NA
			27		38.5	61.5	0	54	7.8	ICE-Guided Energy Delivery with a Non-Irrigated Catheter	NA
Matsuo	2009	Case series	90	ECG, 24-hour Holter monitor, 24-hour ambulatory monitor	0	0	100	56.5	84.4	CFAEs, linear ablation if AF continued (joining right and left superiorPVs), then if it still continued, a mitral isthmus line	NA
Meissner	2009	Case Series	72	24-hour Holter monitor	65.3	18.1	16.7	60.5	68	PVI only	NA
Mesas	2006	Case Series	47	Transtelephonic ECG, Holter monitor	59.6	0	40.4	56.7	74.5	CPVI	NA
Nademanee	2008	Case Series	674	Holter monitor	40	23	37	67	66.6	CFAE ablation only	NA
Neumann	2008	Prospective Cohort Study	293	7-day Holter monitor	100	0	0	59	59	CPVI in PAF patients	NA
			53		0	0	100	59	77.4	CPVI in PeAF patients	NA
O'Neill	2009	Case Series	153	Holter monitor	NR	NR	46	55.6	85	CFAEs, linear ablation (mitral isthmus and LA roof), RA, SVC, linear ablation (CTI)	NA

Author	Year	Study Design	Study N	AF monitoring method	% PAF	% PmAF	% PeAF	Mean Age	% Male	Study specific parameters	
Oral	2006	Case Series	755	Event monitors and/or serial ECGs and 24-hour Holter monitor	64.9	35.1	0	55	76.4	LA RFCA performed in 29% of patients; CPVI in 71% of patients	NA
Oral	2006	RCT	77	Event monitor	0	0	100	55	87	CPVI	NA
			69		0	0	100	58	89.9	NA	Amiodarone/cardioversion
Pappone	2001	Case Series	251	Holter monitor	71.3	0	28.7	NR	NR	CPVI	NA
Pappone	2003	Prospective Cohort Study	589	ECG and 24-hour Holter monitor	69	0	31	65	58	CPVI	NA
			582		71	0	29	65	59	NA	ADT (Amiodarone, propafenone, flecainide, sotalol, quinidine, disopyramide)
Pappone	2006	RCT	99	ECG, 24-hour Holter monitor, event monitor	100	0	0	55	69.7	CPVI	NA
			99		100	0	0	57	64.6	NA	ADT (Amiodarone, flecainide, or sotalol, either as single drugs or in combination at the maximum tolerable doses)
Patel	2010	Prospective Cohort Study	518	Transtelephonic ECG, 48-hour Holter monitor, event monitor	46	0	28	59	0	Posterior wall between PVs, anterior tissue to the right PV along the left septum, SVC, CFAEs; ablation performed in females	NA

Author	Year	Study Design	Study N	AF monitoring method	% PAF	% PmAF	% PeAF	Mean Age	% Male	Study specific parameters	
			2747		55	0	25	56	100	Posterior wall between PVs, anterior tissue to the right PV along the left septum, SVC, CFAEs; ablation performed in males	NA
Pontoppidan	2009	RCT	73	ECG, Holter monitor	52	0	48	56	74	CTI	NA
			76		55	0	45	56	68	PVI only	NA
Rossillo	2008	Retrospective mached cohort study	85	Holter monitor	31.7	17.8	50.5	62	84	SVC	NA
			85		0	0	100	62	84	NA	DC-shock
Saliba	2008	Case Series	40	Holter monitor	72.5	0	27.5	57	NR	SVC	NA
Sawhney	2009	Case Series	71	Event monitor	100	0	0	60	77.5	CPVI and LA linear ablation	NA
Scharf	2009	Case Series	50	7-day ECG	0	0	100	58	NR	PVI only	NA
Shin	2006	Case Series	68	ECG	33	0	67	55.9	93	Non-PV triggers	NA
Siklody	2009	Case Series	30	ECG, 24-hour Holter monitor	73.3	NR	NR	57.7	84	PVI only	NA
Stabile	2006	RCT	68	Transtelephonic ECG recorder, standard ECG, Holter monitor	61.8	0	38.2	62.2	54.4	CPVI with CTI line	NA
			69		72.3	0	27.5	62.3	63.8	NA	ADT (Amiodarone, flecainide, propafenone, sotalol, disopyramide; 30% of control group treated with a drug that had previously failed)
Stabile	2009	Prospective Cohort Study	36	ECG or 24-hour ambulatory monitor	NR	NR	NR	60	80.5	LA, CTI using anatomical approach	NA
			61		NR	NR	NR	59.3	78.7	LA, CTI, using integrated approach	NA

Author	Year	Study Design	Study N	AF monitoring method	% PAF	% PmAF	% PeAF	Mean Age	% Male	Study specific parameters	
Steven	2010	Prospective Cohort Study	30	3-day Holter monitor	NR	NR	NR	62	66.6	Posterior LA wall, ipsilateral veins with robotic navigation of catheter	NA
			30		NR	NR	NR	61	46.7	Posterior LA wall, ipsilateral veins using a conventional approach to catheter ablation	NA
Tamboreo	2009	RCT	60	48-hour Holter monitor	62	20	18	52.5	73	Superior PVs were connected by linear lesions along the LA roof	NA
			60		58	20	22	52.9	80	LA posterior wall isolated by adding a second line connecting the inferior aspect of the 2 inferior PVs	NA
Tan	2009	Case Series	99	48-hour Holter monitor	58	0	42	54	81	PVI only	NA
Themistoclakis	2010	Prospective Cohort Study	2692	ECG, Holter monitor, transtelephonic monitor	62	22	16	57	79	Ostial or antral level PVI; linear lesions, ablation of CFAEs, and isolation of the SVC were performed per institutional preference; discontinued with OAT	NA

Author	Year	Study Design	Study N	AF monitoring method	% PAF	% PmAF	% PeAF	Mean Age	% Male	Study specific parameters	
			663		51	22	26	59	70	Ostial or antral level PVI; linear lesions, ablation of CFAEs, and isolation of the SVC were performed per institutional preference; continued with OAT	NA
Tzou	2010	Case series	123	Transtelephonic monitor, ECG	85	NR	NR	54	80	PVI only	NA
Udyavar	2008	Case Series	97	24-hour Holter monitor	84.5	0	14.5	50	77.3	CPVI with PV carina	NA
Van Belle	2008	Case Series	141	Transtelephonic ECG, 24-hour Holter ECG	NR	NR	NR	56	70.9	CPVI; CTI ablation in 7 patients with isthmus flutter	NA
Wazni	2005	RCT	33	Loop-event recorder; 24-hour Holter monitor	97	0	3	53	NR	PVI only	NA
			37		95	0	5	54	NR	NA	ADT (Flecainide, propafenone, or sotalol.)
Wazni	2009	Case Series	71	Event recorder	43.7	NR	NR	59	NR	SVC, using the Hansen ablation system	NA
Wiesfeld	2004	Case Series	25	24-hour Holter monitor, ambulatory monitor	52	0	48	46	64	LA, RA and respective appendages	NA
Wilber	2010	RCT	106	ECG, transtelephonic ECG, Holter monitor	100	0	0	55.5	68.9	Allowed at discretion of investigator; included left atrial linear lesions, CFAEs and CTI ablation	NA

Author	Year	Study Design	Study N	AF monitoring method	% PAF	% PmAF	% PeAF	Mean Age	% Male	Study specific parameters	
			61		100	0	0	56.1	62	NA	ADT (Previously unused class I or class III (dofetilide, flecainide, propafenone, sotalol, or quinidine; choice of drug at discretion of investigator))
Wokhlu	2010	Case Series	502	Holter monitor	51	35	13	55	82	Some CPVI, other WACA with additional linear lesions along the LA roof and the left inferior isthmus	NA
Wokhlu	2010	Case Series	774	ECG, 24-hour Holter monitor	55	0	34	54	81	Some PVI, some WACA	NA
Yamada	2006	Case Series	55	24-hour Holter and cardiac recordings; event monitor	100	0	0	58	85.5	CPVI	NA
Yamada	2009	Prospective Cohort Study	60	24-hour Holter recordings, event monitor	100	0	0	59	76.7	Segmental PVI with vagal nerve ablation	NA
			60		100	0	0	60	78.3	CPVI with vagal nerve ablation	NA
Yoshida	2009	Case Series	97	24-hour Holter monitor, event monitor	100	0	0	58	76.3	PVI only	NA

Antiarrhythmic agents											
AFFIRM	2003	RCT	106	ECG	NR	NR	NR	67.7	65.1	Amiodarone	200 mg per day
			116		NR	NR	NR	70.1	59.5	Class I	Various
			131		NR	NR	NR	67.9	65.6	Amiodarone	200 mg per day
			125		NR	NR	NR	70.4	63.2	Sotalol	240mg per day

Author	Year	Study Design	Study N	AF monitoring method	% PAF	% PmAF	% PeAF	Mean Age	% Male	Study specific parameters	
			88		NR	NR	NR	70.6	61.4	Sotalol	240mg per day
			95		NR	NR	NR	69.5	62.1	Class I	Various
Aizawa	2010	Case series	381	ECG	100	0	0	65.1	70	ADT	NR
Banchs	2008	Case Series	80	ECG, Holter monitor, or event recorder	33	0	64	64	60	Dofetilide	405 µg BID on creatine clearance
Bellandi	2001	RCT	102	ECG, 24-hour Holter monitor	0	24.9	75.1	50	NR	Propafenone	450 mg per day if body weight was ≤60 kg; 900 mg per day if it was >60 kg
			106		0	24.3	75.7	53	NR	Sotalol	120 mg per day if body weight was ≤60 kg; 240 mg per day if it was >60 kg
			92		0	26.1	73.9	54	NR	Placebo	NR
Carlsson	2003	RCT	100	ECG	NR	NR	NR	65.3	59	ADT	NR
			100		NR	NR	NR	66.2	68	Rate control	NR
Channer	2004	RCT	62	ECG	NR	NR	NR	65	73	Amiodarone - short-term	400mg BID, then 200mg per day for 44 weeks
			63		NR	NR	NR	66	77	Amiodarone - long term	400mg BID, then 200mg per day for 52 weeks
			38		NR	NR	NR	68	79	Placebo	NR
Connolly	2009	RCT	2301	NR	NR	0	NR	72	51	Dronedarone	400 mg BID
			2327		NR	0	NR	72	55	Placebo	400 mg BID
Dogan	2004	RCT	51	ECG	0	0	27	60	42	Propafenone	600 mg
			48		0	0	69	62	48	Placebo	NR
Fetsch	2004	RCT	383	Event recorder (Tele-ECG) and had to record and transmit via telephone at least	NR	NR	NR	62	66	Sotalol	160 mg BID
			88		0	100	0	82	71	Placebo	NR

Author	Year	Study Design	Study N	AF monitoring method	% PAF	% PmAF	% PeAF	Mean Age	% Male	Study specific parameters	
				one ECG per day during follow-up; Holter ECG							
Galperin	2001	RCT	47	ECG, Holter ECG	0	100	0	61.63	63.8	Amiodarone	600 mg
			48		0	100	0	65.1	81.3	Placebo	NR
Hohnloser	2000	RCT	127	ECG	0	0	100	60	72	Amiodarone	200mg per day
			125		0	0	100	61	74	Diltiazem	90 mg 2-3x/day
Hohnloser	2009	RCT	2301	ECG, 24 h Holter monitor	NR	0	NR	71.6	50.8	Dronedarone	400 mg BID
			2327		NR	0	NR	71.7	55.4	Placebo	NR
Kilborn	2002	RCT	550	NR	NR	NR	NR	77	64.2	Amiodarone	NR
			14730		NR	NR	NR	79.1	48.7	Placebo	NR
Kochiadakis	2000	RCT	65	24-hour ambulatory ECG	64.6	35.4	0	63.2	52.3	Amiodarone	200mg per day
			61		63.9	36.1	0	62.8	52.5	Sotalol	480 mg BID
			60		66.7	33.3	0	62.8	51.7	Placebo	NR
Kochiadakis	2004	RCT	85	24-hour ambulatory ECG	58.8	0	41.2	63	50.6	Sotalol	480 mg per day
			86		60.5	0	39.5	63	48.8	Propafenone	150 mg 3x/day
			83		59	0	41	62	51.8	Placebo	3 tablets a day
Kochiadakis	2004	RCT	72	24-h ambulatory ECG	59.7	0	40.3	62	51.4	Amiodarone	200 mg per day
			74		66.2	0	33.8	64	47.3	Propafenone	150 mg per day
Kuhlkamp	2000	RCT	197	ECG	NR	NR	NR	61	71.1	Metoprolol	200 mg per day
			197		NR	NR	NR	59.9	69.5	Placebo	NR
Le Heuzey	2009	RCT	249	ECG	4.4	2	61.8	64.4	70.7	Dronedarone	400mg BID
			255		4.3	3.9	63.9	63.7	71.4	Amiodarone	200mg per day
Li	2004	Prospective Cohor Study	50	NR	0	0	100	69.4	70	ADT	Various
			100		0	0	0	71.3	64	Rate control	Various
Ogawa	2009	RCT	419	ECG	100	0	0	64.9	69	ADT	Various
			404		100	0	0	64.5	69.6	Rate control	Various
Opolski	2004	RCT	104	ECG Holter recordings	0	0	100	60.4	68.3	ADT	Various
			101		0	0	100	61.4	62.4	Rate control	Various
Patten	2004	RCT	264	Trans-telephonic ECG	100	0	0	59.6	65.1	Sotalol	320 mg
			251		100	0	0	60	65.4	Placebo	NR

Author	Year	Study Design	Study N	AF monitoring method	% PAF	% PmAF	% PeAF	Mean Age	% Male	Study specific parameters	
Plewan	2001	RCT	64	ECG, Holter ECG	0	0	100	59	59.4	Sotalol	80mg BID
			64		0	0	100	59	55.6	Bisoprolol	5 mg per day
Pritchett	2003	RCT	126	24-hour Holter ECG, transtelephonic ECG	NR	NR	NR	64	60	Propafenone	225 mg per day
			135		NR	NR	NR	63	59	Propafenone	325 mg per day
			136		NR	NR	NR	63	57	Propafenone	425 mg per day
			126		NR	NR	NR	63	60	Placebo	NR
Roy	2000	RCT	201	ECG	49	0	51	65	55	Amiodarone	200 mg per day
			202		43	0	57	65	56	Sotalol/Propafenone	Various
Roy	2008	RCT	682	ECG	33	0	67	66	78	ADT	Various
			694		30	0	70	67	85	Rate control	Various
Singh	2000	RCT	82	ECG	NR	NR	NR	66	82.9	Dofetilide	125 µg/BID
			82		NR	NR	NR	68	84.2	Dofetilide	250 µg/BID
			77		NR	NR	NR	67	81.8	Dofetilide	500 µg/BID
			84		NR	NR	NR	67	86.9	Placebo	NR
Singh	2005	RCT	267	ECG	NR	NR	NR	67.1	99.3	Amiodarone	200 mg per day
			261		NR	NR	NR	66.8	98.5	Sotalol	1600 mg BID
			137		NR	NR	NR	67.7	99.3	Placebo	NR
Singh	2007	Randomized Controlled Trial	828	Transtelephonic ECG monitor, ECG	NR	NR	NR	63.5	69.8	Dronedarone	400 mg BID
			409		NR	NR	NR	62.2	68.5	Placebo	NR
Touboul	2003	RCT	54	Transtelephonic ECG monitor, ECG	NR	NR	NR	64	57	Dronedarone	800mg BID
			54		NR	NR	NR	63	70	Dronedarone	1200mg BID
			43		NR	NR	NR	62	67	Dronedarone	1600mg BID
			48		NR	NR	NR	65	79	Placebo	NR
Tse	2003	Case Series	25	ECG, Holter monitor	NR	NR	NR	65	75	Sotalol	308mg (mean)
van Gelder	2002	RCT	266	ECG	0	0	100	68	64	ADT	Various
			256		0	0	100	68	63	Rate control	Various
Wyse	2002	RCT	2027	NR	NR	NR	NR	69.8	59.4	Rate control	Various
			2033		NR	NR	NR	69.7	62.1	ADT	Various

Thorascopic, off-pump surgical ablation										Ablation Approach	Energy Type
Bagge	2009	Case Series	43	24-hour Holter recording, ECG	65	21	14	58	67.4	Thoracoscopic off-pump epicardial PVI and GP ablation	Bipolar RF
Beyer	2009	Case Series	100	24-hour Holter monitor	39	32	29	65	70	PVI/autonomic denervation, GP stimulation	Bipolar RF
Castella	2010	Case Series	34	24-hour Holter monitor	NR	NR	NR	54	NR	Thoracoscopic PVI	Bipolar RF
Cui	2010	Case Series	81	ECG analysis, and 24- to 48-hour Holter monitor (for patients in SR with ECG)	60.5	0	39.5	57.6	63	Bilateral PV antrum isolation and division of the LOM	Bipolar RF
Edgerton	2009	Case Series	74	ECG, 14- to 21-day auto-triggered event monitor	62.2	0	37.8	NR	NR	Bilateral PV antrum isolation	Bipolar RF
Edgerton	2009	Case Series	114	ECG and 24-hour Holter monitor OR long-term monitor (a 14 to 21-day auto trigger event monitor)	52.6	28.1	19.3	59.5	69.3	PVI/left-sided "Dallas" set	Bipolar RF
Edgerton	2009	Case Series	30	14- to 21-day event monitor	0	0	33.3	58	86.7	Bilateral PVI/GP stimulation/additional ablation post-testing	Bipolar RF
Edgerton	2010	Case Series	52	ECG, 24-hour Holter monitor, 2-3 week event monitor, or interrogation of implanted pacemaker	100	0	0	60.3	67.3	Bilateral, epicardial PVI and partial autonomic denervation	Bipolar RF
Han	2009	Case Series	45	External loop recorder	73	0	27	64	56	Bilateral PVI/GP ablation/LOM ablation	Unipolar RF

Sirak	2008	Case Series	32	ECG	0	0	100		65.6	Totally thoracoscopic PVI, extended linear ablations across critical segments of atrial substrate	Bipolar RF
Wolf	2005	Case Series	27	ECG or telemetry monitor	66.7	18.5	14.8	57.2	81.5	Bilateral PVI	Bipolar RF
Yilmaz	2010	Case Series	30	ECG and 24-hour Holter monitor	63	10	27	55.6	77	Bilateral PVI/GP ablation	Bipolar RF
				Stroke prevention						**Intervention**	**Dose**
Connolly	2009	RCT	6015	NA	32.1	35.4	32.4	71.4	64.3	Dabigatran	110 mg
			6076		32.6	36	31.4	71.5	63.2	Dabigatran	150 mg
			6022		33.8	34.1	32	71.6	63.3	Warfarin	Adjusted-dose
Holmes	2009	RCT	463	NA	43.2	34.6	21	71.7	70.4	Watchman	NA
			244		40.6	38.1	20.5	72.7	70.1	Warfarin	Adjusted-dose

ADT, antiarrhythmic drug therapy; AF, atrial fibrillation; AFL, atrial flutter; AVN, atrioventricular junction ; BID, twice per day; CFAEs, complex fractionated atrial electrograms; CPVI, circumferential pulmonary vein isolation; CS, coronary sinus; CT, computed tomography; CTI, cavotricuspid isthmus; DC, direct-current; ECG, electrocardiogram; GP, ganglionic plexi; ICD, implantable cardiodefibrillators; ICE, intracardiac echocardiogram; IVC, inferior vena cava; LA, left atrium;LOM, ligament of Marshall; MR, magnetic resonance; NA, not applicable; NR, not reported; OAT, oral anti-coagulation; PAF, paroxysmal atrial fibrillation; PeAF, persistent atrial fibrillation; PmAF, permanent atrial fibrillation; PV, pulmonary vein; PVI, pulmonary vein isolation; RA, right atrium; RCT, randomized controlled trial; RF, radiofrequency; RFCA, radiofrequency catheter ablation; SVC, superior vena cava; WACA, wide-area circumferential ablation

Table B2. Annual Mortality Rates

Author	Year	Study Design	Intervention	Study N	Mean Follow-up, months	Deaths during follow-up period	Annual Mortality Rate
			Catheter ablation				
Bunch	2010	Prospective Cohort Study	WACA, LA linear ablation, CTI; ablation in <80 year olds	717	36	0	0.0%
			WACA, LA linear ablation, CTI; ablation in ≥80 year olds	35	36	0	0.0%
Deisenhofer	2003	Case series	PVI only	75	7.6	0	0.0%
Essebag	2005	Case series	PVI + mitral isthmus line and/or posterior LA line	85	12	0	0.0%
Hsieh	2005	Prospective Cohort Study	PVI + SVC, non-PV foci, and CTI	37	52	3	1.9%
			AVN ablation	32	58	5	3.2%
Hunter	2010	Case series	WACA; for persistent AF: linear ablation and CFAEs	285	32.4	7	0.9%
Jais	2008	RCT	PVI + CTI, linear lesions (LA roof), mitral isthmus	53	12	0	0.0%
			ADT	59	12	2	3.4%
Meissner	2009	Case series	PVI only	72	6	0	0.0%
Nademanee	2008	Case series	CFAE ablation only	517	27.9	29	2.4%
Neumann	2008	Prospective Cohort Study	CPVI in paroxysmal AF patients	293	12	0	0.0%
			CPVI in persistent AF patients	31	12	0	0.0%
Oral	2006	RCT	CPVI	77	12	1	1.3%
			Amiodarone + cardioversion	69	12	NR	NR
Pappone	2003	Prospective Cohort Study	CPVI	589	28.7	38	2.7%
			ADT	582	30.4	83	5.6%
Patel	2010	Prospective Cohort Study	Posterior wall between PVs, anterior tissue to the right PV along the left septum, SVC	518	24.28	5	0.5%
			Posterior wall between PVs, anterior tissue to the right PV along the left septum, SVC, CFAEs	2747	35.57	NR	NR

Author	Year	Study Design	Intervention	Study N	Mean Follow-up, months	Deaths during follow-up period	Annual Mortality Rate
Stabile	2006	RCT	CPVI with CTI line	68	12	1	1.5%
			ADT	69	12	2	2.9%
Themistoclakis	2010	Prospective Cohort Study	Ostial or antral level PVI; linear lesions, ablation of CFAEs, and isolation of the SVC were performed per institutional preference; discontinued with OAT	2692	10	0	0.0%
			Ostial or antral level PVI; linear lesions, ablation of CFAEs, and isolation of the SVC were performed per institutional preference; continued with OAT	663	10	1	0.2%
Wilber	2010	RCT	PVI + left atrial linear lesions, CFAEs and CTI ablation	106	9	1	1.3%
			ADT	61	1	0	0.0%
Antiarrhythmic agents							
AFFIRM	2003	RCT	Amiodarone	106	46	10	2.5%
			Class IC	116	46	26	5.8%
			Amiodarone	131	46	15	3.0%
			Sotalol	125	46	24	5.0%
Channer	2004	RCT	Amiodarone	61	12	0	0.0%
			Amiodarone	62	12	0	0.0%
			Placebo	38	12	0	0.0%
Galperin	2001	RCT	Amiodarone	47	16.03	0	0.0%
			Placebo	48	16.03	0	0.0%
Hohnloser	2000	RCT	Amiodarone	127	12	2	1.6%
			Diltiazem	125	12	2	1.6%
Hohnloser	2009	RCT	Dronedarone	2301	21	116	2.9%
			Placebo	2327	21	139	3.4%
Kilborn	2002	Retrospective Cohort Study	Amiodarone	550	12	196	35.6%
			Placebo	14730	12	4655	31.6%
Kochiadak	2000	RCT	Amiodarone	65	24	0	0.0%

