



## **EFFECTIVENESS GUIDANCE DOCUMENT**

# **Methodological Recommendations for Comparative Effectiveness Research on the Treatment of Atrial Fibrillation**

**FINAL VERSION**

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**How to Provide Comments**

Obtaining feedback is critical to ensuring this Effectiveness Guidance Document reflects the best thinking possible on the design of atrial fibrillation studies. A questionnaire is available [online](#). You may also provide feedback by mail: CMTP, 401 East Pratt Street, Suite 631; Baltimore, MD 21202.

## EXECUTIVE SUMMARY

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The purpose of this Effectiveness Guidance Document (EGD) is to provide specific recommendations to product developers and clinical researchers on the design of comparative effectiveness (CER) studies on treatments for atrial fibrillation (AF). Atrial fibrillation is an abnormal cardiac rhythm in which the electrical activity of the heart's atria becomes hyperactive and uncoordinated. Approximately 2 million people in the US and 20 million people around the world suffer from it. The majority of those who suffer from AF are elderly males. In 2009, the Institute of Medicine (IOM) identified AF as one of the top 25 national priorities for CER, underscoring the need to better evaluate and compare the benefits, risks and costs of different AF treatments.

Despite the fact that AF is common, and despite the fact that numerous papers have been published addressing different treatments for it, the available evidence is inadequate. Consequently, there are uncertainties about whether heart rate or rhythm control produces the most desirable patient outcomes, the roles that surgery and catheter ablation play in AF treatment, the roles of anti-arrhythmic drugs and catheter ablation, optimal approaches to anti-coagulation therapy, how co-morbidities influence treatment decisions, and about the natural history of the disease.

The following “research design recommendations” outline how future studies can improve our knowledge of AF by addressing certain critical aspects of study design. Although these research recommendations are not intended to be all-inclusive; they are intended to increase our knowledge of the treatment of AF.

A set of “priorities” follows the research recommendations. These recommendations are intended to address our lack of understanding of disease progression, optimal timing of treatments, or the natural history of disease. Filling these knowledge gaps will allow for the design of even more informative studies, and we encourage the AF research community to focus on this foundational research.

## ATRIAL FIBRILLATION EFFECTIVENESS GUIDANCE DOCUMENT RECOMMENDATIONS

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### RESEARCH DESIGN RECOMMENDATIONS

RECOMMENDATION 1: Clinical trials should include patients typical of those who have AF, including the elderly and patients with a history of heart failure, coronary artery disease and diabetes.

RECOMMENDATION 2: Information that is meaningful to patients and providers, including information about how patients feel and function, should be collected from all patients enrolled in clinical studies.

RECOMMENDATION 3: Researchers should report outcomes by time since diagnosis in future clinical trials of catheter ablation and surgical procedures for atrial fibrillation.

RECOMMENDATION 4: Trials of catheter ablation and surgical procedures should follow patients for at least five years to assess recurrence.

RECOMMENDATION 5: Researchers should measure and report quality of life as an outcome in all clinical trials of atrial fibrillation using a recommended disease-specific instrument.

### PRIORITY RESEARCH FOR ATRIAL FIBRILLATION

RECOMMENDATION 6: Create a national registry for atrial fibrillation in order to conduct studies and generate hypotheses and evidence about which therapies work best in which patients, at what point in their disease process

RECOMMENDATION 7: Develop a new AF classification system more relevant to both patients and clinicians for use as the basis of inclusion and exclusion criteria for future large-scale clinical trials.

RECOMMENDATION 8: Research should conduct RCTs that assess the impact of different post procedure anticoagulation strategies on stroke rates.

# PREFACE

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## Effectiveness Guidance Documents: Purpose and Process

The Center for Medical Technology Policy (CMTTP) supports the development of Effectiveness Guidance Documents (EGDs) to provide specific recommendations on the design of prospective studies intended to inform decisions by patients, clinicians and payers. EGDs do not provide general methodological advice, but rather offer specific study design recommendations that are relevant to a defined clinical condition and/or category of clinical interventions. The purpose of EGDs is to better align the design of clinical research with the information needs of patients, clinicians, and payers. EGD recommendations will generally address one or more of the following elements of study design: patient inclusion and exclusion criteria, choice of comparators, research settings, selection of outcomes, duration of follow-up and other key elements of trial design that are most relevant to the topic of each guidance. A detailed overview of the purpose of EGDs, topic selection, target audiences, and intended uses is available [on the CMTTP website](#).

The primary audience for an EGD is clinical researchers who develop research protocols for studies that are intended to be helpful to patients, clinicians and payers who make clinical or health policy decisions. This would include researchers from life sciences companies with clinical development responsibilities, or other clinical researchers receiving funding from public sources, foundations, etc. EGDs are intended to be analogous to FDA guidance documents, which are also targeted to product developers and clinical researchers, and provide guidance on the design of clinical studies that are intended to support regulatory decision making. EGD recommendations are not intended to establish standards for research required for coverage, payment or pricing decisions. They are likely, however, to be aligned with the expressed evidence preference of public and private payers, as they are developed with payer input.