Author	Year	Study Design	Intervention	Study N	Mean Follow-up, months	Deaths during follow-up period	Annual Mortality Rate
is			Sotalol	61	24	0	0.0%
			Placebo	60	24	0	0.0%
Heuzey	2009	RCT	Dronedarone	249	7	2	1.4%
			Amiodarone	255	7	5	3.4%
Singh	2005	RCT	Amiodarone	267	12	13	4.9%
			Sotalol	261	12	15	5.7%
			Placebo	137	12	3	2.2%
Singh	2007	RCT	Dronedarone	828	12	8	1.0%
			Placebo	409	12	3	0.7%
Touboul	2003	RCT	Dronedarone	151	12	1	0.7%
			Placebo	48	12	0	0.0%
Thorascopic, off-pump surgical ablation							
Bagge	2009	Case Series	Thoracoscopic off-pump epicardial PVI and GP ablation	43	12	0	0.0%
Beyer	2009	Case Series	PVI/autonomic denervation, GP stimulation	100	13.6	0	0.0%
Castella	2010	Case Series	Thoracoscopic PVI	34	16	0	0.0%
Cui	2010	Case Series	Bilateral PV antrum isolation and division of the LOM	81	12.7	0	0.0%
Edgerton	2009	Case Series	PVI/left-sided "Dallas" set	114	17	1	0.6%
Edgerton	2009	Case Series	Bilateral PVI/GP stimulation/additional ablation post-testing	30	6	0	0.0%
Edgerton	2010	Case Series	Bilateral, epicardial PVI and partial autonomic denervation	52	12	0	0.0%
Han	2009	Case Series	Bilateral PVI/GP ablation/LOM ablation	45	17	0	0.0%
Wolf	2005	Case Series	Bilateral PVI	27	6	0	0.0%
Yilmaz	2010	Case Series	Bilateral PVI/GP ablation	30	11.6	0	0.0%
Stroke prevention							
Connolly	2009	RCT	Dabigatran, 110mg	6015	24	446	3.7%

Author	Year	Study Design	Intervention	Study N	Mean Follow-up, months	Deaths during follow-up period	Annual Mortality Rate
			Dabigatran, 150mg	6076	24	438	3.6%
			Warfarin	6022	24	487	4.0%
Holmes	2009	RCT	Watchman	463	18	21	3.0%
			Warfarin	244	18	18	4.9%

ADT, antiarrhythmic drug therapy; AVN, atrioventricular junction ; CFAEs, complex fractionated atrial electrograms; CPVI, circumferential pulmonary vein isolation; CTI, cavotricuspid isthmus; GP, ganglionic plexi; LA, left atrium; LOM, radiofrequency; LOM, ligament of Marshall; NR, not reported; OAT, oral anti-coagulation; PAF, paroxysmal atrial fibrillation; PeAF, persistent atrial fibrillation; PV, pulmonary vein; PVI, pulmonary vein isolation; RA, right atrium; RCT, randomized controlled trial; SVC, superior vena cava; WACA, wide-area circumferential ablation

Table B3. Annual Stroke Rates

Author	Year	Study Design	Intervention	Study N	Mean Follow-up, months	Strokes during follow-up period	Stroke Type	Annual Stroke Rate
Catheter ablation								
Bunch	2010	Prospective Cohort Study	WACA, LA linear ablation, CTI; ablation in ≥80 year olds	35	36	0	All strokes	0.0%
			WACA, LA linear ablation, CTI; ablation in <80 year olds	717	36	4		0.2%
Cheema	2006	Case Series	CPVI	64	12	0		0.0%
Corrado	2009	RCT	PVI only vs. PVI + SVC	294	12	1		0.3%
Deisenhofer	2003	Case Series	PVI only	75	7.6	0		0.0%
Della Bella	2009	RCT	CartoMerge™	145	14	0		0.0%
			Conventional RFCA procedure	145	14	0		0.0%
Essebag	2005	Case Series	PVI + mitral isthmus line and/or posterior LA line	85	12	1		1.2%
Hsieh	2005	Prospective Cohort Study	PVI + SVC, non-PV foci, and CTI	37	52	1		0.6%
			AVN ablation	32	58	0		0.0%
Hunter	2010	Case Series	WACA; for persistent AF: linear ablation and CFAEs	285	32.4	1		0.1%
Khaykin	2009	RCT	PVI only	30	25.2	0		0.0%

Author	Year	Study Design	Intervention	Study N	Mean Follow-up, months	Strokes during follow-up period	Stroke Type	Annual Stroke Rate
			CPVI, CFAE (30%), mitral isthmus and LA roof lines (77%)	30	25.2	0		0.0%
Lakkireddy	2005	Prospective Cohort Study	PVI in patients with pacemakers or ICD	86	12	0		0.0%
			PVI in patients without pacemakers or ICD	86	12	0		0.0%
Macle	2002	Case Series	Bidirectional CTI block, linear ablation, lateral mitral isthmus line	136	8.8	0		0.0%
Macle	2007	Case Series	Posterior LA	64	16	0		0.0%
Mangrum	2002	Case Series	CPVI; additional ablation for AFL or right AFL: tricuspid annulus/IVC linear lesion(s) and ectopy-initiating AF outside the PV	56	13	3		4.9%
Meissner	2009	Case Series	PVI only	72	6	0		0.0%
Nademanee	2008	Case Series	CFAE ablation only	517	27.9	7		0.6%
Neumann	2008	Prospective Cohort Study	CPVI in paroxysmal AF patients	293	12	0		0.0%
			CPVI in persistent AF patients	31	12	0		0.0%

Author	Year	Study Design	Intervention	Study N	Mean Follow-up, months	Strokes during follow-up period	Stroke Type	Annual Stroke Rate
Oral	2006	Case Series	LA RFA performed in 29% of patients; CPVI in 71% of patients	755	25	2		0.1%
Pappone	2001	Case Series	CPVI	251	10.4	0		0.0%
Pappone	2003	Prospective Cohort Study	PVI only	589	28.7	6		0.4%
			ADT	582	30.4	22		1.5%
Patel	2010	Prospective Cohort Study	Posterior wall bewteen PVs, anterior tissue to the right PV along the left septum, SVC; ablation performed in females	518	24.28	4		0.4%
			Posterior wall bewteen PVs, anterior tissue to the right PV along the left septum, SVC, CFAEs; ablation performed in males	2747	35.57	17		0.2%
Rossillo	2008	Retrospective matched cohort study	PVI only	85	16	0		0.0%
			DC-Shock	85	16	5		4.4%
Sawhney	2009	Case Series	CPVI and LA linear ablation	71	63	0		0.0%
Stabile	2006	RCT	CPVI with CTI line	68	12	0		0.0%
			ADT	69	12	0		0.0%

Author	Year	Study Design	Intervention	Study N	Mean Follow-up, months	Strokes during follow-up period	Stroke Type	Annual Stroke Rate
Steven	2010	Prospective Cohort Study	Posterior LA wall, ipsilateral veins with robotic navigation of catheter	30	12	0		0.0%
			Posterior LA wall, ipsilateral veins using a conventional approach to catheter ablation	30	12	0		0.0%
Tan	2009	Case Series	PVI only	99	6	0		0.0%
Themistoclakis	2010	Prospective Cohort Study	Ostial or antral level PVI; linear lesions, ablation of CFAEs, and isolation of the SVC were performed per institutional preference; discontinued with OAT	2692	10	1		0.0%
			Ostial or antral level PVI; linear lesions, ablation of CFAEs, and isolation of the SVC were performed per institutional preference; continued with OAT	663	10	4		0.7%

Author	Year	Study Design	Intervention	Study N	Mean Follow-up, months	Strokes during follow-up period	Stroke Type	Annual Stroke Rate
Wokhlu	2010	Case Series	Some CPVI, other WACA with additional linear lesions along the LA roof and the left inferior isthmus	323	36	4		0.4%
Antiarrhythmic agents								
Connolly	2009	RCT	Dronedarone	2301	30	46	Total Strokes	0.8%
			Placebo	2327	30	70		1.2%
Connolly	2009	RCT	Dronedarone	2301	30	6	Hemorrhagic	0.1%
			Placebo	2327	30	6		0.1%
Connolly	2009	RCT	Dronedarone	2301	30	33	Ischemic	0.6%
			Placebo	2327	30	49		0.8%
Connolly	2009	RCT	Dronedarone	2301	30	14	Fatal	0.2%
			Placebo	2327	30	21		0.4%
Singh	2005	RCT	Amiodarone	267	12	NR	Major strokes	1.19/100 patient-years
			Placebo	137	12	NR		0.96/100 patient-years
			Amiodarone	267	12	NR	Minor strokes	0.87/100 patient-years
			Placebo	137	12	NR		0.95/100 patient-years
Singh	2007	RCT	Dronedarone	828	12	4	All Strokes	0.5%
			Placebo	409	12	3		0.7%
Thorascopic, off-pump surgical ablation								
No strokes reported during follow-up period								
Stroke prevention								
Connolly	2009	RCT	Dabigatran, 110mg	6015	24	171	Total	1.4%
			Dabigatran, 150mg	6076	24	122		1.0%

Author	Year	Study Design	Intervention	Study N	Mean Follow-up, months	Strokes during follow-up period	Stroke Type	Annual Stroke Rate
			Warfarin	6022	24	185		1.5%
Connolly	2009	RCT	Dabigatran, 110mg	6015	24	159	Ischemic	1.3%
			Dabigatran, 150mg	6076	24	111		0.9%
			Warfarin	6022	24	142		1.2%
Connolly	2009	RCT	Dabigatran, 110mg	6015	24	14	Hemorrhagic	0.1%
			Dabigatran, 150mg	6076	24	12		0.1%
			Warfarin	6022	24	45		0.4%
Holmes	2009	RCT	Watchman	463	24	16	Total	1.7%
			Warfarin	244	24	12		2.5%
Holmes	2009	RCT	Watchman	463	24	15	Ischemic	1.6%
			Warfarin	244	24	6		1.2%
Holmes	2009	RCT	Watchman	463	18	1	Hemorrhagic	0.1%
			Warfarin	244	18	6		1.6%

ADT, antiarrhythmic drug therapy; AFL, atrial flutter; AVN, atrioventricular junction ; CFAEs, complex fractionated atrial electrograms; CPVI, circumferential pulmonary vein isolation; CTI, cavotricuspid isthmus; DC, direct-current; IVC, inferior vena cava; LA, left atrium; NR, not reported; OAT, oral anti-coagulation; PAF, paroxysmal atrial fibrillation; PeAF, persistent atrial fibrillation; PVI, pulmonary vein isolation; RCT, randomized controlled trial; RFCA, radiofrequency catheter ablation; SVC, superior vena cava; WACA, wide-area circumferential ablation

Table B4. Freedom from AF/Maintenance of Sinus rhythm

Author	Year	Study Design	Intervention	Study population	Mean Follow-up, months	Outcome	AF monitoring method	Reported Crude%	Reported Kaplan%
Catheter ablation									
Arentz	2003	Case Series	PVI + SVC, tricuspid annulus/IVC isthmus ablation	55	12	Freedom from AF	ECG, 24-hour Holter monitor	87.3%	NR
Arentz	2003	Case Series	PVI + RA, SVC, LA	47	24	Freedom from AF	24-hour Holter monitor	76.6%	NR
Atienza	2009	Case Series	CPVI + dominant frequency sites	50	9.3	Freedom from AF	ECG	76.0%	NR
Baman	2009	Case Series	PVI + CFAEs in LA and CS	74	16	Freedom from AF	ECG, event monitor	29.7%	NR
Berkowitsch	2009	Prospective Cohort Study	PVI + CFAEs, with RFCA	215	24	Freedom from AF	Symptoms report, 7-day Holter ECG	59.8%	NR
			PVI + CFAEs, with cryoballoon ablation	105				63.1%	NR
Bertaglia	2009	Prospective Cohort Study	Segmental PV ostia isolation	240	11.2	Freedom from AF	24 h ECG Holter or a 7-day ECG recording	44.6%	NR
			CPVI guided by 3D electroanatomical mapping	107	12.3			41.1%	NR
			CPVI guided by electroanatomical mapping integrated with MR/CT images of the left atrium	226	11.2			22.6%	NR
Bunch	2010	Prospective Cohort Study	WACA, LA linear ablation, CTI; ablation in ≥80 year olds	35	36	Freedom from AF	Event monitor	NR	78.0%
			WACA, LA linear ablation, CTI; ablation in <80 year olds	717				NR	75.0%

Author	Year	Study Design	Intervention	Study population	Mean Follow-up, months	Outcome	AF monitoring method	Reported Crude%	Reported Kaplan%
Calvo	2010	Prospective Cohort Study	PVI + LA roof and LA posterior wall, mitral isthmus	33	12	Freedom from AF	24 or 48-hour Holter monitor, ECG	NR	48.0%
			PVI + LA roof and LA posterior wall, mitral isthmus; patients with lone AF who are also athletes	42				NR	59.0%
			PVI + LA roof and LA posterior wall, mitral isthmus; patients with lone AF	107				NR	47.0%
Cheema	2006	Case Series	CPVI	64	13	Freedom from AF	ECG, 7-day Holter monitor, event monitor	62.0%	NR
Corrado	2009	RCT	PVI only	160	12	Sinus rhythm	ECG, 48-hour Holter monitor	74.0%	NR
			PVI + SVC	134				81.0%	NR
Deisenhofer	2003	Case Series	PVI	75	7.6	Sinus rhythm	7-day Holter monitor	51.0%	NR
Deisenhofer	2009	RCT	PVI only	48	19	Freedom from AF	7-day Holter ECG	74.0%	73.9%
			PVI + CFAEs	50				83.0%	83.3%
Della Bella	2009	RCT	CartoMerge™	145	14	Freedom from AF	7-day Holter, 24-hour ECG Holter monitor	NR	89.0%
			Conventional RFCA procedure	145				NR	69.7%
Di Biase	2009	Prospective Cohort Study	PVI + Posterior LA wall, CFAEs, mitral annular/LA roof lesions, CS isolation, and RA ablation; manual approach	193	14.1	Freedom from AF	7-day Holter monitor	81.0%	NR

Author	Year	Study Design	Intervention	Study population	Mean Follow-up, months	Outcome	AF monitoring method	Reported Crude%	Reported Kaplan%
			PVI + Posterior left atrial wall, CFAEs, mitral annular/LA roof lesions, CS isolation, and RA ablation; robotic approach	197	14.1	Freedom from AF		85.0%	NR
Di Biase	2009	RCT	PVI only	35	12	Freedom from AF	48-hour Holter monitor, event recorder	89.0%	NR
			CFAEs ablation only	34	12	Freedom from AF		23.0%	NR
			PVI + CFAEs	34	12	Freedom from AF		91.0%	NR
Essebag	2005	Case Series	PVI + mitral isthmus line and/or posterior LA line	85	12	Freedom from AF	24-hour Holter monitor, 2-week event recorder, or continuous mobile outpatient cardiac telemetry	NR	76.0%
Forleo	2009	RCT	PVI + CTI, roofline connecting superior PVs, isthmus bewteen mitral annulus and left inferior PV	35	12	Freedom from AF	ECG Holter monitor	NR	80.0%
			ADT	35				NR	42.9%
Helms	2009	Case Series	CPVI	73	12	Freedom from AF	Holter or event monitor	66.0%	NR
Hocini	2005	RCT	PVI + linear ablation joining the 2 superior PVs (roofline) + CTI	45	14	Freedom from AF	ECG	87.0%	87.0%
			PVI only	45	15	Freedom from AF		69.0%	69.0%
Hof	2009	Case Series	WACA	146	19	Freedom from AF	ECG with event monitoring and reporting of	66.0%	NR

Author	Year	Study Design	Intervention	Study population	Mean Follow-up, months	Outcome	AF monitoring method	Reported Crude%	Reported Kaplan%
							symptoms		
Hsieh	2005	Prospective Cohort Study	PVI + SVC, non-PV foci, and CTI	37	52	Freedom from AF	ECG	NR	81.0%
			AVN ablation	32	58				100.0%
Hunter	2010	Case Series	WACA; for persistent AF: linear ablation and CFAEs	285	32.4	Freedom from AF	Ambulatory monitor	NR	73.8%
Husser	2004	Case Series	PVI + RA isthmus	78	6	Freedom from AF	ECG, Holter monitor, or event monitor	42.0%	NR
Jais	2008	RCT	PVI + CTI, linear lesions (LA roof), mitral isthmus	53	12	Freedom from AF	ECG, 24-hour Holter monitor	NR	89.0%
			ADT	59				NR	23.0%
Joshi	2009	Case Series	PVI + Linear ablation (mitral isthmus and LA roof)	72	12	Freedom from AF	ECG, Holter monitor, event monitor, loop recorder for AF burden	65.0%	NR
Kanagaratnam	2001	Case Series	PVI only	71	29	Sinus rhythm	48-hour Holter monitor, loop recorder	21.0%	NR
Khaykin	2009	RCT	PVI only	30	25.2	Freedom from AF	ECG, 24-hour Holter monitor	80.0%	NR
			CPVI, CFAE (30%), mitral isthmus and LA roof lines (77%)	30				60.0%	NR
Kim	2010	Prospective Cohort Study	CPVI with ablation of residual potentials	49	23.1	Freedom from AF	ECG or 24-hour Holter monitor	79.6%	NR
			CPVI alone	53	23.4	Freedom from AF		81.1%	NR
Klemm	2006	Case Series	Segmental PVI, RA isthmus ablation	80	6	Sinus rhythm	Transtelephonic ECG, Holter ECG	61.3%	NR

Author	Year	Study Design	Intervention	Study population	Mean Follow-up, months	Outcome	AF monitoring method	Reported Crude%	Reported Kaplan%
Knecht	2010	Prospective Cohort Study	LA and RA appendages, CFAEs, CTI using 3DATG imaging	44	10	Freedom from AF	Ambulatory monitoring	NR	80.0%
			LA and RA appendages, CFAEs, cavotricuspid isthmus using Carto imaging	47				NR	85.0%
Kriatselis	2009	Case Series	PVI only	44	6	Sinus rhythm	24-hour Holter ECG	70.0%	NR
Kumagai	2005	Prospective Cohort Study	Basket catheter-guided ablation	50	12	Freedom from AF	ECG, 24-hour Holter monitor	80.0%	NR
			Circular catheter-guided ablation	50				62.0%	NR
Kusumoto	2009	Case Series	PVI with stepwise ablation: after PVI, linear ablation, CFAEs	240	12	Sinus rhythm	24-hour ambulatory ECG monitor, 30-day event recorder, or 21 day mobile cellular outpatient telemetry	92.1%	NR
Lakkireddy	2005	Prospective Cohort Study	PVI in patients without pacemakers or ICD	86	12	Freedom from AF	Rhythm transmitter, 48-hour Holter monitor	21.0%	79.0%
			PVI in patients with pacemakers or ICD	86	12	Freedom from AF		19.0%	81.0%
Lin	2009	Prospective Cohort Study	PVI + Linear ablation (roof line and lateral mitral line) + CFAEs	30	19	Sinus rhythm	24-hour Holter monitor and/or cardiac event monitor	83.0%	NR
			PVI + Linear ablation (roof line and lateral mitral line)	30				67.0%	NR
Lo	2009	Prospective Cohort Study	PVI + Linear ablation, CFAEs; LA diameter of < 45mm	49	24	Freedom from AF	24-hour Holter monitor and/or cardiac eventmonitor	55.0%	NR

Author	Year	Study Design	Intervention	Study population	Mean Follow-up, months	Outcome	AF monitoring method	Reported Crude%	Reported Kaplan%
			PVI + Linear ablation, CFAEs; LA diameter of ≥45mm	37				45.0%	NR
Macle	2002	Case Series	PVI + Bidirectional CTI block, linear ablation, lateral mitral isthmus line	136	8.8	Freedom from AF	Telephone interview	81.0%	NR
Macle	2007	Case Series	PVI + Posterior LA	64	16	Freedom from AF	ECG, Holter monitor	92.0%	NR
Malmborg	2003	Case Series	PVI only	40	8.9	Freedom from AF	24-hour Holter ECG	52.5%	NR
Mangrum	2002	Case Series	CPVI; additional ablation for AFL or right AFL: tricuspid annulus/IVC linear lesion(s) and ectopy-initiating AF outside the PV	56	13	Freedom from AF	ECG, Holter monitor; 24-h Holter monitor or 30-day event recorder	66.0%	NR
Marrouche	2007	RCT	Open-Irrigation	26	12	Freedom from AF	24-hour Holter monitor	80.8%	NR
			ICE-Guided Energy Delivery with a Non-Irrigated Catheter	27				77.8%	NR
Matsuo	2009	Case Series	PVI + CFAEs, linear ablation if AF continued (joining right and left superior PVs), then if it still continued, a mitral isthmus line	90	28	Freedom from AF	ECG, 24-hour Holter monitor, 24-hour ambulatory monitor	85.0%	NR
Meissner	2009	Case Series	PVI only	72	6	Freedom from AF	24-hour Holter monitor	72.2%	NR
Mesas	2006	Case Series	CPVI	47	12.7	Freedom from AF	Transtelephonic ECG, Holter monitor	58.0%	NR
Nademanee	2008	Case Series	CFAE ablation only	635	27.9	Sinus rhythm	Holter monitor	81.4%	NR

Author	Year	Study Design	Intervention	Study population	Mean Follow-up, months	Outcome	AF monitoring method	Reported Crude%	Reported Kaplan%
Neumann	2008	Prospective Cohort Study	CPVI in paroxysmal AF patients	293	12	Sinus rhythm	7-day Holter monitor	NR	74.0%
			CPVI in persistent AF patients	53	12	Sinus rhythm		NR	42.0%
O'Neill	2009	Case Series	PVI + CFAEs, linear ablation (mitral isthmus and LA roof), RA, SVC, linear ablation (CTI)	153	34	Freedom from AF	Holter monitor	NR	85.0%
Oral	2006	Case Series	PVI + LA RFCA performed in 29% of patients; CPVI in 71% of patients	755	25	Sinus rhythm	Event monitors and/or serial ECGs and 24-hour Holter monitor	69.1%	NR
Oral	2006	RCT	CPVI	77	12	Freedom from AF	Event monitor	74.0%	NR
			ADT	69	12	Freedom from AF		58.0%	NR
Pappone	2001	Case Series	CPVI	251	10.4	Freedom from AF	Holter monitor	80.1%	NR
Pappone	2003	Prospective Cohort Study	CPVI	589	28.7	Freedom from AF	ECG and 24-hour Holter monitor	NR	78.0%
			ADT	582	30.4			NR	37.0%
Pappone	2006	RCT	CPVI	99	12	Freedom from AF	ECG, 24-hour Holter monitor, event monitor	NR	86.0%
			ADT	99				NR	22.0%
Patel	2010	Prospective Cohort Study	PVI + Posterior wall bewteen PVs, anterior tissue to the right PV along the left septum, SVC, CFAEs; ablation performed in females	518	24	Freedom from AF	Transtelephonic ECG, 48-hour Holter monitor, event monitor	NR	68.5%

Author	Year	Study Design	Intervention	Study population	Mean Follow-up, months	Outcome	AF monitoring method	Reported Crude%	Reported Kaplan%
			PVI + Posterior wall bewteen PVs, anterior tissue to the right PV along the left septum, SVC, CFAEs; ablation performed in males	2747	35	Freedom from AF		NR	77.5%
Pontoppidan	2009	RCT	PVI only	76	12	Freedom from AF	ECG, Holter monitor	NR	32.0%
			PVI + CTI	73				NR	34.0%
Rossillo	2008	Retrospective matched cohort study	PVI + SVC	85	15	Freedom from AF	Holter monitor	82.0%	NR
			DC-Shock	85				40.0%	NR
Saliba	2008	Case Series	PVI + SVC	40	12	Freedom from AF	Holter monitor	97.5%	NR
Sawhney	2009	Case Series	CPVI and LA linear ablation	71	63	Freedom from AF	Event monitor	NR	56.0%
Scharf	2009	Case Series	PVI only	50	6.3	Freedom from AF	7-day ECG	70.0%	NR
Shin	2008	Case Series	PVI + Non-PV triggers	68	6	Freedom from AF	ECG	78.0%	NR
Siklody	2009	Case Series	PVI only	30	7.4	Freedom from AF	ECG, 24-hour Holter monitor	73.3%	NR
Stabile	2006	RCT	CPVI with CTI line	68	12	Freedom from AF	Transtelephonic ECG recorder, standard ECG, Holter monitor	55.9%	NR
			ADT	69				8.9%	NR
Stabile	2009	Prospective Cohort Study	PVI + LA, CTI, using integrated approach	61	14.9	Freedom from AF	ECG or 24-hour ambulatory monitor	56.0%	NR
			PVI + LA, CTI using anatomical approach	36	15.2	Freedom from AF		58.0%	NR
Steven	2010	Prospective Cohort Study	PVI + Posterior LA wall, ipsilateral veins with robotic navigation of catheter	30	6	Freedom from AF	3-day Holter monitor	NR	73.0%

Author	Year	Study Design	Intervention	Study population	Mean Follow-up, months	Outcome	AF monitoring method	Reported Crude%	Reported Kaplan%
			PVI + Posterior LA wall, ipsilateral veins using a conventional approach to catheter ablation	30				NR	77.0%
Tan	2009	Case Series	PVI only	99	6	Freedom from AF	48-hour Holter monitor	NR	60.6%
Tamborero	2009	RCT	Superior PVs were connected by linear lesions along the LA roof	60	9.8	Freedom from AF	48-hour Holter monitor	NR	47.0%
			PVI + LA posterior wall isolated by adding a second line connecting the inferior aspect of the 2 inferior PVs	60			48-hour Holter monitor	NR	45.0%
Themistoclakis	2010	Prospective Cohort Study	Ostial or antral level PVI; linear lesions, ablation of CFAEs, and isolation of the SVC were performed per institutional preference; discontinued with OAT	2692	10	Freedom from AF	ECG, Holter monitor, transtelephonic monitor	97.1%	NR
			Ostial or antral level PVI; linear lesions, ablation of CFAEs, and isolation of the SVC were performed per institutional preference; continued with OAT	663				NR	NR
Tzou	2010	Case Series	PVI only	120	60	Freedom from AF	Transtelephonic monitor, ECG	NR	71.0%

Author	Year	Study Design	Intervention	Study population	Mean Follow-up, months	Outcome	AF monitoring method	Reported Crude%	Reported Kaplan%
Udyavar	2008	Case Series	CPVI with PV carina	97	12.9	Freedom from AF	24-hour Holter monitor	74.2%	NR
Van Belle	2008	Case Series	CPVI; CTI ablation in 7 patients with isthmus flutter	141	24	Freedom from AF	Transtelephonic ECG, 24-hour Holter ECG	NR	86.0%
Wazni	2005	RCT	PVI only	33	12	Freedom from AF	Loop-event recorder; 24-hour Holter monitor	NR	63.0%
			ADT	37				NR	37.0%
Wazni	2009	Case Series	SVC, using the Hansen ablation system	63	6	Freedom from AF	Event recorder	76.0%	NR
Wiesfeld	2004	Case Series	PVI + LA, RA and respective appendages	25	28	Freedom from AF	24-hour Holter monitor, ambulatory monitor	NR	32.0%
Wilber	2010	RCT	PVI - Allowed at discretion of investigator; included left atrial linear lesions, CFAEs and CTI ablation	106	9	Freedom from AF	ECG, transtelephonic ECG, Holter monitor	NR	66.0%
			ADT	61				NR	16.0%
Wokhlu	2010	Case Series	Some CPVI, other WACA with additional linear lesions along the LA roof and the left inferior isthmus	323	24	Freedom from AF	Holter monitor	87.0%	NR
Wokhlu	2010	Case Series	Some PVI, some WACA	774	36	Freedom from AF	ECG, 24-hour Holter monitor	64.2%	NR
Yamada	2006	Case Series	CPVI	55	17	Freedom from AF	24-hour Holter and cardiac recordings; event monitor	92.7%	NR
Yamada	2009	Prospective Cohort Study	CPVI with vagal nerve ablation	60	12	Freedom from AF	24-hour Holter recordings, event	66.7%	NR

Author	Year	Study Design	Intervention	Study population	Mean Follow-up, months	Outcome	AF monitoring method	Reported Crude%	Reported Kaplan%
			Segmental PVI with vagal nerve ablation	60			monitor	46.7%	NR
Yoshida	2009	Case Series	PVI only	77	12	Freedom from AF	24-hour Holter monitor, event monitor	NR	66.2%
Antiarrhythmic agents									
AFFIRM	2003	RCT	Amiodarone	106	60	Freedom from AF	ECG	NR	31.0%
			Class I	116	60	Freedom from AF		NR	21.0%
			Amiodarone	131	60	Freedom from AF		NR	37.0%
			Sotalol	125	60	Freedom from AF		NR	15.0%
Channer	2004	RCT	Amiodarone	62	12	Sinus rhythm	ECG	33.0%	NR
			Amiodarone	63	12	Sinus rhythm		49.0%	NR
			Placebo	38	12	Sinus rhythm		5.0%	NR
Galperin	2001	RCT	Amiodarone	47	16.03	Sinus rhythm	ECG, Holter ECG	62.9%	NR
			Placebo	48	16.03	Sinus rhythm		20.0%	NR
Hohnloser	2000	RCT	Amiodarone	127	12	Sinus rhythm	ECG	56.0%	NR
			Diltiazem	125	12	Sinus rhythm		10.0%	NR
Kochiadakis	2000	RCT	Amiodarone	65	24	Sinus rhythm	24 hour ambulatory ECG	NR	42.6%
			Sotalol	61	24	Sinus rhythm		NR	13.3%
			Placebo	60	24	Sinus rhythm		NR	10.0%
Kochiadakis	2004	RCT	Amiodarone	72	21	Freedom from AF	24-h ambulatory ECG	NR	59.0%
			Propafenone	74	19			NR	52.0%
Le Heuzey	2009	RCT	Dronedarone	249	7	Freedom from AF	ECG	NR	36.5%
			Amiodarone	255	7	Freedom from AF		NR	58.0%
Roy	2000	RCT	Amiodarone	201	15.6	Freedom from AF	ECG	64.7%	NR
			Sotalol/Propafenone	202	15.6	Freedom from		37.1%	NR

Author	Year	Study Design	Intervention	Study population	Mean Follow-up, months	Outcome	AF monitoring method	Reported Crude%	Reported Kaplan%
						AF			
Singh	2005	RCT	Amiodarone	267	12	Freedom from AF	ECG	NR	52.0%
			Sotalol	261	12	Freedom from AF		NR	32.0%
			Placebo	137	12	Freedom from AF		NR	13.0%
Singh	2007	RCT	Dronedarone	828	12	Freedom from AF	Transtelephonic ECG monitor, ECG	NR	35.9%
			Placebo	409	12	Freedom from AF		NR	24.8%
Touboul	2003	RCT	Dronedarone	151	12	Freedom from AF	Transtelephonic ECG monitor, ECG	23.2%	NR
			Placebo	48	12	Freedom from AF		10.0%	NR
Thorascopic, off-pump surgical ablation									
Bagge	2009	Case Series	Thoracoscopic off-pump epicardial PVI and GP ablation	43	12	Freedom from AF	24-hour Holter recording, ECG	76.0%	NR
Beyer	2009	Case Series	PVI/autonomic denervation, GP stimulation	100	13.6	Sinus rhythm	24-hour Holter monitor	NR	87.0%
Castella	2010	Case Series	Thoracoscopic PVI	34	16	Freedom from AF	24-hour Holter monitor	62.0%	NR
Cui	2010	Case Series	Bilateral PV antrum isolation and division of the LOM	81	12.7	Sinus rhythm	ECG analysis, and 24- to 48-hour Holter monitor (for patients in SR with ECG)	79.6%	86.0%
Edgerton	2009	Case Series	Bilateral PV antrum isolation	74	6	Freedom from AF	ECG, 14- to 21-day auto-triggered event monitor	74.2%	NR
Edgerton	2009	Case Series	PVI/left-sided "Dallas" set	114	6	Sinus rhythm	ECG and 24-hour Holter monitor OR long-term monitor (a 14 to 21-day auto	71.1%	NR

Author	Year	Study Design	Intervention	Study population	Mean Follow-up, months	Outcome	AF monitoring method	Reported Crude%	Reported Kaplan%
							trigger event monitor)		
Edgerton	2009	Case Series	Bilateral PVI/GP stimulation/additional ablation post-testing	30	6	Freedom from AF	14- to 21-day event monitoring	80.0%	NR
Edgerton	2010	Case Series	Bilateral, epicardial PVI and partial autonomic denervation	52	12	Sinus rhythm	24-hour Holter monitor, 2-3 week event monitor, or interrogation of implanted pacemaker	80.8%	NR
Han	2009	Case Series	Bilateral PVI/GP ablation/LOM ablation	43	17	Freedom from AF	External loop recorder	65.0%	NR
Sirak	2008	Case Series	Totally thoracoscopic PVI, extended linear ablations across critical segments of atrial substrate	32	13	Freedom from AF	ECG	87.5%	NR
Wolf	2005	Case Series	Cox Maze IV	23	3	Freedom from AF	ECG or telemetry monitor	91.0%	NR
Yilmaz	2010	Case Series	Minimally invasive Cryomaze	30	11.6	Freedom from AF	ECG and 24-hour Holter monitor	77.0%	NR

ADT, antiarrhythmic drug therapy; AF, atrial fibrillation; AFL, atrial flutter; AVN, atrioventricular junction ; CFAEs, complex fractionated atrial electrograms; CPVI, circumferential pulmonary vein isolation; CS, coronary sinus; CT, computed tomography; CTI, cavotricuspid isthmus; DC, direct-current; ECG, electrocardiogram; GP, ganglionic plexi; ICD, implantable cardiodefibrillators; ICE, intracardiac echocardiogram; IVC, inferior vena cava; LA, left atrium; LOM, ligament of Marshall; MR, magnetic resonance; NR, not reported; OAT, oral anti-coagulation; PAF, paroxysmal atrial fibrillation; PeAF, persistent atrial fibrillation; PV, pulmonary vein; PVI, pulmonary vein isolation; RA, right atrium; RCT, randomized controlled trial; RF, radiofrequency; RFCA, radiofrequency catheter ablation; SVC, superior vena cava; WACA, wide-area circumferential ablation

Table B5. Hospitalizations

Author	Year	Study Design	Intervention	Study N	Mean Follow-up, months	Hospitalization Type	No. Hospitalizations	% Hospitalizations
Catheter ablation								
Forleo	2009	RCT	PVI + CTI, roofline connecting superior PVs, isthmus between mitral annulus and left inferior PV	35	12	Hospitalization	3	8.6%
			ADT	35	12	Hospitalization	12	34.4%
Kusumoto	2009	Case Series	PVI with stepwise ablation: after PVI, linear ablation, CFAEs	240	12	Hospitalization	9	3.8%
Pappone	2006	RCT	CPVI	99	12	Total hospitalizations	24	NA
			ADT	99	12	Total hospitalizations	167	NA
Themistoclakis	2010	Prospective Cohort Study	Ostial or antral level PVI; linear lesions, ablation of CFAEs, and isolation of the SVC were performed per institutional preference; discontinued with OAT	2692	10	Hospitalization	1	0.0%

Author	Year	Study Design	Intervention	Study N	Mean Follow-up, months	Hospitalization Type	No. Hospitalizations	% Hospitalizations
			Ostial or antral level PVI; linear lesions, ablation of CFAEs, and isolation of the SVC were performed per institutional preference; continued with OAT	663	10	Hospitalization	13	2.0%
Antiarrhythmic agents								
Hohnloser	2000	RCT	Amiodarone	127	12	Hospitalization	87	68.5%
		RCT	Diltiazem	125	12	Hospitalization	30	24.0%
Connolly	2009	RCT	Dronedarone	2301	30	Stroke-related hospitalizations	38	1.7%
			Placebo	2327	30	Stroke-related hospitalizations	55	2.4%
Hohnloser	2009	RCT	Dronedarone	2301	21	Cardiovascular events-related hospitalizations	675	29.3%
			Placebo	2327	21	Cardiovascular events-related hospitalizations	859	36.9%
Hohnloser	2009	RCT	Dronedarone	2301	21	Hospitalization for Atrial fibrillation	335	14.6%
			Placebo	2327	21	Hospitalization for Atrial fibrillation	510	21.9%

Thorascopic, off-pump surgical ablation								
No hospitalizations reported during follow-up period								
Stroke prevention								
Connolly	2009	RCT	Dabigatran, 110 mg	6015	24	Hospitalization	2311	38.4%
			Dabigatran, 150 mg	6076	24	Hospitalization	2430	40.0%
			Placebo	6022	24	Hospitalization	2458	40.8%

ADT, antiarrhythmic drug therapy; CFAEs, complex fractionated atrial electrograms; CPVI, circumferential pulmonary vein isolation; CS, coronary sinus; CTI, cavotricuspid isthmus; DC, direct-current; NR, not reported; OAT, oral anti-coagulation; PVI, pulmonary vein isolation; RCT, randomized controlled trial; SVC, superior vena cava; WACA, wide-area circumferential ablation

Table B6. Quality of Life

Author	Year	Study Design	Intervention	Study N	Measure	Mean Δ in measurement score, treatment	Mean Δ in measurement score, control	p-value
Catheter ablation								
Jais	2008	RCT	PVI + CTI, linear lesions (LA roof), mitral isthmus	53	SF-36 physical, 12 months	8	5	0.01
					SF-36 mental, 12 months	10	7	0.01
			ADT	58	Symptom frequency, 12 months	-11	-4	0.002
					Symptom severity, 12 months	-12	-8	<0.0001
Khaykin	2009	RCT	PVI only	30	SF-36 physical, 6 months	9	1	0.29
					SF-36 physical role, 6 months	25	10	0.73
				30	SF-36 emotional role, 6 months	12	8	0.95

Author	Year	Study Design	Intervention	Study N	Measure	Mean Δ in measurement score, treatment	Mean Δ in measurement score, control	p-value
					SF-36 social functioning, 6 months	15	-4	0.32
			CPVI, CFAE (30%), mitral isthmus and LA roof lines (77%)	30	SF-36 bodily pain, 6 months	1	3	0.48
					SF-36 general health, 6 months	-5	-2	0.79
					Energy, 6 months	15	1	0.07
					Emotional well-being, 6 months	0	2	0.83
Pappone	2003	Prospective Cohort Study	CPVI	589	SF-36 physical, 12 months	10	1	ND
			ADT	582	SF-36 mental, 12 months	8	1	ND
Wazni	2005	Randomized Controlled Trial	PVI only	33	SF-36 general health, 6 months	22	11	<0.001
			ADT		SF-36 physical, 6 months	26	6	0.001

Author	Year	Study Design	Intervention	Study N	Measure	Mean Δ in measurement score, treatment	Mean Δ in measurement score, control	p-value
				37	SF-36 mental, 6 months	0	4	0.62
Wilber	2010	Randomized Controlled Trial	PVI - Allowed at discretion of investigator; included left atrial linear lesions, CFAEs and CTI ablation	106	SF-36 mental, 3 months	8.5	1.6	<0.001
					SF-36 physical, 3 months	6.9	0.4	<0.001
			ADT	61	Symptom frequency	-11.1	0.7	<0.001
					Symptom severity	-9.4	0	<0.001

Author	Year	Study Design	Intervention	Study N	Measure	Baseline Value (sd)	Post-ablation value (sd)	p-value
Wokhlu	2010	Case Series	Some CPVI, other WACA with additional linear lesions along the LA roof and the left inferior isthmus	323	SF-36 total score, 3 months	63.9 ± 19.2	80.8 ± 15.6	<0.001
					SF-36 total score, 12 months		80.6 ± 15.7	<0.001
					SF-36 total score, 24 months		80.5 ± 16.5	<0.001
					SF-36 physical score, 24 months	58.8 ± 20.1	76.2 ± 19.2	<0.001
					SF-36 mental score, 24 months	65.3 ± 18.6	79.8 ± 15.8	<0.001
Antiarrhythmic agents								
Hohnloser	2000	RCT	Amiodarone	127	SF-36 physical, 12 months	8	7	0.76
					SF-36 physical role, 12 months	17	20	0.66

Author	Year	Study Design	Intervention	Study N	Measure	Mean Δ in measurement score, treatment	Mean Δ in measurement score, control	p-value
					SF-36 bodily pain, 12 months	8	10	0.64
					SF-36 vitality, 12 months	7	10	0.24
			Diltiazem	125	SF-36 social functioning, 12 months	10	8	0.58
					SF-36 emotional role, 12 months	0	3	0.62
					SF-36 mental, 12 months	4	5	0.67
					SF-36 general health, 12 months	3	3	0.99
Thorascopic, off-pump surgical ablation								
Author	**Year**	**Study Design**	**Intervention**	**Study N**	**Measure**	**Baseline Value (95% CI)**	**Post-ablation value (95% CI)**	**p-value**
Bagge	2009	Case Series	Thoracoscopic off-pump epicardial PVI and GP ablation	43	SF-36 bodily pain, 12 months	72 (60-80)	74 (62-81)	0.39
					SF-36 general health, 12 months	52 (44-60)	64 (59-77)	0.007
					SF-36 vitality, 12 months	42 (36-46)	60 (48-70)	<0.001
					SF-36 social function, 12 months	63 (57-76)	82 (77-91)	<0.001
					SF-36 role function limited due to emotional problems, 12 months	45 (37-59)	78 (62-89)	<0.001
					SF-36 mental health, 12 months	64 (60-78)	78 (74-84)	<0.001

Author	Year	Study Design	Intervention	Study N	Measure	Mean Δ in measurement score, treatment	Mean Δ in measurement score, control	p-value
					SF-36 physical functioning, 12 months	67 (60-72)	80 (78-88)	0.0019
					SF-36 role function limited due to physical problems, 12 months	33 (20-42)	58 (44-75)	0.0078
					Symptoms- palpitation, 6 months	2.6 (2.1–3.1)	1.8 (1.1–2.4)	0.09
					Symptoms- fatigue, 6 months	3.6 (3.2–4.1)	2.2 (1.5–3.0)	0.018
					Symptoms- dizziness, 6 months	2.1 (1.7–2.5)	1.9 (1.2–2.7)	0.35
					Symptoms- lack of energy, 6 months	3.9 (3.5–4.3)	2.5 (1.6–3.4)	0.07
					Symptoms- dyspnea, 6 months	2.9 (2.5–3.4)	1.9 (1.2–2.7)	0.07
					Symptoms- palpitation, 12 months	2.6 (2.1–3.1)	2.2 (1.7–2.6)	0.28
					Symptoms- fatigue, 12 months	3.6 (3.2–4.1)	2.2 (1.7–2.7)	0.004
					Symptoms- dizziness, 12 months	2.1 (1.7–2.5)	1.8 (1.4–2.3)	0.67
					Symptoms- lack of energy, 12 months	3.9 (3.5–4.3)	2.5 (2.0–3.0)	0.006
					Symptoms- dyspnea, 12 months	2.9 (2.5–3.4)	2.0 (1.5–2.4)	<0.001

ADT, antiarrhythmic drug therapy; CFAEs, complex fractionated atrial electrograms; CPVI, circumferential pulmonary vein isolation; CTI, cavotricuspid isthmus; LA, left atrium; PVI, pulmonary vein isolation; RCT, randomized controlled trial; RFCA, radiofrequency catheter ablation; WACA, wide-area circumferential ablation

Table B7. Cessation of Anticoagulation

Author	Year	Study Design	Intervention	Study population	No. discontinuations	%Discontinued OAT	CVAs during follow-up
Jais	2008	RCT	PVI + CTI, linear lesions (LA roof), mitral isthmus	52	31	59.6%	NR
			ADT	53	18	34.0%	NR
Nademanee	2008	Case Series	CFAE ablation only	517	434	83.9%	5
Oral	2006	Case Series	CPVI	755	383	50.7%	0
Pappone	2006	RCT	CPVI	85	82	96.5%	NR
			ADT	NR	NR	NR	NR
Rossillo	2008	Retrospective matched cohort study	PVI + SVC	85	77	90.6%	0
			DC-Shock	85	29	34.1%	5
Themistoclakis	2008	Prospective Cohort Study	Ostial or antral level PVI; linear lesions, ablation of CFAEs, and isolation of the SVC were performed per institutional preference; discontinued with OAT	2692	2692	100.0%	2

Author	Year	Study Design	Intervention	Study population	No. discontinuations	%Discontinued OAT	CVAs during follow-up
			Ostial or antral level PVI; linear lesions, ablation of CFAEs, and isolation of the SVC were performed per institutional preference; continued with OAT	663	0	0.0%	3
Wokhlu	2010	Case Series	Some CPVI, other WACA with additional linear lesions along the LA roof and the left inferior isthmus	306	210	68.6%	NR

ADT, antiarrhythmic drug therapy; AF, atrial fibrillation; CFAEs, complex fractionated atrial electrograms; CPVI, circumferential pulmonary vein isolation; CTI, cavotricuspid isthmus; DC, direct-current; NR, not reported; OAT, oral anti-coagulation; PVI, pulmonary vein isolation; RA, right atrium; RCT, randomized controlled trial; SVC, superior vena cava; WACA, wide-area circumferential ablation

Table B8. Repeat Ablations

Author	Year	Study Design	Intervention	Study N	# with Repeat ablation	Total # ablations	No. procedures per patient	% with repeat ablations	Blanking Period	Ablations during BP/Early ablations	Ablations Post-BP/Late ablations
Arentz	2003	Case Series	PVI + SVC, tricuspid annulus/IVC isthmus ablation	55	15	NR	1.27	27.3%	NR	NR	NR
Arentz	2003	Case Series	PVI + RA, SVC, LA	47	5	NR	1.6	10.6%	NR	NR	NR
Atienza	2009	Case Series	CPVI + dominant frequency sites	50	9	60	1.2	18.0%	2	NR	NR
Bunch	2010	Prospective Cohort Study	WACA, LA linear ablation, CTI; ablation in <80 year olds	717	559	NR	NR	78.0%	3	NR	NR
Bunch	2010	Prospective Cohort Study	WACA, LA linear ablation, CTI; ablation in ≥80 year olds	35	28	NR	NR	80.0%	3	NR	NR
Calvo	2010	Case Series	PVI + LA roof and LA posterior wall, mitral isthmus	182	67	NR	NR	36.8%	NR	NR	NR
Cheema	2006	Case Series	CPVI	64	19	NR	NR	29.7%	3	NR	NR
Corrado	2009	RCT (both arms)	PVI only //PVI + SVC	294	11	NR	NR	3.7%	2	NR	NR
Deisenhofer	2003	Case Series	PVI	75	34	109	1.5	45.3%	NR	23	11
Deisenhofer	2009	RCT	PVI only	48	15	NR	1.3	31.3%	1	0	15
Deisenhofer	2009	RCT	PVI + CFAEs	50	17	NR	1.4	34.0%	1	0	17
Essebag	2005	Case Series	PVI + mitral isthmus line and/or posterior LA line	85	5	NR	NR	5.9%	NR	NR	NR
Helms	2009	Case Series	CPVI	73	9	NR	NR	12.3%	1	NR	NR
Hof	2009	Case Series	WACA	146	15	NR	NR	10.3%	3	NR	NR