The methods recommendations in EGDs are guided by the objective of achieving an acceptable balance across a number of desirable dimensions, including internal validity, relevance, feasibility and timeliness. Overall, the objective of EGDs is to offer study design recommendations that would give decision makers a reasonable level of confidence that the intervention studies would improve net health outcomes.

There are a number of potential benefits of the creation and use of EGDs. First and foremost, they could help increase the degree to which clinical research reflects the information needs articulated by patients, clinicians and payers. In addition, EGDs could contribute to greater consistency of trial design across studies of related treatments within specific clinical conditions, allowing for higher quality meta-analysis and systematic reviews due to reduced heterogeneity across multiple studies. By considering existing regulatory guidance in the EGD process, it is hoped that EGDs will help to achieve optimal alignment between study design elements intended for regulatory approval and study design elements targeted to clinical and health policy decision making.

There are three primary features that distinguish EGDs from the majority of other methods guidance documents. First, EGDs focus on a specific clinical area or category of interventions, while other available methods guidance are more general and apply across a broad range of clinical conditions or technologies. Second, a number of the other documents provide guidance on reviewing the quality of existing studies, while EGDs provide recommendations for the design of future studies. Finally, we are not aware of any other documents that actively engage patients, clinicians, and payers in the process of

developing recommendations, with the goal of ensuring that the information needs of these decision makers are given significant attention in generating methods recommendations.

EGD recommendations are developed through an extensive consultative process involving a broad range of expert stakeholders, and include mechanisms for broad public review and comment. CMTP develops EGD recommendations with the support of a Technical Working Group (TWG) consisting of experts in clinical care and research methods specific to the clinical domain that is the focus of the EGD, and also includes patient, clinician and payer representatives. Draft EGDs are made available for public comment through targeted distribution to all key stakeholders, draft documents posted on the CMTP web site, and public meetings including one or more invitation methods symposia to address the most complex or controversial issues. All feedback on the draft EGD is reviewed by CMTP staff and the Technical Working Group in developing a “final” version of the EGD, which is then posted at the CMTP website and widely distributed.

# INTRODUCTION

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## Clinical Framework

Atrial fibrillation (AF) is an abnormal cardiac rhythm in which the electrical activity of the heart's atria becomes hyperactive and uncoordinated.<sup>1</sup> Approximately 2 million people in the US and 20 million people around the globe have been diagnosed with AF<sup>2</sup>, but many others may have undiagnosed AF. The majority is elderly males, and AF develops in men at 1.5 times the rate of women. It is primarily a disease of the elderly; the median age of patients is 75 and 84% of patients are older than 65.<sup>3</sup>

Although all AF is characterized by abnormal electrical activity, no two AF patients exhibit the same abnormal electrical activity. The cause of the abnormality differs among patients, and is often impossible to pinpoint. Usually, the electrical signals of the heart begin in the sinoatrial node; however, in AF, they begin in another part of the atria or even in the pulmonary veins. These signals spread throughout the atria in an erratic path, causing fibrillation to occur.

In addition to this physiologic heterogeneity, patients often experience AF quite differently. AF is often paroxysmal, with symptomatic and asymptomatic episodes occurring with varying frequency between patients and within the same patient. Some people are not aware of their AF episodes because they do not experience easily recognizable symptoms.<sup>4</sup> In the absence of an irregular or pounding heart beat, AF patients simply may not attribute other nonspecific symptoms, such as fatigue, to their abnormal heart rhythm.

Multiple factors can lead to, or increase the odds of a person developing AF. Age and genetics play an important role. Coronary heart disease, cardiomyopathy, high blood pressure, and other cardiac disorders are also associated with increased risk of developing AF.<sup>1</sup> AF is also associated with diabetes, obesity, sleep apnea, thyroid disease, pneumonia, and prior cardiac-related complications.<sup>1</sup> AF generally progresses with age and becomes more severe with the appearance of co-morbidities, such as hypertension and diabetes.<sup>5</sup> These co-morbidities may cause AF episodes to become more persistent or the arrhythmia to become permanent. Some AF patients have an underlying cause that may be readily reversible, such as hyperthyroidism or acute exacerbation of pulmonary diseases. However, most patients do not have a fully reversible AF "trigger."

Common symptoms of AF include heart palpitations; shortness of breath; chest pain; a pounding, fluttering or racing sensation in the chest; and dizziness.<sup>6</sup> These physical symptoms often make it difficult for patients to perform day-to-day activities without significant discomfort. In addition, AF can impact patients' mental wellbeing, including not only the frustration of living with the disorder and the inability to perform everyday activities, but also over job restrictions imposed by employers.