Author	Year	Study Design	Intervention	Study N	# with Repeat ablation	Total # ablations	No. procedures per patient	% with repeat ablations	Blanking Period	Ablations during BP/Early ablations	Ablations Post-BP/Late ablations
Hunter	2010	Case Series	WACA; for persistent AF: linear ablation and CFAEs	285	163	530	1.9	NA	3	0	530
Jais	2008	RCT	PVI + CTI, linear lesions (LA roof), mitral isthmus	53	23	155	1.8	43.4%	3	0	23
Joshi	2009	Case Series	PVI + Linear ablation (mitral isthmus and LA roof)	72	7	NR	NR	9.7%	3	NR	NR
Klemm	2006	Case Series	Segmental PVI, RA isthmus ablation	80	18	NR	NR	22.5%	NR	NR	NR
Kumagai	2005	Prospective Cohort Study (both arms)	Basket catheter-guided ablation//Circular catheter-guided ablation	50	34	100	2.0	68.0%	NR	NR	NR
Kusumoto	2009	Case Series	PVI with stepwise ablation: after PVI, linear ablation, CFAEs	240	38	NR	NR	15.8%	3	NR	NR
Lin	2009	Prospective Cohort Study	PVI + Linear ablation (roof line and lateral mitral line)	30	18	NR	NR	60.0%	2	0	18
Lin	2009	Prospective Cohort Study	PVI + Linear ablation (roof line and lateral mitral line) + CFAEs	30	6	NR	NR	20.0%	2	0	6

Author	Year	Study Design	Intervention	Study N	# with Repeat ablation	Total # ablations	No. procedures per patient	% with repeat ablations	Blanking Period	Ablations during BP/Early ablations	Ablations Post-BP/Late ablations
Lo	2009	Prospective Cohort Study	PVI + Linear ablation, CFAEs; LA diameter of < 45mm	49	14	NR	NR	28.6%	NR	NR	NR
Lo	2009	Prospective Cohort Study	PVI + Linear ablation, CFAEs; LA diameter of ≥45mm	37	7	NR	NR	18.9%	NR	NR	NR
Macle	2002	Case Series	PVI + Bidirectional CTI block, linear ablation, lateral mitral isthmus line	136	67	NR	NR	49.3%	NR	NR	NR
Macle	2007	Case Series	PVI + Posterior LA	64	38	100	1.6	59.4%	NR	NR	NR
Mangrum	2002	Case Series	CPVI; additional ablation for AFL or right AFL: tricuspid annulus/IVC linear lesion(s) and ectopy-initiating AF outside the PV	64	7	NR	NR	10.9%	NR	NR	NR
Marrouche	2007	RCT	Open-Irrigation	26	2	NR	NR	7.7%	NR	NR	NR
Marrouche	2007	RCT	ICE-Guided Energy Delivery with a Non-Irrigated Catheter	27	2	NR	NR	7.4%	NR	NR	NR
Mesas	2006	Case Series	CPVI	47	47	NR	NR	100.0%	NR	NR	NR
O'Neill	2009	Case Series	PVI + CFAEs, linear ablation (mitral isthmus and LA roof), RA, SVC, linear ablation (CTI)	153	79	NR	NR	51.6%	1	0	79

Author	Year	Study Design	Intervention	Study N	# with Repeat ablation	Total # ablations	No. procedures per patient	% with repeat ablations	Blanking Period	Ablations during BP/Early ablations	Ablations Post-BP/Late ablations
Oral	2006	RCT	PVI + LA RFCA performed in 29% of patients; CPVI in 71% of patients	755	25	929	1.2	3.3%	2	0	25
Pappone	2006	RCT	CPVI	99	6	NR	NR	6.1%	1.75	0	6
Sawhney	2009	Case Series	CPVI and LA linear ablation	71	31	114	1.6	43.7%	1.5	0	31
Scharf	2009	Case Series	PVI only	50	25	NR	NR	50.0%	NR	NR	NR
Shin	2008	Case Series	PVI + Non-PV triggers	15	3	NR	NR	20.0%	NR	NR	NR
Tan	2009	Case Series	PVI only	99	41	NR	NR	41.4%	NR	NR	NR
Tzou	2010	Case Series	PVI only	123	15	NR	1.3	12.2%	NR	NR	NR
Van Belle	2008	Case Series	CPVI; CTI ablation in 7 patients with isthmus flutter	141	24	NR	NR	17.0%	3	NR	NR
Wazni	2005	RCT	PVI only	33	0	NR	NR	0.0%	2	NA	NA
Wazni	2009	Case Series	SVC, using the Hansen ablation system	71	5	NR	NR	7.0%	2	NR	NR
Wilber	2010	RCT	PVI - Allowed at discretion of investigator; included left atrial linear lesions, CFAEs and CTI ablation	106	13	NR	NR	12.3%	3	NR	NR
Yamada	2006	Case Series	CPVI	55	7	NR	NR	12.7%	NR	NR	NR
Yamada	2009	Prospective Cohort Study	Segmental PVI with vagal nerve ablation	60	15	NR	NR	25.0%	NR	NR	NR
Yamada	2009	Prospective Cohort	CPVI with vagal nerve ablation	60	8	NR	NR	13.3%	NR	NR	NR

Author	Year	Study Design	Intervention	Study N	# with Repeat ablation	Total # ablations	No. procedures per patient	% with repeat ablations	Blanking Period	Ablations during BP/Early ablations	Ablations Post-BP/Late ablations
Yoshida	2009	Case Series	PVI only	97	18	NR	NR	18.6%	NR	NR	NR

AFL, atrial flutter; BP: blanking period; CFAEs, complex fractionated atrial electrograms; CPVI, circumferential pulmonary vein isolation; CTI, cavotricuspid isthmus; ICD, implantable cardiodefibrillators; ICE, intracardiac echocardiogram; IVC, inferior vena cava; LA, left atrium; NA, not applicable; NR, not reported; PeAF, persistent atrial fibrillation; PV, pulmonary vein; PVI, pulmonary vein isolation; RA, right atrium; RCT, randomized controlled trial; RFCA, radiofrequency catheter ablation; SVC, superior vena cava; WACA, wide-area circumferential ablation

Table B9. Harms

Author	Year	Study Design	Intervention	Study N	Mean Follow-up, months	Intervention-specific harms			
Catheter ablation						**Periop. Mort.**	**Periop. Stroke**	**%Major compl.**	**%Minor compl.**
Arentz	2003	Case Series	PVI + SVC, tricuspid annulus/IVC isthmus ablation	55	12	NR	NR	3.6%	1.8%
Arentz	2003	Case Series	PVI + RA, SVC, LA	47	24	NR	NR	2.1%	27.7%
Atienza	2009	Case Series	CPVI + dominant frequency sites	50	9.3	NR	NR	0.0%	8.0%
Baman	2009	Case Series	PVI + CFAEs in LA and CS	93	16	NR	NR	0.0%	0.0%
Berkowitsch	2009	Prospective Cohort Study	PVI + CFAEs, with RFCA	215	24	NR	NR	0.0%	0.0%
Berkowitsch	2009	Prospective Cohort Study	PVI + CFAEs, with cryoballoon ablation	105	24	NR	NR	0.0%	0.0%
Bertaglia	2009	Prospective Cohort Study	Segmental PV ostia isolation	240	11.6	NR	NR	2.5%	5.4%
Bunch	2010	Prospective Cohort Study	WACA, LA linear ablation, CTI; ablation in <80 year olds	717	36	0.7%	NR	1.5%	1.3%
Bunch	2010	Prospective Cohort Study	WACA, LA linear ablation, CTI; ablation in ≥80 year olds	35	36	0.0%	NR	5.7%	2.9%

Author	Year	Study Design	Intervention	Study N	Mean Follow-up, months	Intervention-specific harms			
Calvo	2010	Prospective Cohort Study	PVI + LA roof and LA posterior wall, mitral isthmus	182	18.69	NR	NR	1.6%	1.1%
Cheema	2006	Case Series	CPVI	64	13	0.0%	0.0%	3.1%	3.1%
Corrado	2009	RCT	PVI only	160	12	NR	NR	1.3%	0.0%
Corrado	2009	RCT	PVI + SVC	134	12.0	NR	NR	0.0%	1.5%
Deisenhofer	2003	Case Series	PVI	75	19.2	0.0%	0.0%	10.7%	14.7%
Deisenhofer	2009	RCT	PVI only	48	19	NR	NR	0.0%	2.1%
Deisenhofer	2009	RCT	PVI + CFAEs	50	19	NR	NR	0.0%	4.0%
Della Bella	2009	RCT	CartoMerge™	145	14	NR	0.0%	1.4%	0.7%
Della Bella	2009	RCT	Conventional RFCA procedure	145	14	NR	0.0%	0.0%	0.7%
Di Biase	2009	Prospective Cohort Study	PVI + Posterior left atrial wall, CFAEs, mitral annular/LA roof lesions, CS isolation, and RA ablation; robotic approach	197	13.7	NR	NR	0.5%	0.5%
Di Biase	2009	Prospective Cohort Study	PVI + Posterior LA wall, CFAEs, mitral annular/LA roof lesions, CS isolation, and RA ablation; manual approach	193	14.6	NR	NR	1.0%	0.5%
Di Biase	2009	RCT	PVI only	35	13.7	NR	NR	0.0%	0.0%
Di Biase	2009	RCT	CFAEs ablation	34	13.7	NR	NR	0.0%	0.0%

Author	Year	Study Design	Intervention	Study N	Mean Follow-up, months	Intervention-specific harms			
			only						
Di Biase	2009	RCT	PVI + CFAEs	34	13.7	NR	NR	0.0%	0.0%
Essebag	2005	Case Series	PVI + mitral isthmus line and/or posterior LA line	85	15.8	0.0%	NR	2.4%	1.2%
Forleo	2009	RCT	PVI + CTI, roofline connecting superior PVs, isthmus between mitral annulus and left inferior PV	35	12	NR	NR	5.7%	5.7%
Helms	2009	Case Series	CPVI	73	12	NR	NR	0.0%	0.0%
Hocini	2005	Prospective Cohort Study	PVI + linear ablation joining the 2 superior PVs (roofline) + CTI//PVI only	90	14.5	NR	NR	2.2%	1.1%
Hof	2009	Case Series	WACA	146	19	NR	NR	0.0%	0.0%
Hsieh	2005	Prospective Cohort Study	PVI + SVC, non-PV foci, and CTI	37	58	0.0%	NR	0.0%	0.0%
Hsieh	2005	Prospective Cohort Study	AVN ablation	32	52	0.0%	NR	0.0%	0.0%
Hunter	2010	Case series	WACA; for persistent AF: linear ablation and CFAEs	285	32.4	0.0%	1.1%	3.2%	27.4%

Author	Year	Study Design	Intervention	Study N	Mean Follow-up, months	Intervention-specific harms			
Husser	2004	Case Series	PVI + RA isthmus	79	60.84	NR	NR	1.3%	2.5%
Jais	2008	RCT	PVI + CTI, linear lesions (LA roof), mitral isthmus	53	12	NR	NR	1.9%	3.8%
Joshi	2009	Case Series	PVI + Linear ablation (mitral isthmus and LA roof)	72	12	NR	NR	0.0%	0.0%
Kanagaratnam	2001	Case Series	PVI only	71	29	NR	NR	7.0%	19.7%
Khaykin	2009	RCT	PVI only	30	25.2	0.0%	0.0%	0.0%	3.3%
Khaykin	2009	RCT	CPVI, CFAE (30%), mitral isthmus and LA roof lines (77%)	30	25.2	0.0%	0.0%	0.0%	0.0%
Kim	2010	Prospective Cohort Study	CPVI with ablation of residual potentials	49	23.1	NR	NR	0.0%	0.0%
Kim	2010	Prospective Cohort Study	CPVI alone	53	23.4	NR	NR	0.0%	0.0%
Klemm	2006	Case Series	Segmental PVI, RA isthmus ablation	80	6	NR	NR	0.0%	0.0%
Knecht	2010	Prospective Cohort Study	LA and RA appendages, CFAEs, CTI using Carto imaging	47	10	NR	NR	0.0%	0.0%
Knecht	2010	Prospective Cohort Study	LA and RA appendages, CFAEs, CTI using 3DATG imaging	44	10	NR	NR	0.0%	0.0%

Author	Year	Study Design	Intervention	Study N	Mean Follow-up, months	Intervention-specific harms			
Kriatselis	2009	Case series	PVI only	44	6	NR	NR	0.0%	4.5%
Kumagai	2005	Prospective Cohort Study	Circular catheter-guided ablation	50	12	NR	NR	0.0%	28.0%
Kumagai	2005	Prospective Cohort Study	Basket catheter-guided ablation	50	12	NR	NR	0.0%	12.0%
Kusumoto	2009	Case Series	PVI with stepwise ablation: after PVI, linear ablation, CFAEs	240	12	NR	NR	0.0%	0.8%
Lakkireddy	2005	Prospective Cohort Study	PVI in patients with pacemakers or ICD	86	12	NR	1.2%	2.3%	1.2%
Lakkireddy	2005	Prospective Cohort Study	PVI in patients without pacemakers or ICD	86	12	NR	1.2%	1.2%	0.0%
Lin	2009	Prospective Cohort Study	PVI + Linear ablation (roof line and lateral mitral line) + CFAEs	30	19	NR	NR	0.0%	0.0%
Lin	2009	Prospective Cohort Study	PVI + Linear ablation (roof line and lateral mitral line)	30	19	NR	NR	0.0%	0.0%
Lo	2009	Prospective Cohort Study	PVI + Linear ablation, CFAEs; LA diameter of < 45mm	49	21	NR	NR	0.0%	2.0%

Author	Year	Study Design	Intervention	Study N	Mean Follow-up, months	Intervention-specific harms			
Lo	2009	Prospective Cohort Study	PVI + Linear ablation, CFAEs; LA diameter of ≥45mm	37	21	NR	NR	0.0%	0.0%
Macle	2002	Case Series	PVI + Bidirectional CTI block, linear ablation, lateral mitral isthmus line	136	8.8	NR	0.0%	0.0%	1.5%
Macle	2007	Case Series	PVI + Posterior LA	64	16	NR	0.0%	3.1%	0.0%
Malmborg	2003	Case Series	PVI only	40	8.9	NR	NR	0.0%	20.0%
Mangrum	2002	Case Series	CPVI; additional ablation for AFL or right AFL: tricuspid annulus/IVC linear lesion(s) and ectopy-initiating AF outside the PV	64	13	NR	NR	1.6%	4.7%
Marrouche	2007	RCT	Open-Irrigation	26	14	NR	NR	0.0%	19.2%
Marrouche	2007	RCT	ICE-Guided Energy Delivery with a Non-Irrigated Catheter	27	14	NR	NR	0.0%	29.6%
Matsuo	2009	Case series	PVI + CFAEs, linear ablation if AF continued (joining right and left superior PVs), then if it still continued, a mitral	90	28	NR	NR	0.0%	0.0%

Author	Year	Study Design	Intervention	Study N	Mean Follow-up, months	Intervention-specific harms			
			isthmus line						
Meissner	2009	Case Series	PVI only	72	6	0.0%	0.0%	0.0%	4.2%
Mesas	2006	Case Series	CPVI	72	12.7	NR	NR	0.0%	0.0%
Nademanee	2008	Case Series	CFAE ablation only	517	27.9	0.2%	0.4%	2.9%	2.3%
Neumann	2008	Prospective Cohort Study	CPVI in paroxysmal and persistent AF patients	346	12	0.0%	0.0%	0.6%	2.0%
O'Neill	2009	Case Series	PVI + CFAEs, linear ablation (mitral isthmus and LA roof), RA, SVC, linear ablation (CTI)	153	32	NR	NR	1.3%	2.6%
Oral	2006	Case series	PVI + LA RFCA performed in 29% of patients; CPVI in 71% of patients	755	25	NR	0.9%	0.0%	0.0%
Oral	2006	RCT	CPVI	77	12	0.0%	NR	1.3%	0.0%
Pappone	2001	Case Series	CPVI	251	10.4	NR	0.0%	0.8%	0.8%
Pappone	2003	Prospective Cohort Study	CPVI	589	28.7	NR	0.0%	5.6%	0.2%

Author	Year	Study Design	Intervention	Study N	Mean Follow-up, months	Intervention-specific harms			
Pappone	2006	RCT	CPVI	99	12	NR	NR	0.0%	0.0%
Patel	2010	Prospective Cohort Study	PVI + Posterior wall between PVs, anterior tissue to the right PV along the left septum, SVC, CFAEs; ablation performed in females	518	24.28	NR	NR	0.0%	4.2%
Patel	2010	Prospective Cohort Study	PVI + Posterior wall between PVs, anterior tissue to the right PV along the left septum, SVC, CFAEs; ablation performed in males	2747	35.57	NR	NR	0.0%	3.2%
Pontoppidan	2009	RCT	PVI + CTI	73	31	NR	1.5%	5.5%	0.0%
Pontoppidan	2009	RCT	PVI only	76	37	NR	0.0%	2.6%	1.3%
Rossillo	2008	Retrospective matched cohort study	PVI + SVC//DC-Shock	170		NR	0.0%	0.0%	3.5%
Saliba	2008	Case Series	PVI + SVC	40	12	NR	NR	5.0%	0.0%
Sawhney	2009	Case Series	CPVI and LA linear ablation	71	42.2	NR	0.0%	0.0%	4.2%
Scharf	2009	Case	PVI only	50	20	NR	NR	4.0%	8.0%

Author	Year	Study Design	Intervention	Study N	Mean Follow-up, months	Intervention-specific harms			
		Series							
Shin	2006	Case Series	PVI + Non-PV triggers	68	6	NR	NR	0.0%	0.0%
Siklody	2009	Case Series	PVI only	30	7.4	NR	NR	0.0%	20.0%
Stabile	2006	RCT	CPVI with CTI line	68	12	NR	1.5%	0.0%	4.4%
Stabile	2009	Prospective Cohort Study	PVI + LA, CTI, using integrated approach	36	15.2	NR	NR	0.0%	2.8%
Stabile	2009	Prospective Cohort Study	PVI + LA, CTI using anatomical approach	61	14.9	NR	NR	0.0%	0.0%
Steven	2010	Prospective Cohort Study	PVI + Posterior LA wall, ipsilateral veins with robotic navigation of catheter	30	15.2	NR	0.0%	0.0%	0.0%
Steven	2010	Prospective Cohort Study	PVI + Posterior LA wall, ipsilateral veins using a conventional approach to catheter ablation	30	15.2	NR	0.0%	0.0%	0.0%
Tamborero	2009	RCT	Superior PVs were connected by linear lesions along the LA roof	60	9.8	NR	NR	0.0%	1.7%
Tamborero	2009	RCT	LA posterior wall isolated by adding a second line connecting the inferior aspect of	60	9.8	NR	NR	0.0%	3.3%

Author	Year	Study Design	Intervention	Study N	Mean Follow-up, months	Intervention-specific harms			
			the 2 inferior PVs						
Tan	2009	Case Series	Catheter ablation	99	6	NR	1.0%	1.0%	5.1%
Themistoclakis	2010	Prospective Cohort Study	No-OAT/Catheter ablation	2692	10	NR	0.2%	0.0%	0.0%
Themistoclakis	2010	Prospective Cohort Study	OAT/Catheter ablation	663	10	NR	0.0%	0.0%	0.0%
Tzou	2010	Case series	PVI only	123	70.8	NR	NR	0.0%	0.0%
Udyavar	2008	Case Series	CPVI with PV carina	97	12.9	NR	NR	0.0%	0.0%
Van Belle	2008	Case Series	CPVI; CTI ablation in 7 patients with isthmus flutter	141	24	NR	NR	1.4%	5.7%
Wazni	2005	RCT	PVI only	32	12	NR	NR	6.3%	6.3%
Wazni	2009	Case Series	SVC, using the Hansen ablation system	71	6	0.0%	NR	9.9%	8.5%
Wiesfeld	2004	Case Series	PVI + LA, RA and respective appendages	25	28	NR	NR	8.0%	12.0%
Wilber	2010	RCT	PVI - Allowed at discretion of investigator; included left atrial linear lesions, CFAEs and CTI	106	9	0.0%	NR	1.9%	2.8%

Author	Year	Study Design	Intervention	Study N	Mean Follow-up, months	Intervention-specific harms			
			ablation						
Wokhlu	2010	Case Series	Some CPVI, other WACA with additional linear lesions along the LA roof and the left inferior isthmus	502	36	NR	1.2%	3.4%	7.4%
Wokhlu	2010	Case Series	Some PVI, some WACA	774	36	NR	NR	0.0%	0.0%
Yamada	2006	Case Series	CPVI	55	11	NR	NR	0.0%	0.0%
Yamada	2009	Prospective Cohort Study	CPVI with vagal nerve ablation	60	12	NR	NR	0.0%	0.0%
Yamada	2009	Prospective Cohort Study	Segmental PVI with vagal nerve ablation	60	12	NR	NR	0.0%	0.0%
Yoshida	2009	Case Series	PVI only	77	12	NR	NR	0.0%	0.0%

Antiarrhythmic agents						Annual Rate – Pulm. toxicity	Annual Rate - Thyroid toxicity	Annual Rate - Premature discont.
AFFIRM	2003	RCT	Amiodarone	154	46	0.5%	NR	NR
AFFIRM	2003		Placebo	135	46	0.1%	NR	NR
Channer	2004	RCT	Amiodarone	62	12	1.6%	0.0%	8.1%

Author	Year	Study Design	Intervention	Study N	Mean Follow-up, months	Intervention-specific harms		
Channer	2004		Amiodarone	63	12	0.0%	6.3%	17.5%
Channer	2004		Placebo	38	12	2.6%	0.0%	2.6%
Connolly	2009	RCT	Dronedarone	2301	30	NR	NR	NR
Connolly	2009		Placebo	2327	30	NR	NR	NR
Galperin	2001	RCT	Amiodarone	47	16.03	NR	1.6%	1.6%
Galperin	2001		Placebo	48	16.03	NR	0.0%	0.0%
Hohnloser	2000	RCT	Amiodarone	127	12	NR	5.5%	24.4%
Hohnloser	2000		Diltiazem	125	12	NR	0.0%	13.6%
Hohnloser	2009	RCT	Dronedarone	2301	21	0.1%	0.4%	7.2%
Hohnloser	2009		Placebo	2327	21	0.1%	0.3%	4.6%
Killborn	2002	Prospective Cohort Study	Amiodarone	550	12	NR	NR	NR
Killborn	2002		Placebo	14730	12	NR	NR	NR
Kochiadakis	2000	RCT	Amiodarone	65	24	NR	6.2%	11.5%
Kochiadakis	2000		Sotalol	61	24	NR	0.0%	1.6%
Kochiadakis	2000		Placebo	60	24	0.0%	0.0%	0.0%
Kochiadakis	2004	RCT	Amiodarone	72	19	NR	12.3%	10.5%
Kochiadakis	2004		Propafenone	72	21	NR	NR	1.6%
Le Heuzey	2009	RCT	Dronedarone	249	7	0.0%	2.8%	9.0%
Le Heuzey	2009		Amiodarone	255	7	0.0%	10.1%	18.8%
Roy	2000	RCT	Amiodarone	201	15.6	1.5%	1.1%	26.0%
Roy	2000		Sotalol/Propafenone	202	15.6	0.0%	0.0%	35.4%
Singh	2005	RCT	Amiodarone	267	12	0.7%	NR	NR
Singh	2005		Sotalol	261	12	0.0%	NR	NR

Author	Year	Study Design	Intervention	Study N	Mean Follow-up, months	Intervention-specific harms		
Singh	2005		Placebo	137	12	0.7%	NR	NR
Singh	2007	RCT	Dronedarone	828	12	NR	13.4%	17.9%
Singh	2007		Placebo	409	12	NR	17.1%	14.9%
Touboul	2003	RCT	Dronedarone	54	12	NR	NR	0.0%
Touboul	2003		Dronedarone	54	12	NR	NR	5.6%
Touboul	2003		Dronedarone	43	12	NR	NR	11.6%
Touboul	2003		Placebo	48	12	NR	NR	29.2%
Thorascopic, off-pump surgical ablation						**Periop. Mort.**	**Periop. Stroke**	**%Major compl.**	**%Minor compl.**
Bagge	2009	Case Series	Thoracoscopic off-pump epicardial PVI and GP ablation	43	12	0.0%	2.3%	14.0%	23.3%
Beyer	2009	Case Series	PVI/autonomic denervation, GP stimulation	100	13.6	0.0%	NR	4.0%	8.0%
Castella	2010	Case Series	Thoracoscopic PVI	34	16	0.0%	2.9%	8.8%	2.9%
Cui	2010	Case Series	Bilateral PV antrum isolation and division of the LOM	81	12.7	1.2%	1.2%	3.7%	4.9%
Edgerton	2009	Case Series	Bilateral PV antrum isolation	74	6	NR	NR	0.0%	0.0%
Edgerton	2009	Case Series	PVI/left-sided "Dallas" set	114	17	1.8%	NR	4.4%	6.1%

Author	Year	Study Design	Intervention	Study N	Mean Follow-up, months	Intervention-specific harms				
Edgerton	2009	Case Series	Bilateral PVI/GP stimulation/additional ablation post-testing	30	6	0.0%	0.0%	0.0%	16.7%	
Edgerton	2010	Case series	Bilateral, epicardial PVI and partial autonomic denervation	52	12	0.0%	0.0%	0.0%	7.7%	
Han	2009	Case Series	Bilateral PVI/GP ablation/LOM ablation	45	17	0.0%	NR	0.0%	11.1%	
Sirak	2008	Case Series	Totally thoracoscopic PVI, extended linear ablations across critical segments of atrial substrate	32	13	0.0%	0.0%	3.1%	0.0%	
Wolf	2005	Case Series	Cox Maze IV	27	14.5	0.0%	0.0%	3.7%	11.1%	
Yilmaz	2010	Case Series	Minimally invasive Cryomaze	30	11.6	0.0%	0.0%	3.3%	6.7%	

Stroke prevention - Dabigatran						Annual Rate - Major bleeding	Annual Rate - Minor bleeding	Annual Rate - Intracranial bleeding	Annual Rate - Extracranial bleeding	Annual Rate - Discontinuation
Connolly	2009	RCT	Dabigatran, 110 mg	6015	24	2.71	13.16	0.23	2.51	9.7%
			Dabigatran, 150 mg	6076	24	3.11	14.84	0.3	2.84	10.0%
			Warfarin	6022	24	3.36	16.37	0.74	2.67	7.5%

Author	Year	Study Design	Intervention	Study N	Mean Follow-up, months	Intervention-specific harms		
Stroke prevention - Watchman						**Periop. Mort.**	**Periop. Stroke**	**Procedural Compl.**
Holmes	2009	RCT	Watchman	463	18	0	1.1%	6.50%
			Warfarin	244	18	NR	0	NR

ADT, antiarrhythmic drug therapy; AFL, atrial flutter; AVN, atrioventricular junction ; CFAEs, complex fractionated atrial electrograms; Compl., complications; CPVI, circumferential pulmonary vein isolation; CS, coronary sinus; CT, computed tomography; CTI, cavotricuspid isthmus; DC, direct-current; ECG, electrocardiogram; GP, ganglionic plexi; ICD, implantable cardiodefibrillators; ICE, intracardiac echocardiogram; IVC, inferior vena cava; LA, left atrium; LOM, ligament of Marshall; MR, magnetic resonance; Mort., mortality; NR, not reported; OAT, oral anti-coagulation; periop., perioperative; PeAF, persistent atrial fibrillation; PV, pulmonary vein; PVI, pulmonary vein isolation; RA, right atrium; RCT, randomized controlled trial; RFCA, radiofrequency catheter ablation; SVC, superior vena cava; WACA, wide-area circumferential ablation

APPENDIX C

META-ANALYSES

Figure C1. Meta-analysis of all-cause mortality for catheter ablation vs. AADs.

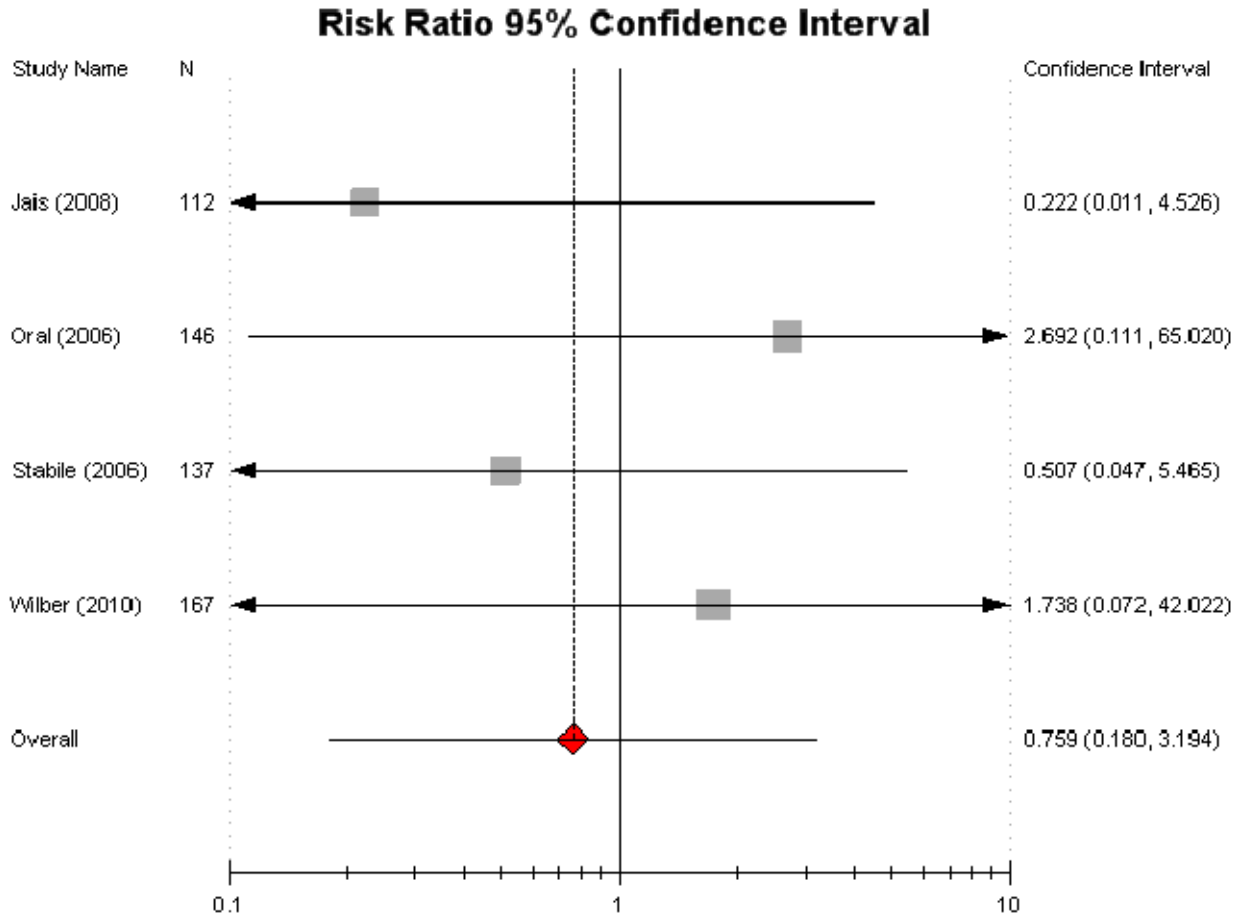


Figure C2. Meta-analysis of short-term freedom from AF for catheter ablation vs. AADs.

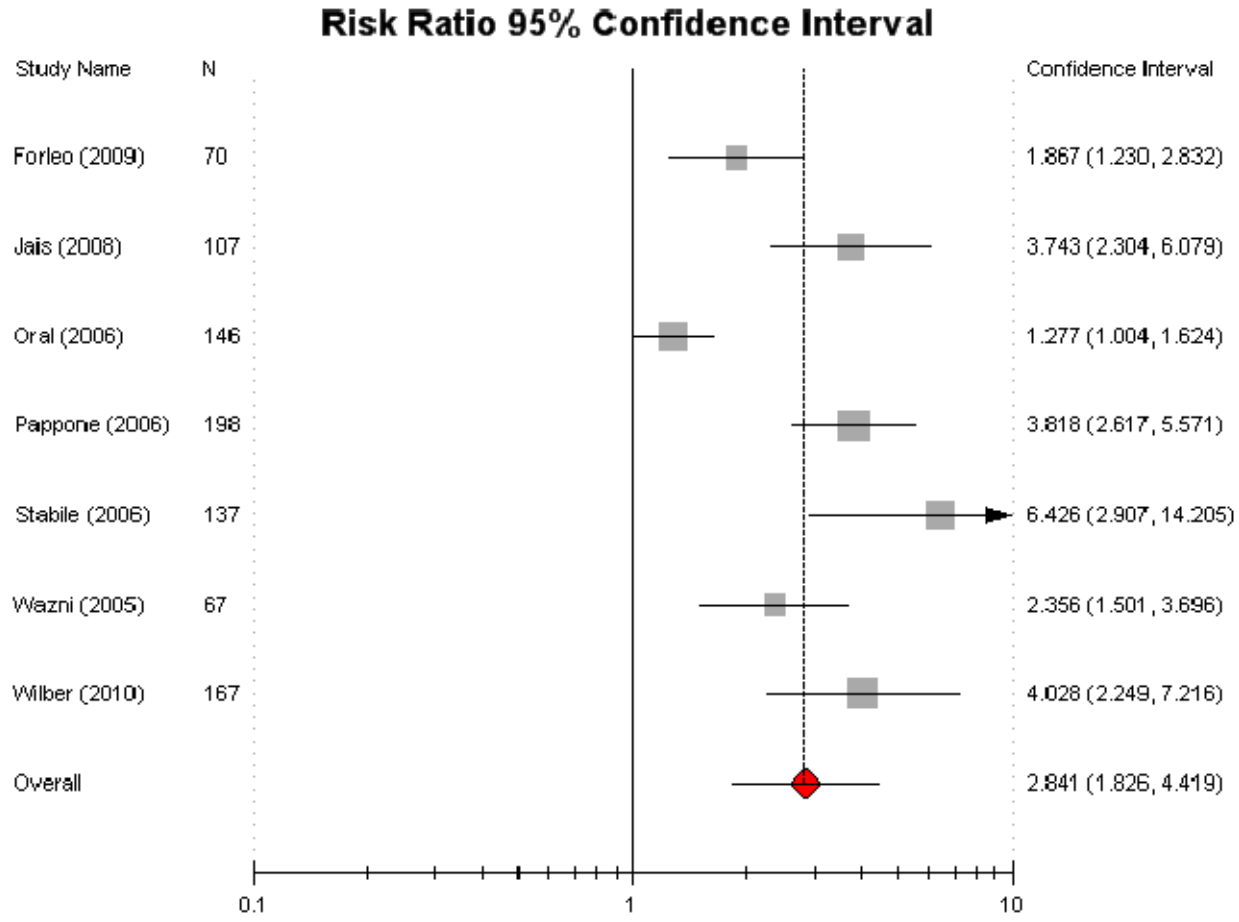


Figure C3. Meta-analysis of short-term freedom from AF for catheter ablation vs. AADs; predominantly paroxysmal AF populations.

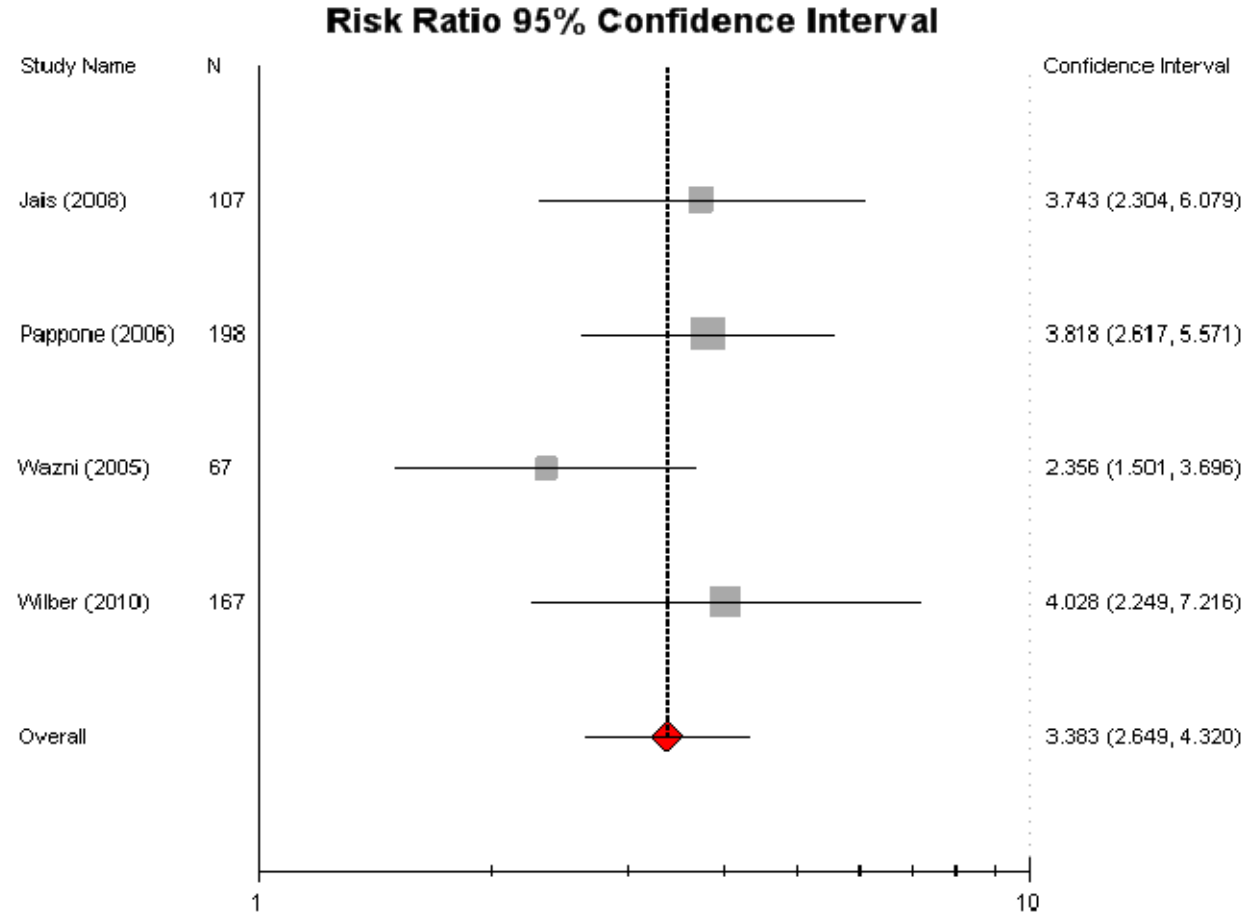


Figure C4. Meta-analysis of short-term freedom from AF for catheter ablation vs. AADs; mixed AF populations.

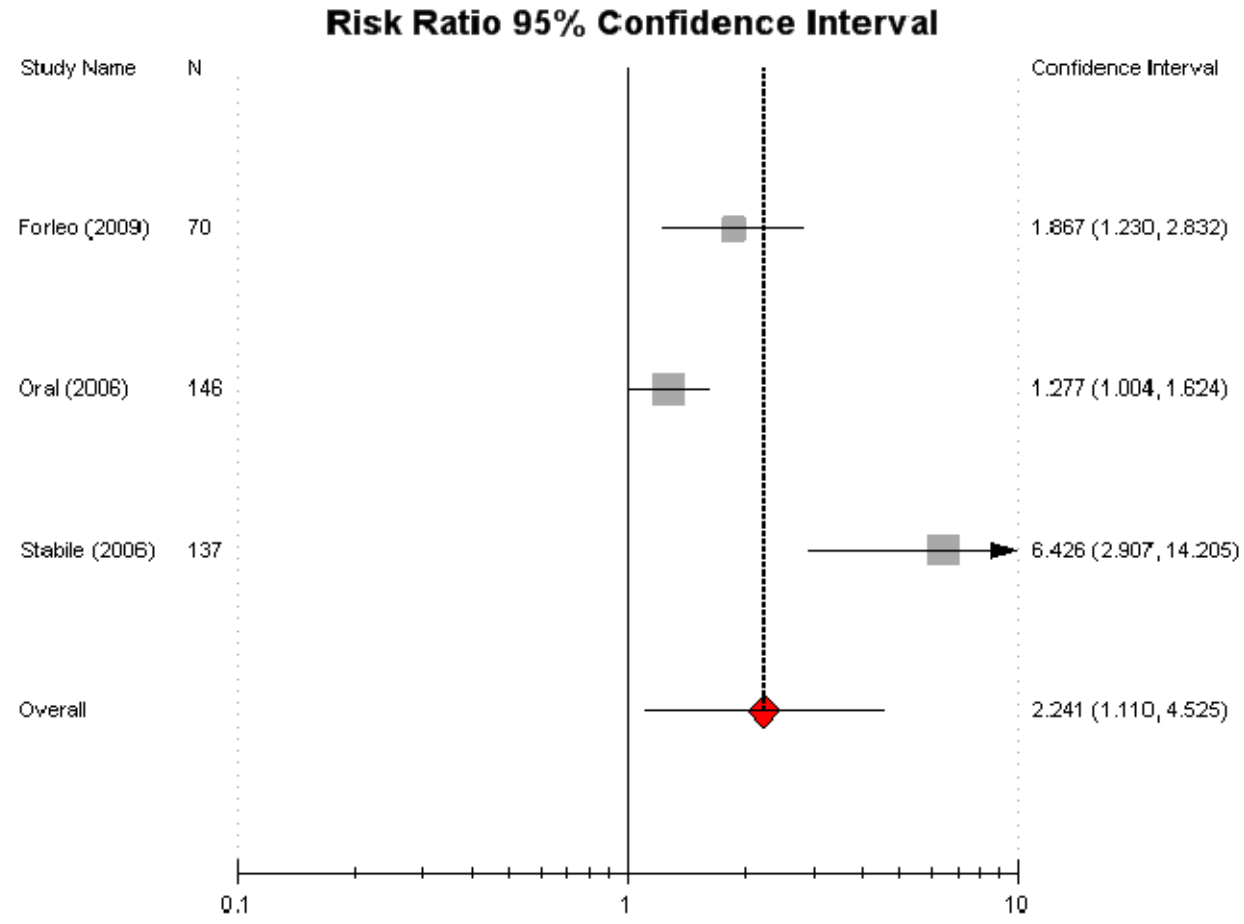


Figure C5. Pooled estimate of impact of amiodarone on all-cause mortality.

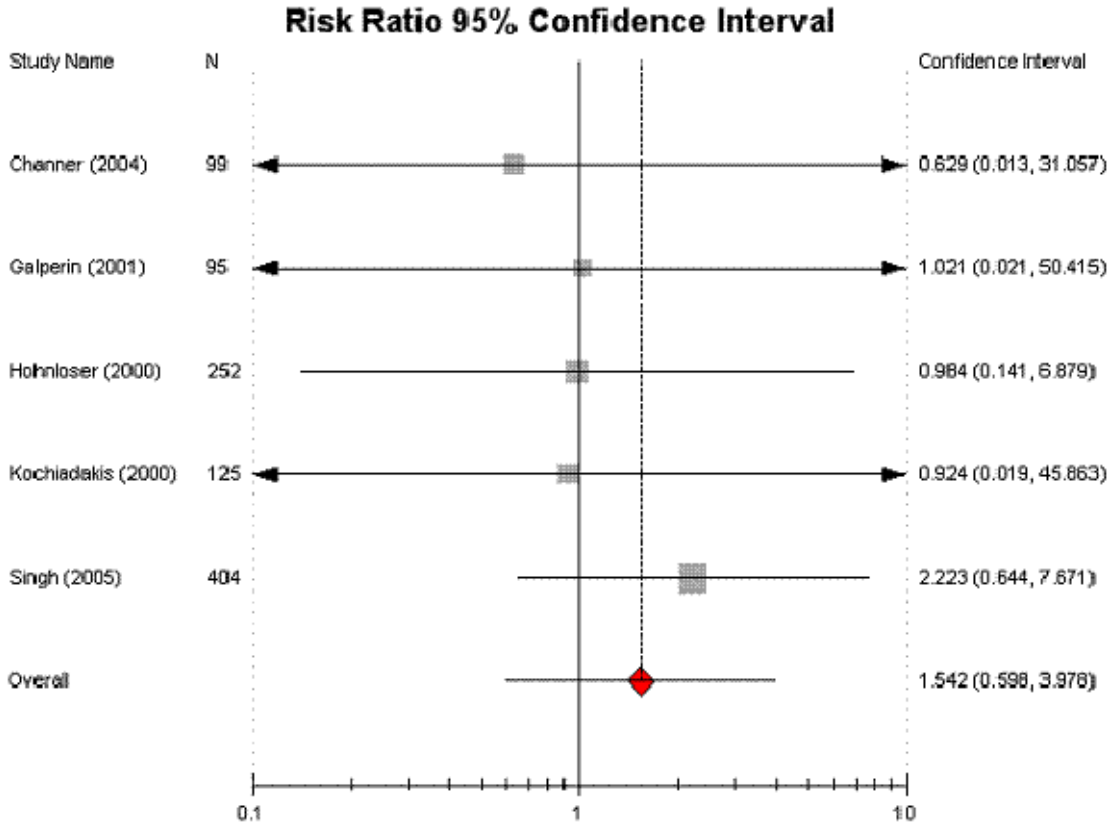


Figure C6. Pooled estimate of impact of dronedarone on all-cause mortality.

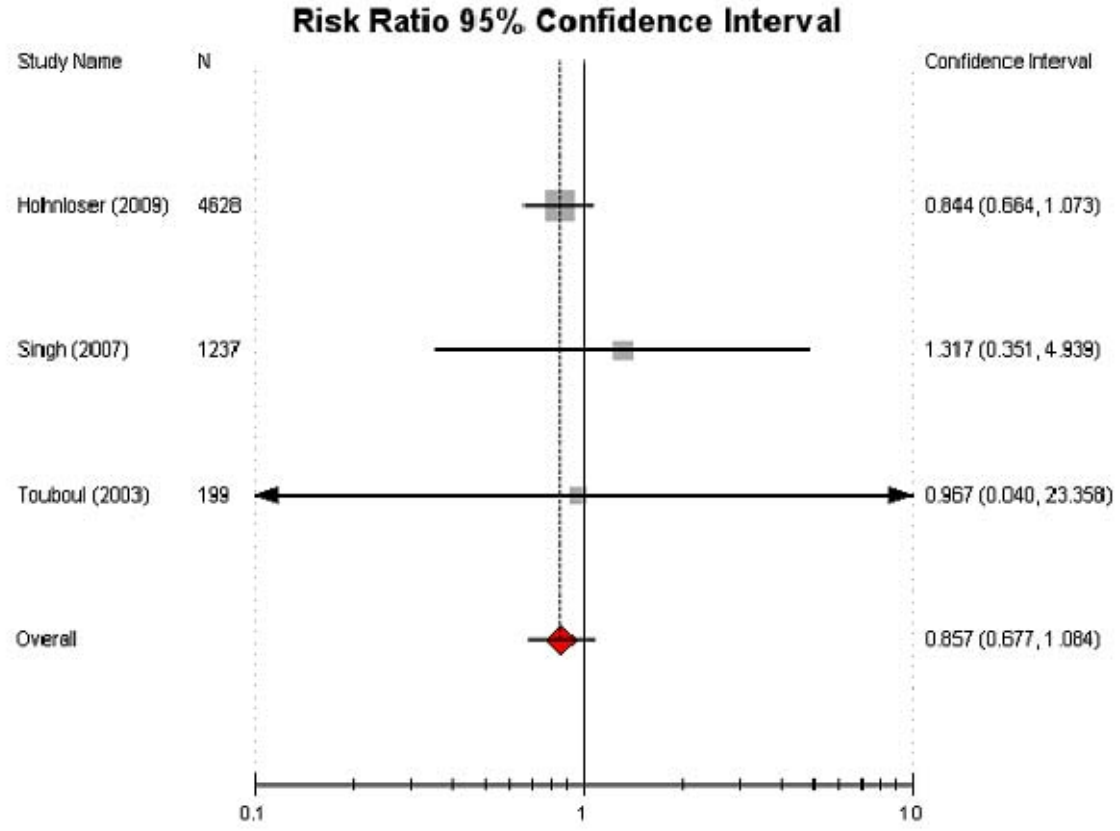


Table C1. Results of mixed treatment comparison of likelihood of freedom from AF at 6-12 months, by agent and comparison.

	Amiodarone	Sotalol	Dronedarone
	Odds Ratio (95% CI)		
Control	5.68 (3.23, 9.66)	2.16 (0.96, 4.20)	1.67 (0.68, 3.66)
Amiodarone		0.39 (0.18, 0.74)	0.31 (0.12, 0.68)
Sotalol			0.88 (0.27, 2.27)

Note: Results are presented as agent in column vs. agent in row
CI: Confidence interval

Table C2. Results of mixed treatment comparison of likelihood of drug discontinuation due to adverse effects, by agent and comparison.

	Amiodarone	Sotalol	Dronedarone
	Odds Ratio (95% CI)		
Control	5.82 (1.14, 20.01)	2.23 (0.13, 11.16)	8.89 (0.71, 43.41)
Amiodarone		0.46 (0.03, 2.20)	2.02 (0.14, 9.62)
Sotalol			12.86 (0.26, 74.58)

Note: Results are presented as agent in column vs. agent in row
CI: Confidence interval

APPENDIX D

COMPARATIVE VALUE EVIDENCE TABLES

Table D1. Estimated lifetime clinical outcomes for cardiovascular management

Outcome	Rate Control	CA (Primary)	CA (Secondary)	TOP (Secondary)	Rhythm Control (Amiodarone)	Rhythm Control (Dronedarone)	Rhythm Control (Dronedarone First)
Age 60 Paroxysmal AF							
Life Years	20.484	20.407	20.216	19.92	20.28	20.28	20.28
AF Time	16.42	3.364	2.475	2.342	12.569	14.557	10.858
QALYs	11.032	11.629	11.507	11.463	11.116	11.022	11.217
Microsimulation							
Procedures		2.216	1.876	1.879	0	0	0
LACAs	0	2.216	1.861	0.988	0	0	0
Major complications	0	0.026	0.024	0.046	0	0	0
Minor complications	0	0.081	0.069	0.108	0	0	0
Stroke peri-procedure	0	0.009	0.007	0.009	0	0	0
Drug toxicity episodes	0.251	0.000	0.406	0.406	0.605	0.467	0.666
Strokes, Total	0.093	0.105	0.103	0.085	0.094	0.097	0.096
Intracranial hemorrhage	0.054	0.055	0.080	0.040	0.057	0.057	0.057
Deaths AF or AF related	0.026	0.017	0.029	0.024	0.038	0.039	0.037
Deaths peri-procedure	0.000	0.004	0.004	0.007	0.000	0	0.000
Death from all causes	0.962	0.957	0.948	0.954	0.949	0.948	0.951
Age 65 Persistent AF w/CHF							
Life Years	16.786	16.718	16.562	16.348	16.619	16.619	16.619
AF Time	13.013	5.011	3.554	3.405	9.602	11.335	8.091
QALYs	8.574	8.964	8.902	8.882	8.67	8.585	8.762
Microsimulation							
Procedures	0	2.416	1.975	1.981	0	0	0
LACAs	0	2.416	1.948	1.116	0	0	0
Major complications	0	0.028	0.025	0.046	0	0	0

Outcome	Rate Control	CA (Primary)	CA (Secondary)	TOP (Secondary)	Rhythm Control (Amiodarone)	Rhythm Control (Dronedarone)	Rhythm Control (Dronedarone First)
Minor complications	0	0.091	0.078	0.11	0	0	0
Stroke peri-procedure	0	0.008	0.006	0.009	0	0	0
Drug toxicity episodes	0.198	0	0.394	0.394	0.550	0.414	0.603
Strokes, Total	0.122	0.125	0.129	0.099	0.119	0.120	0.119
Intracranial hemorrhage	0.052	0.051	0.100	0.053	0.051	0.052	0.050
Deaths AF or AF related	0.027	0.017	0.029	0.027	0.040	0.040	0.039
Deaths peri-procedure	0	0.003	0.003	0.006	0	0	0
Death from all causes	0.961	0.957	0.949	0.952	0.948	0.948	0.949
Age 75 DM/HTN/ Persistent AF							
Life Years	10.525	10.492	10.393	10.014	10.42	10.42	10.42
AF Time	7.747	2.11	1.405	1.258	5.206	6.424	4.119
QALYs	5.703	6.003	5.944	5.828	5.797	5.733	5.87
Microsimulation							
Procedures	0	2.117	1.535	1.516	0	0	0
LACAs	0	2.117	1.515	0.754	0	0	0
Major complications	0	0.024	0.017	0.035	0	0	0
Minor complications	0	0.079	0.054	0.085	0	0	0
Stroke peri-procedure	0	0.008	0.006	0.008	0	0	0
Drug toxicity episodes	0.124	0	0.343	0.343	0.427	0.314	0.466
Strokes, Total	0.101	0.111	0.106	0.114	0.100	0.102	0.102
Intracranial hemorrhage	0.049	0.045	0.084	0.043	0.044	0.047	0.049
Deaths AF or AF related	0.020	0.013	0.024	0.025	0.028	0.029	0.029
Deaths peri-procedure	0	0.003	0.002	0.005	0	0	0
Death from all causes	0.966	0.961	0.953	0.951	0.956	0.954	0.956

Table D2. Estimated lifetime clinical outcomes for stroke prevention

Outcome	Warfarin/Aspirin	Dabigatran 110 mg	Dabigatran 150 mg	WATCHMAN
Age 60 Paroxysmal AF				
Life Years	20.484	20.783	20.814	20.221
AF Time	16.42	13.416	13.481	16.549
QALYs	11.032	11.401	11.417	11.011
Microsimulation				
Procedures		0	0	0.997
LACAs	0	0	0	0
Major complications	0	0	0	0.030
Minor complications	0	0	0	0.052
Stroke peri-procedure	0	0	0	0.010
Drug toxicity episodes	0.251	0.624	0.625	0.259
Strokes, Total	0.093	0.059	0.039	0.069
Intracranial hemorrhage	0.054	0.019	0.028	0.030
Deaths AF or AF related	0.026	0.026	0.023	0.018
Deaths peri-procedure	0.000	0.000	0.000	0.000
Death from all causes	0.962	0.960	0.963	0.975
Age 65 Persistent AF w/CHF				
Life Years	16.786	17.049	17.101	16.535
AF Time	13.013	10.305	10.406	13.147
QALYs	8.574	8.935	8.962	8.564
Microsimulation				
Procedures	0	0	0	1.00
LACAs	0	0	0	0
Major complications	0	0	0	0.033
Minor complications	0	0	0	0.054
Stroke peri-procedure	0	0	0	0.010
Drug toxicity episodes	0.198	0.571	0.571	0.212
Strokes, Total	0.122	0.076	0.051	0.088
Intracranial hemorrhage	0.052	0.015	0.024	0.024
Deaths AF or AF related	0.027	0.029	0.026	0.020
Deaths peri-procedure	0	0	0	0
Death from all causes	0.961	0.958	0.960	0.971
Age 75 DM/HTN/ Persistent AF				
Life Years	10.525	10.493	10.554	10.109
AF Time	7.747	5.391	5.488	7.565
QALYs	5.703	5.934	5.97	5.602

Outcome	Warfarin/Aspirin	Dabigatran 110 mg	Dabigatran 150 mg	WATCHMAN
Microsimulation				
Procedures	0	0	0	0.988
LACAs	0	0	0	0
Major complications	0	0	0	0.029
Minor complications	0	0	0	0.053
Stroke peri-procedure	0	0	0	0.010
Drug toxicity episodes	0.124	0.432	0.438	0.125
Strokes, Total	0.101	0.096	0.068	0.094
Intracranial hemorrhage	0.049	0.013	0.019	0.017
Deaths AF or AF related	0.020	0.031	0.027	0.018
Deaths peri-procedure	0	0	0	0
Death from all causes	0.966	0.953	0.956	0.969

Table D3. Estimated lifetime costs for cardiovascular management

Outcome	Rate Control	CA (Primary)	CA (Secondary)	TOP (Secondary)	Rhythm Control (Amiodarone)	Rhythm Control (Dronedarone)	Rhythm Control (Dronedarone First)
Age 60 Paroxysmal AF							
Total Costs	$ 15,299	$ 34,044	$ 35,038	$ 43,976	$ 20,265	$ 27,749	$ 30,700
Procedure Costs	$ -	$ 22,172	$ 17,285	$ 29,715	$ -	$ -	$ -
Complication Costs	$ -	$ 324	$ 249	$ 503	$ -	$ -	$ -
Drug Costs	$ 7,042	$ 2,766	$ 5,273	$ 4,139	$ 9,267	$ 11,116	$ 17,924
Adverse Event Costs	$ 8,192	$ 8,376	$ 8,218	$ 5,895	$ 8,182	$ 6,066	$ 8,182
Age 65 Persistent AF w/CHF							
Total Costs	$ 15,721	$ 38,245	$ 37,522	$ 46,163	$ 20,332	$ 27,829	$ 30,536
Procedure Costs	$ -	$ 24,868	$ 18,837	$ 30,918	$ -	$ -	$ -
Complication Costs	$ -	$ 361	$ 268	$ 521	$ -	$ -	$ -
Drug Costs	$ 6,675	$ 3,605	$ 5,515	$ 4,413	$ 8,554	$ 10,588	$ 17,019
Adverse Event Costs	$ 8,984	$ 9,051	$ 8,943	$ 6,580	$ 8,965	$ 6,520	$ 8,965
Age 75 DM/HTN/ Persistent AF							
Total Costs	$ 13,792	$ 34,410	$ 32,081	$ 39,744	$ 17,759	$ 24,334	$ 26,560
Procedure Costs	$ -	$ 22,527	$ 15,469	$ 26,146	$ -	$ -	$ -
Complication Costs	$ -	$ 311	$ 211	$ 477	$ -	$ -	$ -
Drug Costs	$ 6,708	$ 3,756	$ 4,877	$ 3,174	$ 7,939	$ 9,014	$ 15,120
Adverse Event Costs	$ 7,014	$ 6,877	$ 6,889	$ 5,753	$ 7,024	$ 5,306	$ 7,024

Table D4. Estimated lifetime costs for stroke prevention

Outcome	Warfarin/Aspirin	Dabigatran 110	Dabigatran 150	WATCHMAN
Age 60 Paroxysmal AF				
Total Costs	$ 15,299	$ 83,015	$ 82,780	$ 23,053
Procedure Costs	$ -	$ -	$ -	$ 11,306
Complication Costs	$ -	$ -	$ -	$ 98
Drug Costs	$ 7,042	$ 76,046	$ 76,232	$ 6,423
Adverse Event Costs	$ 8,192	$ 4,153	$ 3,731	$ 5,001
Age 65 Persistent AF w/CHF				
Total Costs	$ 15,721	$ 72,795	$ 72,451	$ 22,659
Procedure Costs	$ -	$ -	$ -	$ 11,290
Complication Costs	$ -	$ -	$ -	$ 98
Drug Costs	$ 6,675	$ 65,255	$ 65,613	$ 5,764
Adverse Event Costs	$ 8,984	$ 4,726	$ 4,025	$ 5,287
Age 75 DM/HTN/ Persistent AF				
Total Costs	$ 13,792	$ 51,351	$ 50,944	$ 20,625
Procedure Costs	$ -	$ -	$ -	$ 11,215
Complication Costs	$ -	$ -	$ -	$ 97
Drug Costs	$ 6,708	$ 43,597	$ 44,078	$ 4,555
Adverse Event Costs	$ 7,014	$ 4,957	$ 4,069	$ 4,543

Table D5. Estimated 5-year clinical outcomes for cardiovascular management

Outcome	Rate Control	CA (Primary)	CA (Secondary)	TOP (Secondary)	Rhythm Control	Rhythm Control (Dronedarone)	Rhythm Control (Dronedarone First)
Age 60 Paroxysmal AF							
Life Years	4.83	4.821	4.778	4.772	4.783	4.783	4.783
AF Time	3.348	0.207	0.223	0.218	1.728	2.354	1.15
QALYs	3.548	3.739	3.675	3.672	3.627	3,589	3.675
Microsimulation							
Procedures	0	1.502	0.920	0.917	0	0	0
LACAs	0	1.502	0.910	0.252	0	0	0
Major complications	0	0.019	0.013	0.028	0	0	0
Minor complications	0	0.055	0.033	0.062	0	0	0
Stroke peri-procedure	0	0.006	0.003	0.005	0	0	0
Drug toxicity episodes	0	0.316	0.290	0.290	0.061	0.226	0.327
Strokes, Total	0.020	0.024	0.023	0.023	0.021	0.021	0.021
Intracranial hemorrhage	0.008	0.008	0.027	0.015	0.008	0.008	0.008
Deaths AF or AF related	0.006	0.002	0.015	0.015	0.017	0.017	0.017
Deaths peri-procedure	0.000	0.002	0.002	0.003	0.000	0	0
Death from all causes	0.063	0.063	0.062	0.063	0.061	0.061	0.058
Age 65 Persistent AF w/CHF							
Life Years	4.754	4.743	4.701	4.696	4.708	4.708	4.708
AF Time	3.275	0.38	0.289	0.274	1.689	2.3	1.125
QALYs	3.205	3.38	3.327	3.325	3.286	3.249	3.334

Outcome	Rate Control	CA (Primary)	CA (Secondary)	TOP (Secondary)	Rhythm Control	Rhythm Control (Dronedarone)	Rhythm Control (Dronedarone First)
Microsimulation							
Procedures	0	1.801	1.066	1.06	0	0	0
LACAs	0	1.801	1.049	0.398	0	0	0
Major complications	0	0.021	0.014	0.029	0	0	0
Minor complications	0	0.069	0.04	0.066	0	0	0
Stroke peri-procedure	0	0.006	0.003	0.005	0	0	0
Drug toxicity episodes	0.059	0	0.279	0.279	0.305	0.215	0.321
Strokes, Total	0.038	0.037	0.039	0.035	0.035	0.036	0.037
Intracranial hemorrhage	0.008	0.007	0.044	0.023	0.010	0.009	0.007
Deaths AF or AF related	0.009	0.004	0.014	0.014	0.017	0.017	0.017
Deaths peri-procedure	0.000	0.002	0.002	0.004	0.000	0	0
Death from all causes	0.094	0.093	0.093	0.096	0.093	0.094	0.094
Age 75 DM/HTN/ Persistent AF							
Life Years	4.452	4.445	4.404	4.378	4.409	4.409	4.409
AF Time	3.036	0.356	0.275	0.262	1.558	2.122	1.041
QALYs	2.817	2.982	2.931	2.935	2.896	2.861	2.94
Microsimulation							
Procedures	0	1.744	1.001	0.998	0	0	0
LACAs	0	1.744	0.984	0.367	0	0	0
Major complications	0	0.02	0.012	0.03	0	0	0
Minor complications	0	0.065	0.035	0.06	0	0	0
Stroke peri-procedure	0	0.007	0.003	0.004	0	0	0

Outcome	Rate Control	CA (Primary)	CA (Secondary)	TOP (Secondary)	Rhythm Control	Rhythm Control (Dronedarone)	Rhythm Control (Dronedarone First)
Drug toxicity episodes	0.054	0	0.267	0.267	0.292	0.211	0.307
Strokes, Total	0.039	0.046	0.043	0.046	0.037	0.039	0.040
Intracranial hemorrhage	0.021	0.016	0.053	0.028	0.022	0.022	0.022
Deaths AF or AF related	0.007	0.004	0.016	0.016	0.018	0.018	0.019
Deaths peri-procedure	0	0.002	0.002	0.003	0	0	0
Death from all causes	0.228	0.226	0.222	0.231	0.221	0.224	0.220

Table D6. Estimated 5-year clinical outcomes for stroke prevention

Outcome	Warfarin/Aspirin	Dabigatran 110 mg	Dabigatran 150 mg	WATCHMAN
Age 60 Paroxysmal AF				
Life Years	4.83	4.798	4.799	4.824
AF Time	3.348	1.746	1.746	3.343
QALYs	3.548	3.641	3.642	3.545
Microsimulation				
Procedures	0	0	0	0.997
LACAs	0	0	0	0
Major complications	0	0	0	0.035
Minor complications	0	0	0	0.052
Stroke peri-procedure	0	0	0	0.011
Drug toxicity episodes	0	0.318	0.318	0.062
Strokes, Total	0.020	0.008	0.005	0.019
Intracranial hemorrhage	0.008	0.004	0.006	0.006
Deaths AF or AF related	0.006	0.014	0.014	0.004
Deaths peri-procedure	0.000	0	0	0
Death from all causes	0.063	0.059	0.059	0.064
Age 65 Persistent AF w/CHF				
Life Years	4.754	4.73	4.731	4.748
AF Time	3.275	1.715	1.717	3.282
QALYs	3.205	3.307	3.308	3.206
Microsimulation				
Procedures	0	0	0	0.995
LACAs	0	0	0	0
Major complications	0	0	0	0.032
Minor complications	0	0	0	0.055
Stroke peri-procedure	0	0	0	0.008
Drug toxicity episodes	0.059	0.308	0.308	0.060
Strokes, Total	0.038	0.014	0.009	0.024
Intracranial hemorrhage	0.008	0.004	0.005	0.006
Deaths AF or AF related	0.009	0.013	0.012	0.005
Deaths peri-procedure	0.000	0	0	0
Death from all causes	0.094	0.089	0.089	0.096
Age 75 DM/HTN/ Persistent AF				
Life Years	4.452	4.411	4.415	4.407
AF Time	3.036	1.574	1.58	3.019
QALYs	2.817	2.946	2.951	2.828

Outcome	Warfarin/Aspirin	Dabigatran 110 mg	Dabigatran 150 mg	WATCHMAN
Microsimulation				
Procedures	0	0	0	0.988
LACAs	0	0	0	0
Major complications	0	0	0	0.030
Minor complications	0	0	0	0.052
Stroke peri-procedure	0	0	0	0.010
Drug toxicity episodes	0.054	0.293	0.294	0.058
Strokes, Total	0.039	0.038	0.027	0.041
Intracranial hemorrhage	0.021	0.005	0.007	0.007
Deaths AF or AF related	0.007	0.018	0.016	0.008
Deaths peri-procedure	0	0	0	0
Death from all causes	0.228	0.221	0.220	0.241

Table D7. Estimated 5-year costs for cardiovascular management

Outcome	Rate Control	CA (Primary)	CA (Secondary)	TOP (Secondary)	Rhythm Control (Amiodarone)	Rhythm Control (Dronedarone)	Rhythm Control (Dronedarone First)
Age 60 Paroxysmal AF							
Total Costs	$ 2,631	$ 17,925	$ 15,337	$ 25,207	$ 6,062	$ 11,160	$ 12,941
Procedure Costs	$ -	$ 16,531	$ 9,741	$ 19,520	$ -	$ -	$ -
Complication Costs	$ -	$ 205	$ 118	$ 348	$ -	$ -	$ -
Drug Costs	$ 1,663	$ 135	$ 1,088	$ 1,066	$ 2,285	$ 3,082	$ 7,634
Adverse Event Costs	$ 953	$ 908	$ 917	$ 841	$ 960	$ 786	$ 960
Age 65 Persistent AF w/CHF							
Total Costs	$ 3,052	$ 21,657	$ 17,340	$ 27,009	$ 6,464	$ 11,541	$ 13,299
Procedure Costs	$ -	$ 19,750	$ 11,302	$ 20,944	$ -	$ -	$ -
Complication Costs	$ -	$ 257	$ 142	$ 367	$ -	$ -	$ -
Drug Costs	$ 1,647	$ 214	$ 1,111	$ 1,104	$ 2,258	$ 3,108	$ 7,579
Adverse Event Costs	$ 1,391	$ 1,265	$ 1,299	$ 1,154	$ 1,393	$ 1,101	$ 1,393
Age 75 DM/HTN/ Persistent AF							
Total Costs	$ 5,377	$ 23,495	$ 18,988	$ 27,383	$ 8,710	$ 13,605	$ 15,286
Procedure Costs	$ -	$ 19,219	$ 10,657	$ 19,812	$ -	$ -	$ -
Complication Costs	$ -	$ 244	$ 132	$ 362	$ -	$ -	$ -
Drug Costs	$ 3,246	$ 1,433	$ 2,088	$ 1,523	$ 3,799	$ 4,182	$ 8,919
Adverse Event Costs	$ 2,096	$ 1,926	$ 2,024	$ 1,828	$ 2,114	$ 1,712	$ 2,114

Table D8. Estimated 5-year costs for stroke prevention

Outcome	Warfarin/Aspirin	Rhythm Control (Dabigatran 110)	Rhythm Control (Dabigatran 150)	WATCHMAN
Age 60 Paroxysmal AF				
Total Costs	$ 2,631	$ 26,586	$ 26,581	$ 14,756
Procedure Costs	$ -	$ -	$ -	$ 11,306
Complication Costs	$ -	$ -	$ -	$ 98
Drug Costs	$ 1,663	$ 23,243	$ 23,248	$ 2,329
Adverse Event Costs	$ 953	$ 526	$ 515	$ 819
Age 65 Persistent AF w/CHF				
Total Costs	$ 3,052	$ 26,385	$ 26,343	$ 14,894
Procedure Costs	$ -	$ -	$ -	$ 11,290
Complication Costs	$ -	$ -	$ -	$ 98
Drug Costs	$ 1,647	$ 22,883	$ 22,904	$ 2,307
Adverse Event Costs	$ 1,391	$ 688	$ 626	$ 996
Age 75 DM/HTN/ Persistent AF				
Total Costs	$ 5,377	$ 25,536	$ 25,386	$ 15,549
Procedure Costs	$ -	$ -	$ -	$ 11,215
Complication Costs	$ -	$ -	$ -	$ 97
Drug Costs	$ 3,246	$ 21,222	$ 21,292	$ 2,551
Adverse Event Costs	$ 2,096	$ 1,517	$ 1,297	$ 1,481

Table D9. Lifetime costs and effectiveness of rate control with digoxin/atenolol vs. amiodarone with secondary rate control for AAD failure, by patient cohort

Strategy	Cost	Incremental Cost	Effectiveness (QALYs)	Incremental Effectiveness (QALYs)	ICER ($/QALYs)
60 M Paroxysmal AF					
Rate Control	$ 15,299		11.032		
Rhythm Control	$ 20,265	$ 4,967	11.116	0.084	$ 59,179
65 M CHF and Persistent AF					
Rate Control	$ 15,721		8.574		
Rhythm Control	$ 20,332	$ 4,611	8.670	0.095	$ 48,384
75 M DM HTN Persistent AF					
Rate Control	$ 13,792		5.703		
Rhythm Control	$ 17,759	$ 3,967	5.797	0.093	$ 42,606

D10. Lifetime costs and effectiveness of amiodarone with secondary rate control for AAD failure vs. amiodarone with LACA for AAD failure, by patient cohort

Strategy	Cost	Incremental Cost	Effectiveness (QALYs)	Incremental Effectiveness (QALYs)	ICER ($/QALYs)
60 M Paroxysmal AF					
Rhythm Control	$ 20,265		11.116		
Secondary LA Catheter Ablation	$ 35,038	$ 14,773	11.507	0.391	$ 37,808
65 M CHF and Persistent AF					
Rhythm Control	$ 20,332		8.670		
Secondary LA Catheter Ablation	$ 37,522	$ 17,190	8.902	0.232	$ 73,947
75 M DM HTN Persistent AF					
Rhythm Control	$ 17,759		5.797		
Secondary LA Catheter Ablation	$ 32,081	$ 14,322	5.944	0.148	$ 96,846

Table D11. Lifetime costs and effectiveness of primary LA catheter ablation vs. rhythm control with amiodarone, by patient cohort

Strategy	Cost	Incremental Cost	Effectiveness (QALYs)	Incremental Effectiveness (QALYs)	ICER ($/QALYs)
60 M Paroxysmal AF					
Rhythm Control	$ 20,265		11.116		
Primary LA Catheter Ablation	$ 34,044	$ 13,779	11.629	0.512	$ 22,172
65 M CHF and Persistent AF					
Rhythm Control	$ 20,332		8.67		
Primary LA Catheter Ablation	$ 38,245	$ 17,913	8.964	0.295	$ 60,804
75 M DM HTN Persistent AF					
Rhythm Control	$ 17,759		5.797		
Primary LA Catheter Ablation	$ 34,410	$ 16,651	6.003	0.207	$ 80,615

Table D12. Lifetime costs and effectiveness of thorascopic, off-pump surgical ablation vs. secondary LA catheter ablation, by patient cohort

Strategy	Cost	Incremental Cost	Effectiveness (QALYs)	Incremental Effectiveness (QALYs)	ICER ($/QALYs)
60 M Paroxysmal AF					
Secondary LA Catheter Ablation	$ 35,038		11.507		
Thorascopic, Off-Pump Surgical Ablation	$ 43,978	$ 8,937	11.463	-0.043	Dominated
65 M CHF and Persistent AF					
Secondary LA Catheter Ablation	$ 37,522		8.902		
T Surgical Ablation	$ 46,163	$ 8,641	8.882	-0.02	Dominated
75 M DM HTN Persistent AF					
Secondary LA Catheter Ablation	$ 32,081		5.944		
Thorascopic, Off-Pump Surgical Ablation	$ 39,744	$ 7,663	5.828	-0.117	Dominated

Table D13. Lifetime costs and effectiveness of amiodarone, dronedarone alone, and dronedarone first with amiodarone for recurrent AF, by patient cohort

Strategy	Cost	Incremental Cost	Effectiveness (QALYs)	Incremental Effectiveness (QALYs)	ICER ($/QALYs)
60 M Paroxysmal AF					
Amiodarone	$ 20,265		11.116		
Dronedarone	$ 27,749	$ 7,484	11.022	-0.094	Dominated
Dronedarone First	$ 30,700	$ 10,435	11.217	0.1	$ 103,892
65 M CHF and Persistent AF					
Amiodarone	$ 20,332		8.670		
Dronedarone	$ 27,829	$ 7,497	8.585	-0.085	Dominated
Dronedarone First	$ 30,536	$ 10,204	8.762	0.092	$ 110,440
75 M DM HTN Persistent AF					
Amiodarone	$ 17,759		5.797		
Dronedarone	$ 24,334	$ 6,575	5.733	-0.064	Dominated
Dronedarone First	$ 26,560	$ 8,801	5.870	0.073	$ 120,398

Dronedarone strategies compared to Amiodarone.

Table D14. Lifetime costs and effectiveness of dabigatran (110 mg and 150 mg doses) vs. warfarin, by patient cohort

Strategy	Cost	Incremental Cost	Effectiveness (QALYs)	Incremental Effectiveness (QALYs)	ICER ($/QALYs)
60 M Paroxysmal AF					
Rhythm Control (Warfarin)	$ 20,265		11.116		
Rhythm Control (Dabigatran 150 mg)	$ 82,780	$ 62,514	11.417	0.301	$ 207,760
Rhythm Control (Dabigatran 110 mg)	$ 83,015	$ 62,750	11.401	0.285	$ 220,212
65 M CHF and Persistent AF					
Rhythm Control (Warfarin)	$ 20,332		8.670		
Rhythm Control (Dabigatran 150 mg)	$ 72,451	$ 52,119	8.962	0.292	$ 178,483
Rhythm Control (Dabigatran 110 mg)	$ 72,795	$ 52,463	8.935	0.266	$ 197,321
75 M DM HTN Persistent AF					
Rhythm Control (Warfarin)	$ 17,759		5.797		
Rhythm Control (Dabigatran 150 mg)	$ 50,944	$ 33,184	5.970	0.173	$ 191,757
Rhythm Control (Dabigatran 110 mg)	$ 51,351	$ 33,592	5.934	0.138	$ 244,121

All strategies compared to common baseline Rhythm Control.

Table D15. Lifetime costs and effectiveness of WATCHMAN vs. warfarin, by patient cohort

Strategy	Cost	Incremental Cost	Effectiveness (QALYs)	Incremental Effectiveness (QALYs)	ICER ($/QALYs)
60 M Paroxysmal AF					
Rate Control (Digoxin/Atenolol)	$ 15,299		11.032		
Rate Control - WATCHMAN	$ 23,053	$7,754	11.011	-0.021	Dominated
65 M CHF and Persistent AF					
Rate Control (Digoxin/Atenolol)	$ 15,721		8.574		
Rate Control - WATCHMAN	$ 22,659	$6,938	8.564	-0.01	Dominated
75 M DM HTN Persistent AF					
Rate Control (Digoxin/Atenolol)	$ 13,792		5.703		
Rate Control - WATCHMAN	$ 20,625	$6,833	5.602	-0.10	Dominated

All strategies compared to Rate Control.

Table D16. 5-year costs and effectiveness of rate control with digoxin/atenolol vs. amiodarone with secondary rate control for AAD failure, by patient cohort

Strategy	Cost	Incremental Cost	Effectiveness (QALYs)	Incremental Effectiveness (QALYs)	ICER ($/QALYs)
60 M Paroxysmal AF					
Rate Control	$ 2,631		3.548		
Rhythm Control	$ 6,062	$ 3,431	3.627	0.079	$ 43,354
65 M CHF and Persistent AF					
Rate Control	$ 3,052		3.205		
Rhythm Control	$ 6,464	$ 3,412	3.286	0.081	$ 42,323
75 M DM HTN Persistent AF					
Rate Control	$ 5,377		2.817		
Rhythm Control	$ 8,710	$ 3,333	2.896	0.078	$ 42,511

Table D17. 5-year costs and effectiveness of amiodarone with secondary rate control for AAD failure vs. amiodarone with LACA for AAD failure, by patient cohort

Strategy	Cost	Incremental Cost	Effectiveness (QALYs)	Incremental Effectiveness (QALYs)	ICER ($/QALYs)
60 M Paroxysmal AF					
Rhythm Control	$ 6,062		3.627		
Secondary LA Catheter Ablation	$ 15,337	$ 9,275	3.675	0.048	$ 193,272
65 M CHF and Persistent AF					
Rhythm Control	$ 6,464		3.286		
Secondary LA Catheter Ablation	$ 17,340	$ 10,876	3.327	0.041	$ 267,261
75 M DM HTN Persistent AF					
Rhythm Control	$ 8,710		2.896		
Secondary LA Catheter Ablation	$ 18,988	$ 10,278	2.931	0.035	$ 294,599

Table D18. 5-year costs and effectiveness of primary LA catheter ablation vs. rhythm control with amiodarone, by patient cohort

Strategy	Cost	Incremental Cost	Effectiveness (QALYs)	Incremental Effectiveness (QALYs)	ICER ($/QALYs)
60 M Paroxysmal AF					
Rhythm Control	$ 6,062		3.627		
Primary LA Catheter Ablation	$ 17,925	$ 11,863	3.739	0.112	$ 105,907
65 M CHF and Persistent AF					
Rhythm Control	$ 6,464		3.286		
Primary LA Catheter Ablation	$ 21,657	$ 15,193	3.38	0.094	$ 161,090
75 M DM HTN Persistent AF					
Rhythm Control	$ 8,710		2.896		
Primary LA Catheter Ablation	$ 23,495	$ 14,785	2.982	0.086	$ 171,729

Table D19. 5-year costs and effectiveness of thorascopic, off-pump surgical ablation vs. secondary LA catheter ablation, by patient cohort

Strategy	Cost	Incremental Cost	Effectiveness (QALYs)	Incremental Effectiveness (QALYs)	ICER ($/QALYs)
60 M Paroxysmal AF					
Secondary LA Catheter Ablation	$ 15,337		3.675		
Thorascopic, Off-Pump Surgical Ablation	$ 25,207	$ 9,870	3.672	-0.003	Dominated
65 M CHF and Persistent AF					
Secodary LA Catheter Ablation	$ 17,340		3.327		
Thorascopic, Off-Pump Surgical Ablation	$ 27,009	$ 9,669	3.325	-0.002	Dominated
75 M DM HTN Persistent AF					
Secondary LA Catheter Ablation	$ 18,988		2.931		
Thorascopic, Off-Pump Surgical Ablation	$ 27,383	$ 8,395	2.935	0.004	$ 1,935,135

Table D20. 5-year costs and effectiveness of amiodarone, dronedarone alone, and dronedarone first with amiodarone for recurrent AF, by patient cohort

Strategy	Cost	Incremental Cost	Effectiveness (QALYs)	Incremental Effectiveness (QALYs)	ICER ($/QALYs)
60 M Paroxysmal AF					
Amiodarone	$ 6,062		3.627		
Dronedarone	$ 11,160	$ 5,098	3.589	-0.038	Dominated
Dronedarone First	$ 12,941	$ 6,879	3.675	0.049	$ 141,458
65 M CHF and Persistent AF					
Amiodarone	$ 6,464		3.286		
Dronedarone	$ 11,541	$ 5,077	3.249	-0.037	Dominated
Dronedarone First	$ 13,299	$ 6,835	3.334	0.048	$ 143,441
75 M DM HTN Persistent AF					
Amiodarone	$ 8,710		2.896		
Dronedarone	$ 13,605	$ 4,896	2.861	-0.034	Dominated
Dronedarone First	$ 15,286	$ 6,576	2.940	0.044	$ 148,128

Dronedarone strategies compared to Amiodarone.

Table D21. 5-year costs and effectiveness of dabigatran (110 mg and 150 mg doses) vs. warfarin, by patient cohort

Strategy	Cost	Incremental Cost	Effectiveness (QALYs)	Incremental Effectiveness (QALYs)	ICER ($/QALYs)
60 M Paroxysmal AF					
Rhythm Control (Warfarin)	$ 6,062		3.627		
Rhythm Control (Dabigatran 150 mg)	$ 26,581	$ 20,519	3.642	0.015	$ 1,359,423
Rhythm Control (Dabigatran 110 mg)	$ 26,586	$ 20,524	3.641	0.015	$ 1,405,036
65 M CHF and Persistent AF					
Rhythm Control (Warfarin)	$ 6,464		3.286		
Rhythm Control (Dabigatran 150 mg)	$ 26,343	$ 19,879	3.308	0.022	$ 896,653
Rhythm Control (Dabigatran 110 mg)	$ 26,385	$ 19,921	3.307	0.021	$ 958,922
75 M DM HTN Persistent AF					
Rhythm Control (Warfarin)	$ 8,710		2.896		
Rhythm Control (Dabigatran 150 mg)	$ 25,386	$ 16,676	2.951	0.055	$ 303,755
Rhythm Control (Dabigatran 110 mg)	$ 25,536	$ 16,827	2.946	0.05	$ 334,567

All strategies compared to common baseline Rhythm Control.

Table D22. 5-year costs and effectiveness of WATCHMAN vs. warfarin, by patient cohort

Strategy	Cost	Incremental Cost	Effectiveness (QALYs)	Incremental Effectiveness (QALYs)	ICER ($/QALYs)
60 M Paroxysmal AF					
Rate Control (Digoxin/Atenolol)	$ 2,631		3.548		
Rate Control - WATCHMAN	$ 14,756	$ 12,125	3.545	-0.003	Dominated
65 M CHF and Persistent AF					
Rate Control (Digoxin/Atenolol)	$ 3,052		3.205		
Rate Control - WATCHMAN	$ 14,894	$ 11,842	3.206	0	$77,657,857
75 M DM HTN Persistent AF					
Rate Control (Digoxin/Atenolol)	$ 5,377		2.817		
Rate Control - WATCHMAN	$ 15,549	$ 10,172	2.828	0.011	$ 953,220

All strategies compared to Rate Control.

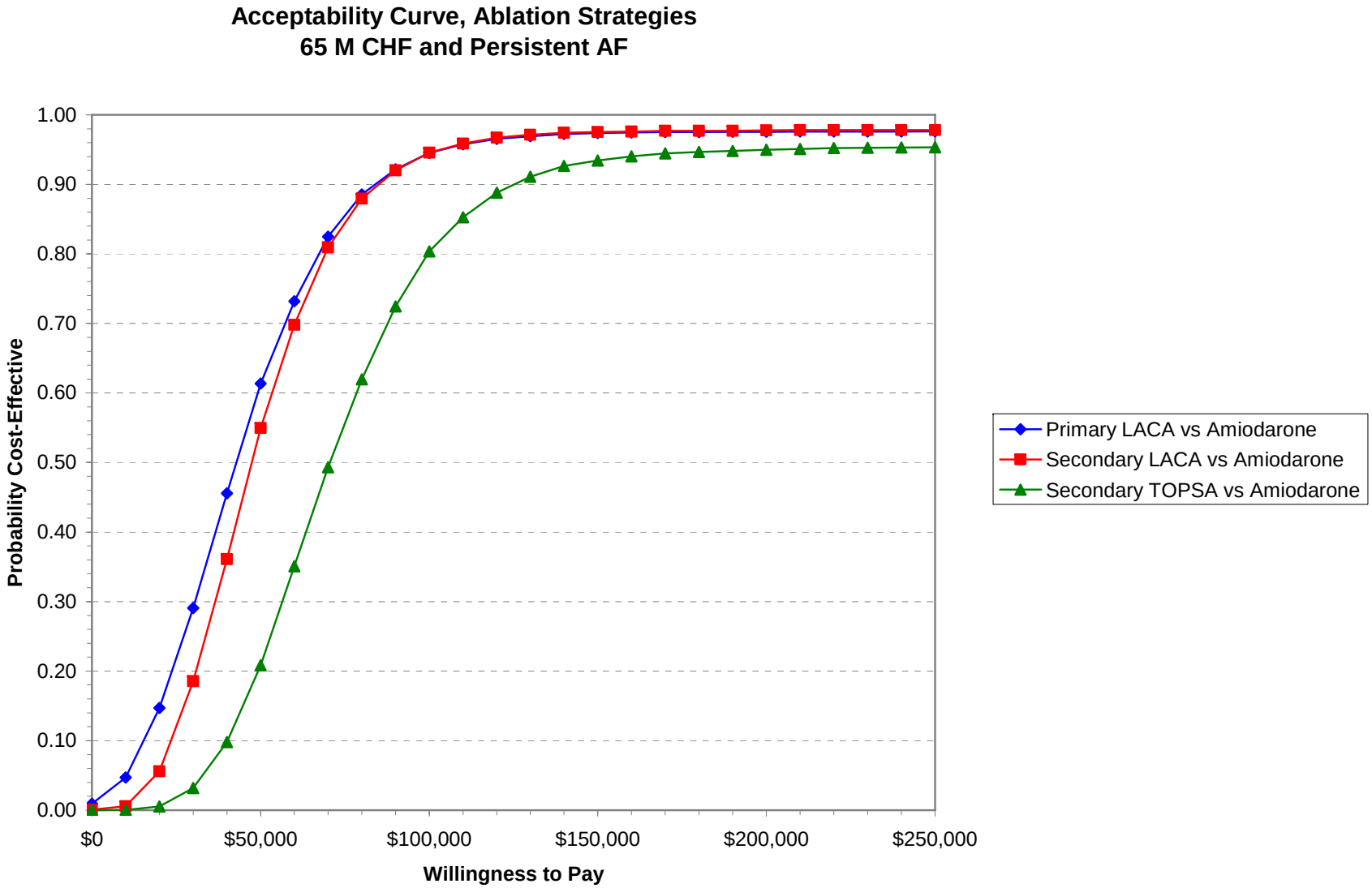
APPENDIX E

PARAMETERS FOR PROBABILISTIC SENSITIVITY ANALYSES & COST-EFFECTIVENESS ACCEPTABILITY CURVES

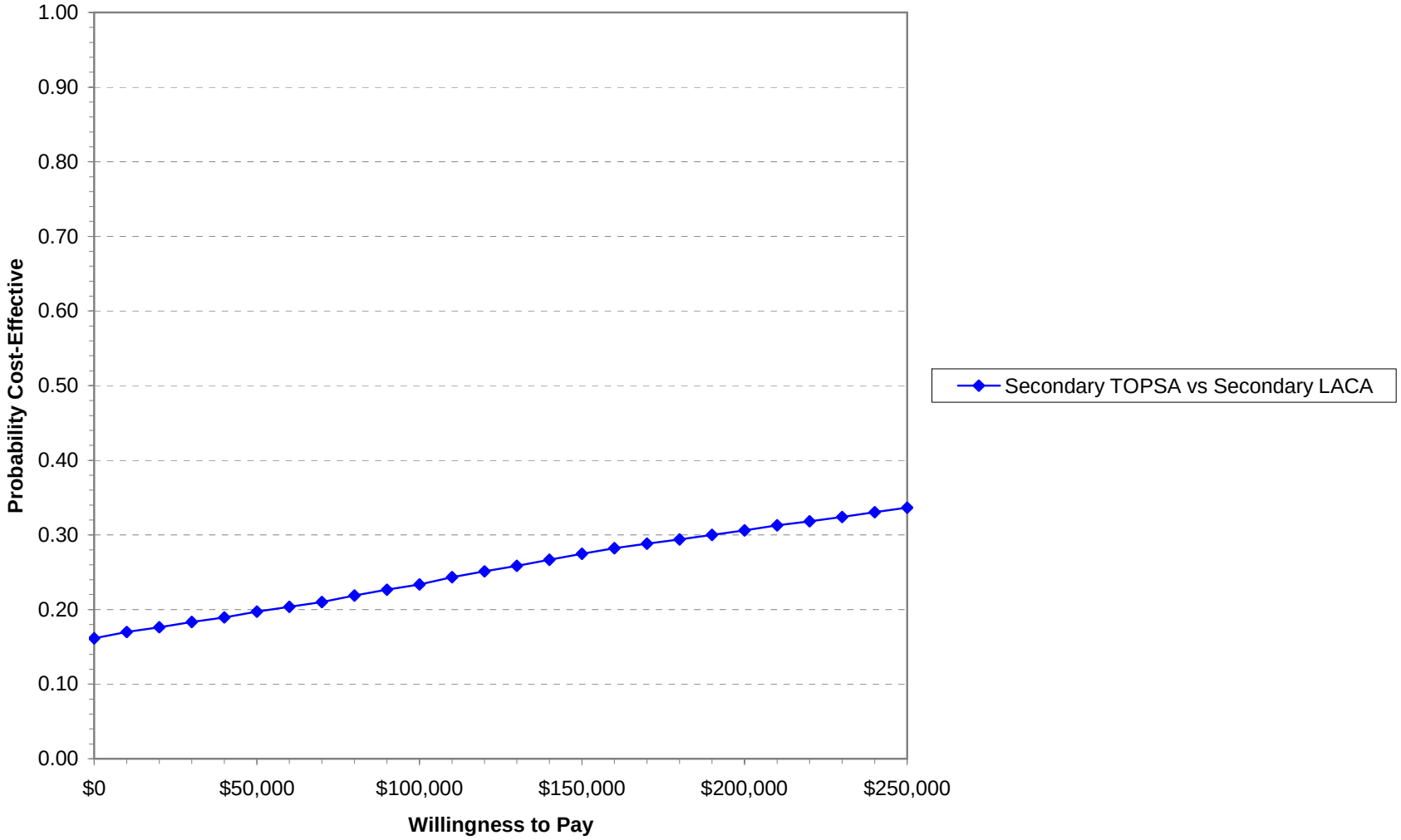
Variable	Value	Lower 95% CI	Upper 95% CI	Distribution	Parameter Estimation Input Mean *	Parameter Estimation Input SD *	Distribution Parameters Parameter 1 *	Distribution Parameters Parameter 2 *	Comments
Costs									
LACA									
Cost of LACA	$11,231	$5,616	$22,462	Gamma	$11,231	$4,298	6.8295	0.0006	
Cost of LACA, with CC/CC	$17,024	$8,512	$34,048	Gamma	$17,024	$6,514	6.8295	0.0004	
Thorascopic, Off-Pump (TOP) Surgical Ablation									
Top Surgical Ablation	$26,818	$13,409	$53,636	Gamma	$26,818	$10,262	6.8295	0.0003	
Top Surgical Ablation w/minor complication	$32,270	$16,135	$64,540	Gamma	$32,270	$12,348	6.8295	0.0002	
Top Surgical Ablation w/major complication or comorbidity	$46,358	$23,179	$92,716	Gamma	$46,358	$17,739	6.8295	0.0001	
WATCHMAN									
WATCHMAN Implantation Procedure	$11,340	$5,670	$22,680	Gamma	$11,340	$4,339	6.8295	0.0006	
WATCHMAN w/comorbidity or complications	$17,133	$8,567	$34,266	Gamma	$17,133	$6,556	6.8295	0.0004	
Annual Drug Costs									
Aspirin	$23	$12	$46	Gamma	$23	$9	6.8295	0.2969	
Amiodarone	$4,434	$2,217	$8,868	Gamma	$4,434	$1,697	6.8295	0.0015	
Atenolol	$80	$40	$160	Gamma	$80	$31	6.8295	0.0854	
Clopidogril	$3,192	$1,596	$6,384	Gamma	$3,192	$1,221	6.8295	0.0021	
Dabigatran	$4,734	$2,367	$9,468	Gamma	$4,734	$1,811	6.8295	0.0014	
Digoxin	$263	$132	$526	Gamma	$263	$101	6.8295	0.0260	
Dronedarone	$3,120	$1,560	$6,240	Gamma	$3,120	$1,194	6.8295	0.0022	
Warfarin	$440	$220	$880	Gamma	$440	$168	6.8295	0.0155	
Drug Toxicity Costs									
Reversible (Thyroid) Drug toxicity	$100	$50	$200	Gamma	$100	$38	6.8295	0.0683	
Acute Amiodarone Pulmonary Toxicity	$4,250	$2,125	$8,500	Gamma	$4,250	$1,626	6.8295	0.0016	
Chronic Amiodarone Pulmonary Toxicity	$4,025	$2,013	$8,050	Gamma	$4,025	$1,540	6.8295	0.0017	
Rates									
Drug Toxicty Rates									
Rate of reversible (thyroid) toxicity	0.101	0.052	0.150	Gamma	0.1010	0.0250	16.3216	161.6000	Assume sd=0.025
Rate of permanent amiodarone pulmonary toxicity	0.011	0.006	0.016	Gamma	0.0110	0.0025	19.3600	1760.0000	Assume sd=0.0025
Probabilities									
LACA Complications				Dirichlet					
No Complications	0.945			Gamma	0.9450		0.9450	1.0000	
Major Complications	0.037			Gamma	0.0370		0.0370	1.0000	
Minor Complications	0.013			Gamma	0.0130		0.0130	1.0000	
Stroke	0.004			Gamma	0.0040		0.0040	1.0000	
Death	0.001			Gamma	0.0010		0.0010	1.0000	
TOP Surgical Ablation Complications				Dirichlet					
No Complications	0.945			Gamma	0.9450		0.9450	1.0000	
Major Complications	0.037			Gamma	0.0370		0.0370	1.0000	
Minor Complications	0.013			Gamma	0.0130		0.0130	1.0000	
Stroke	0.004			Gamma	0.0040		0.0040	1.0000	
Death	0.001			Gamma	0.0010		0.0010	1.0000	
WATCHMAN Complications				Dirichlet					
No Complications	0.897			Gamma	0.8970		0.8970	1.0000	
Major Complications	0.035			Gamma	0.0350		0.0350	2.0000	
Minor Complications	0.058			Gamma	0.0580		0.0580	3.0000	
Stroke (peri-procedure)	0.01			Gamma	0.0100		0.0100	4.0000	

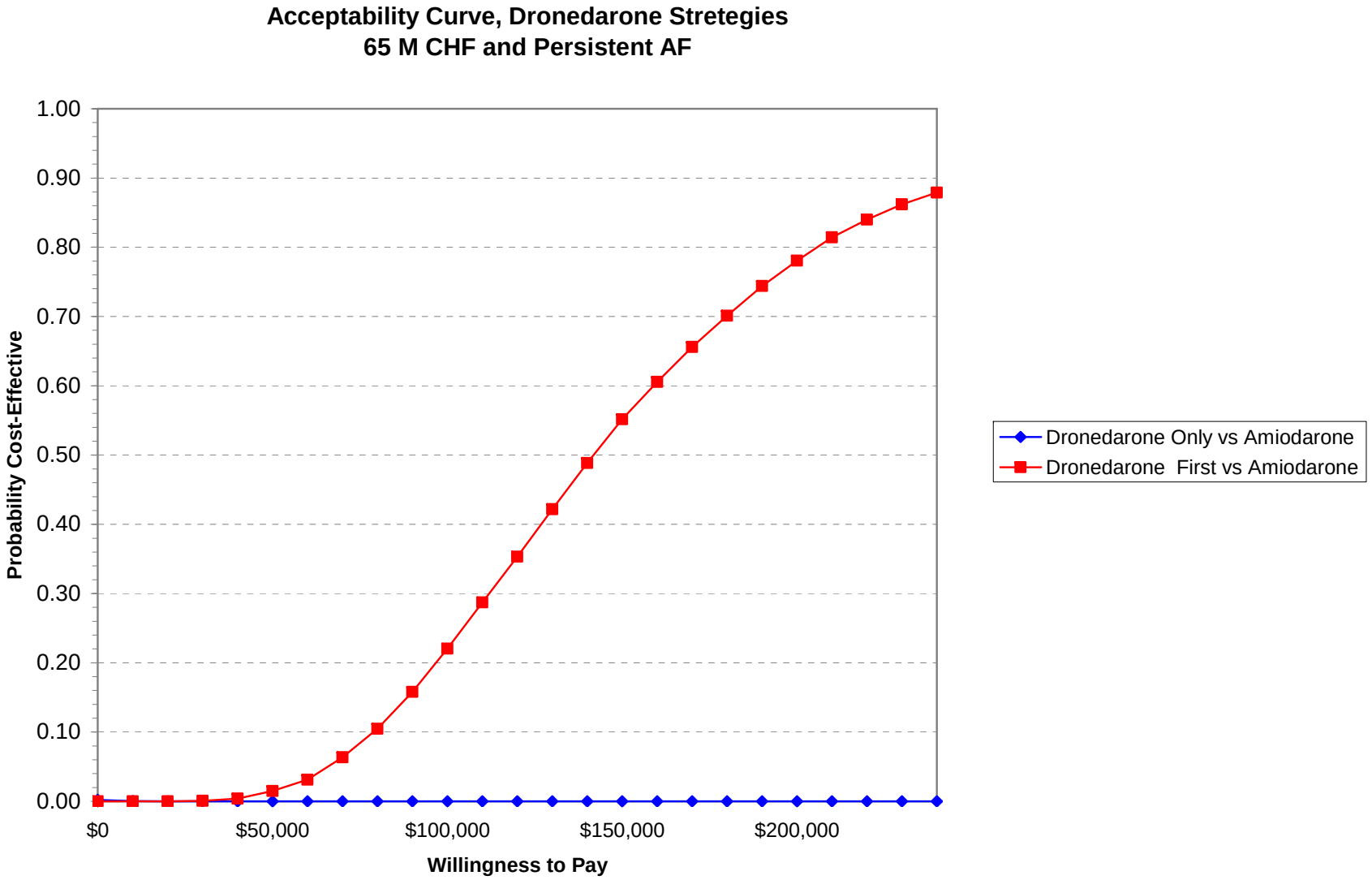
Variable	Value	Lower 95% CI	Upper 95% CI	Distribution	Parameter Estimation Input Mean *	Parameter Estimation Input SD *	Distribution Parameters Parameter 1 *	Distribution Parameters Parameter 2 *	Comments
LACA Cardiac Rhythm Outcomes									
Probability of NSR after LACA 1 year, paroxysmal	0.821	0.771	0.871	Beta (Real Parameters)	0.8210	0.0255	185.4007	40.4223	
Probablity of NSR after LACA 1 year, persistent	0.698	0.648	0.748	Beta (Real Parameters)	0.6980	0.0255	226.0945	97.8231	
TOP Surgical Ablation Cardiac Rhythm Outcomes									
Probability of NSR after LACA 1 year, paroxysmal	0.821	0.771	0.871	Beta (Real Parameters)	0.8210	0.0255	185.4007	40.4223	Same as LACA
Probablity of NSR after LACA 1 year, persistent	0.698	0.648	0.748	Beta (Real Parameters)	0.6980	0.0255	226.0945	97.8231	
RR Stroke	0.6			Beta (Real Parameters)	0.6000	0.0500	57.6000	38.4000	
WATCHMAN									
Probability of Successful LA Implantion	0.91			Beta (Real Parameters)	0.9100	0.0130	441.0000	43.6154	
Probablity of LAA exclusion	0.86			Beta (Real Parameters)	0.8600	0.0160	404.4688	65.8438	
Amiodarone									
Probability of NSR after recurrent AF with dronedarone	0.777	0.731	0.833	Beta (Real Parameters)	0.7770	0.0160	525.9046	150.9353	
Relative Risks									
WATCHMAN									
RR of Stroke after WATCHMAN	0.71	0.34	1.24	LogNormal	-0.342	0.330	-0.342	0.330	
Dronedarone									
RR Recurrent AF Dronedarone vs Amiodarone	1.59	1.28	1.98	LogNormal	0.464	0.111	0.464	0.111	
RR Drug Toxicity Dronedarone vs Amiodarone	0.80	0.60	1.07	LogNormal	-0.223	0.148	-0.223	0.148	
Dabigatran									
RR Hemorrhage Dabigatran 110 mg vs warfarin	0.80	0.69	0.93	LogNormal	-0.223	0.076	-0.223	0.076	
RR Hemorrhage Dabigatran 150 mg vs warfarin	0.93	0.81	1.07	LogNormal	-0.073	0.071	-0.073	0.071	
RR ICH Dabigatran 110 mg vs warfarin	0.31	0.69	0.93	LogNormal	-1.171	0.076	-1.171	0.076	
RR ICH Dabigatran 150 mg vs warfarin	0.40	0.27	0.60	LogNormal	-0.916	0.204	-0.916	0.204	
RR Stroke Dabigatran 110 mg vs warfarin	0.92	0.74	1.13	LogNormal	-0.083	0.108	-0.083	0.108	
RR Stroke Dabigatran 150 mg vs warfarin	0.64	0.51	0.81	LogNormal	-0.446	0.118	-0.446	0.118	
Amiodarone									
Probability of Initial NSR	0.73			Beta (Integer Parameters	182	249	0.731	0.028	
Dronedarone									
Probability of Initial NSR	0.82			Beta (Integer Parameters	210	255	0.824	0.024	
Quality of Life									
Quality of Life (Disutility)									
Atrial Fibrillation	0.065			Beta (Real Parameters)	0.0650	0.0100	39.5038	568.2463	Assume sd=0.01
Warfarin	0.013			Beta (Real Parameters)	0.0130	0.0118	1.1980	90.9523	sd=0.0118
Procedure Morbidity	0.5			Beta (Real Parameters)	0.5000	0.0250	200.0000	200.0000	Assume SD=0.025

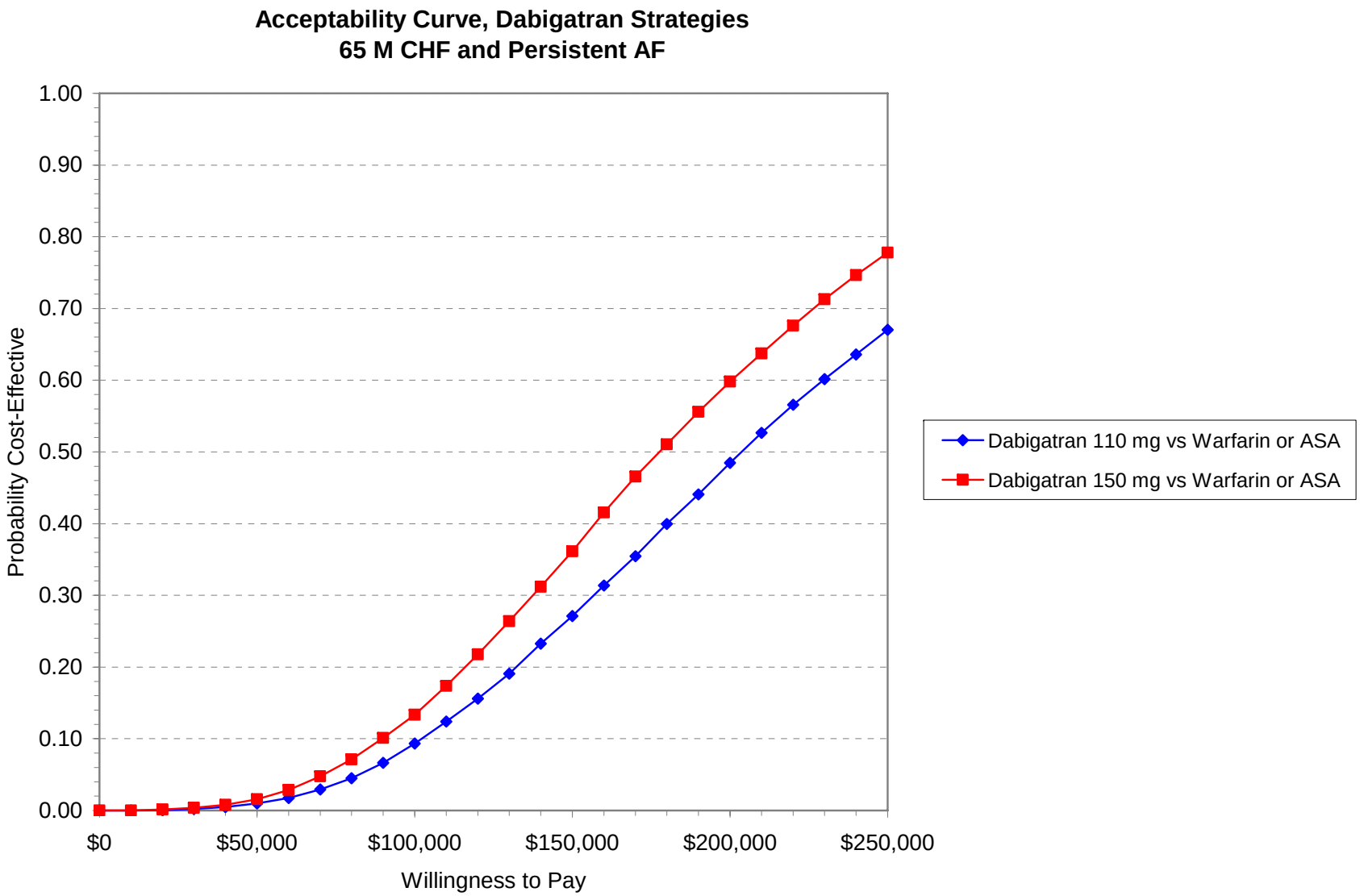
* Distribution Parameters for TreeAge Software, 2009
Beta Distribution (alpha, beta) for probabilities and QoL with parameters estimated from mean value & 95% CIs
Gamma Distribution (alpha, lambda) with parameters estimated from mean and 95% Cis
LogNormal Distribution for relative risks with parameters estimated from ln(mean), sd of ln(95% CIs)
Dirichlet Distribution for nodes with multiple brances estimated from mean branch probabilties, equivalent to Gamma (mean probability, 1) for each branch probability
SD directly estimated if 95% Cis not available



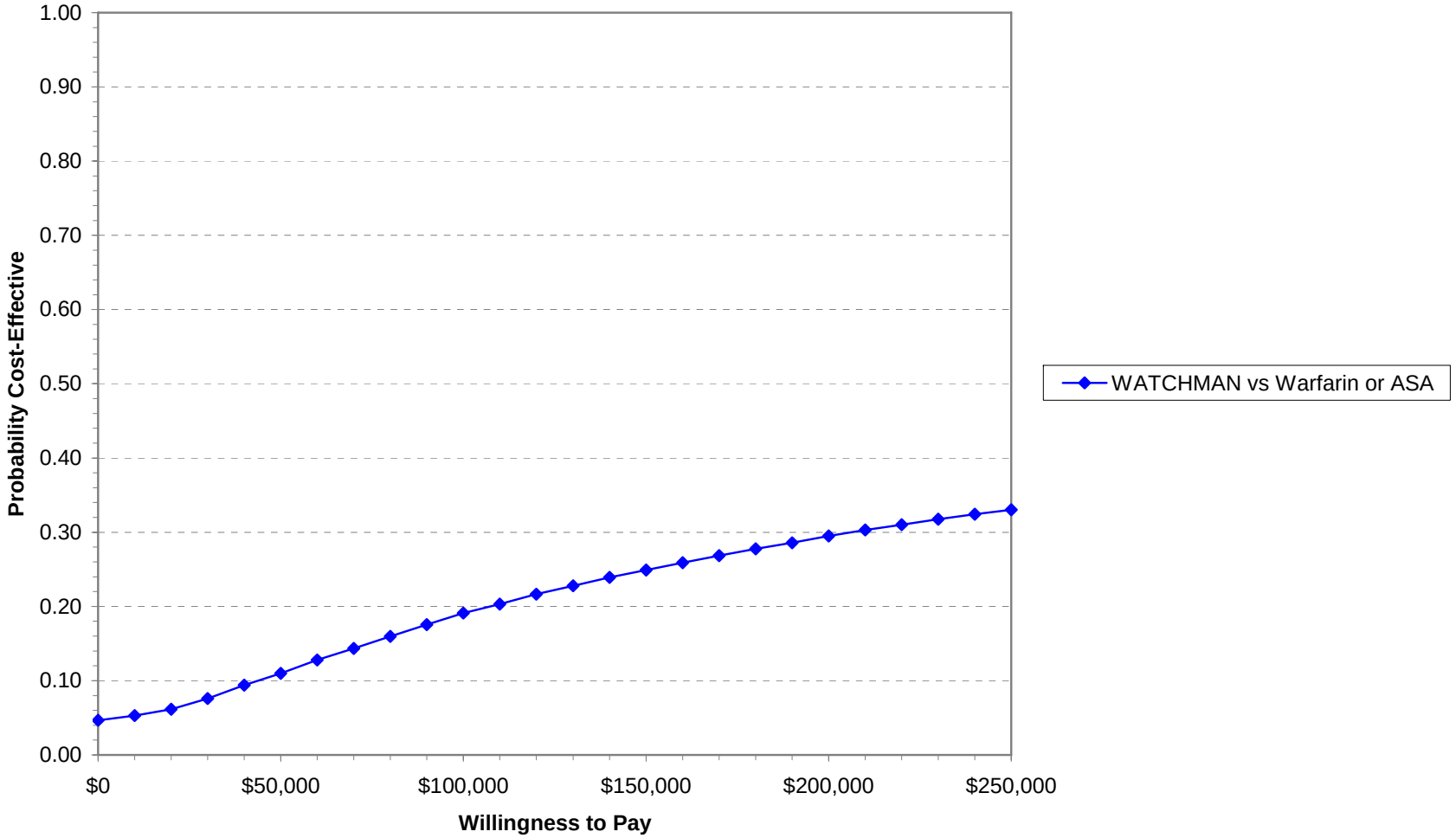
Acceptability Curve, Secondary TOP Surgical Ablation vs Secondary LACA Strategy
65 M CHF and Persistent AF







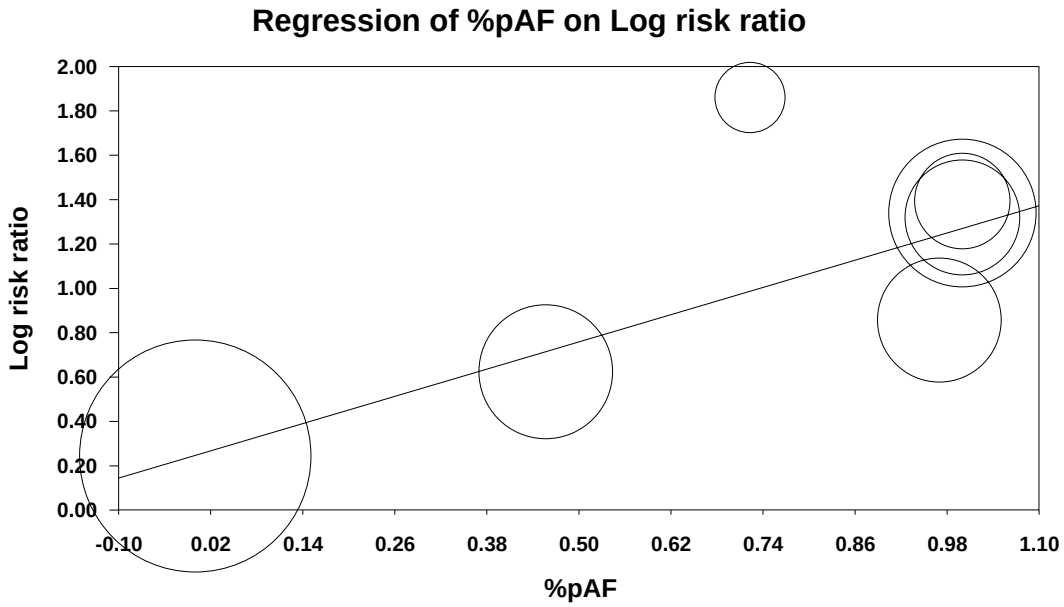
Acceptability Curve, WATCHMAN Device Strategy
65 M CHF and Persistent AF



APPENDIX F

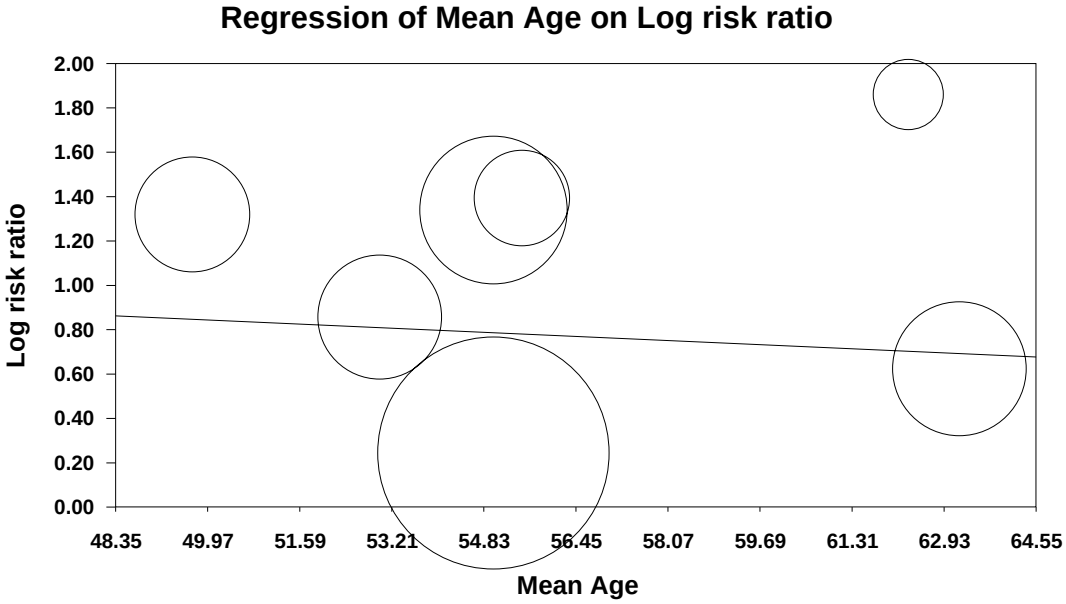
META-REGRESSION & PUBLICATION BIAS ANALYSES

Meta-Regression
Dependent Variable: Rate ratio of freedom from AF
Independent Variable: % of study participants w/paroxysmal AF



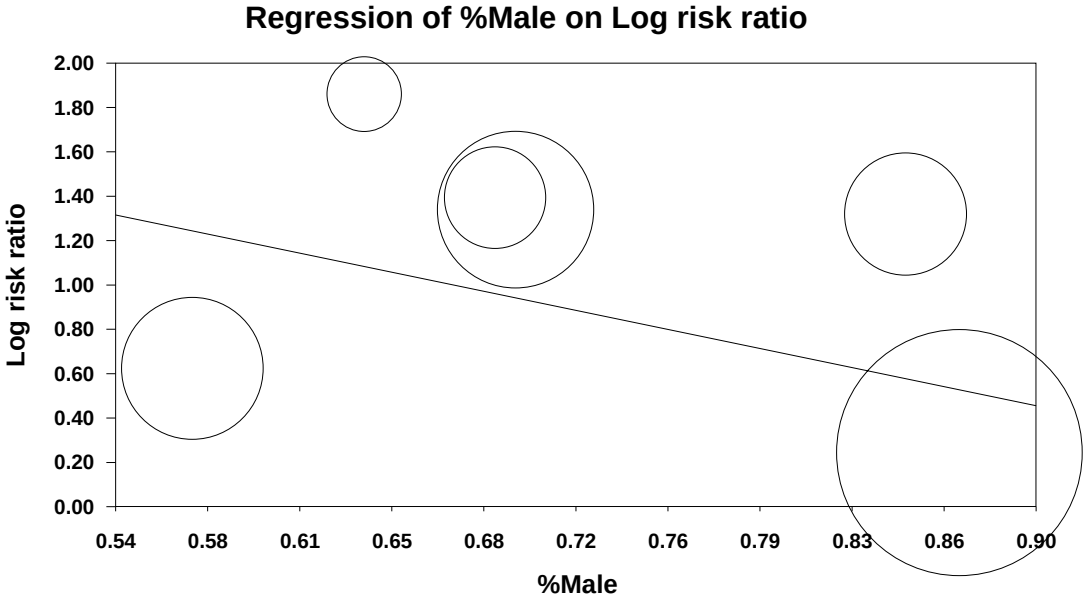
Mixed effects regression
Q: 44.25654
df: 6
p: <.0001

Meta-Regression
Dependent Variable: Rate ratio of freedom from AF
Independent Variable: Mean age of study participants



Mixed effects regression
Q: 6.91780
df: 6
p: 0.3285

Meta-Regression
Dependent Variable: Rate ratio of freedom from AF
Independent Variable: % of male study participants



Mixed effects regression
Q: 6.49291
df: 6
p: 0.2612

EVIDENCE DISSEMINATION BIAS

Current outcome measure	RR
Current weighting method	DL
Current model	Random effects
Original meta-analysis outcome	2.841
95% CI lower limit	1.8263
95% CI upper limit	4.4194
Effect assessment	
Rank correlation tau-b (continuity corrected)	0.2857
Ties	0
P-Q (se)	7 (6.6583)
z	0.9011
p-value (two-tailed)	0.3675
Regression method	Egger
Regressor weighting	None
Intercept	6.2944
95% CI lower limit	1.811
95% CI upper limit	10.7779
p-value (two-tailed)	0.0154
Sensitivity analysis	
Fail-safe N	231
Tolerance level	45
Trim-and-fill method (automatic)	L0
Number of imputed studies	2
Resulting meta-analysis outcome	2.3683
95% CI lower limit	1.6
95% CI upper limit	3.5056

RR: Rate ratio; DL: Dersimonial-Laird; CI: Confidence interval