AF is a progressive disease. As patients age, the amount of time they spend in AF often increases as episodes become more frequent. AF is categorized based on severity and duration:<sup>7</sup>

- **Paroxysmal**, defined as recurrent AF (greater than 2 episodes) that terminates spontaneously within seven days;
- **Persistent**, defined as AF lasting more than seven days, or lasting less than seven days, but necessitating pharmacologic or electrical cardioversion during that time;

- **Permanent**, when cardioversion has either failed or not been attempted, and AF is accepted as the patient's permanent heart rhythm.

There are also several miscellaneous categories, such as lone AF, which has several definitions, but generally refers to young individuals (under 60 y of age) without clinical or echocardiographic evidence of cardiopulmonary disease, including hypertension.<sup>8</sup>

This categorization scheme does not perfectly identify different types of patients, meaning that its use does not necessarily lead to appropriate treatment options. Other factors may be important to consider when classifying a patient's disease. Additionally, gray areas exist, and, as the disease progresses, distinctions between categories become increasingly blurred. Because there is no common or expected natural history for the progression of AF, it is difficult to estimate when potentially clinically significant transitions will occur.

AF can increase the risk of ischemic stroke by as much as a factor of five.<sup>9</sup> Also, 15% of people who suffer from a stroke also have AF.<sup>4</sup> Stroke risk in AF patients is estimated by calculating a CHADS<sub>2</sub> score, which increases with history of congestive heart failure, hypertension, age over 75 years, diabetes, stroke, and transient ischemic attack (TIA). The estimated rate of stroke ranges from 0.5 events per 100 person-years in AF patients with a CHADS<sub>2</sub> score of 0, to 6.9 events per 100 person-years for a score of 5 or 6.<sup>10</sup> The newer CHADS<sub>2</sub>-VASc attempts to improve risk estimation in individuals at the lower end of the risk stratum by including additional risk factors of female sex, any vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque), and age 65 to 74 years.<sup>11</sup>

Initial evaluations of patients focus on identifying potentially reversible causes of AF. Chemical or electrical cardioversion is commonly used to stop an acute AF episode and restore normal heart rhythm in patients with new onset AF. However, in most cases, cardioversion is a temporary measure, and other treatments are commonly required to prevent or treat recurrences.

AF treatment falls into two major categories of rate control and rhythm control. Control of ventricular rate is critical to managing AF. The majority of symptoms patients experience are due to tachycardia (rapid heart rate), which may also result in myocardial dysfunction. Restoration of a normal heart rhythm can often improve AF symptoms and cardiac performance. A number of drugs are used to convert an AF patient to and maintain normal heart rhythm, such as flecainide, propafenone, sotalol, dofetilide, amiodarone, and dronedarone..

Non-pharmacological treatments for AF are currently of great interest. Surgical, thoracoscopic and percutaneous catheter-based vascular techniques attempt to isolate and destroy the areas within the atria that trigger abnormal electrical signals and perpetuate the arrhythmia. Surgical ablation can be accomplished via an open- or closed-chest approach.<sup>12</sup> Open chest procedures are performed on a beating or a stopped heart, with circulation supported by an artificial heart pump. Surgery can involve exclusion or removal of the left atrial appendage (LAA) and intra-operative electrophysiologic testing to determine the effectiveness of the lesions.

In recent years, catheter ablation has been increasingly used to restore and maintain normal heart rhythm. The standard lesion set is similar to that of the surgical Cox-MAZE procedure. In general, the pattern, thickness, and number of lesions that electrophysiologists are able to create varies according to their experience with these complex procedures, their access to electrical mapping systems, and patient

factors. While electrophysiologists have traditionally used catheter tips that deliver heat in the form of radiofrequency energy to create lesions, other energy sources and technologies such as ultrasound, laser, and chilled catheter tip or balloon approaches are either in widespread use or development. AF patients may also undergo placement of an LAA occluder device to reduce risk of stroke.

Because AF patients are at increased risk of stroke, treatment of AF is designed to not only mitigate the symptoms of AF, but also to reduce stroke risk. Very low risk patients, do not require prophylaxis. Patients at high risk are often given the anticoagulant warfarin.<sup>13-16</sup> While effective as an anticoagulant, warfarin doubles the risk of intracranial hemorrhage, can cause bleeding complications, and requires frequent monitoring, careful dietary restrictions, and attention to drug interactions.<sup>9</sup> Other anticoagulants recently approved by the U.S. Food and Drug Administration (FDA) may overcome some of these limitations.

AF patients are increasingly opting for catheter ablation earlier in their treatment. Reasons include the relative long term inefficacy and potential side effects of anti-arrhythmic drugs; symptom burden, patients' hopes/beliefs that catheter ablation will "cure" them, and the prospect that they may be able to stop anticoagulation. Some clinicians are concerned that patients will stop using warfarin after catheter ablation procedures with or without their knowledge or consent. Such patients could still have significant stroke risk, not least of all because a high percentage of AF episodes are not associated with symptoms and can go unnoticed by both patients and clinicians.

## State of the Evidence

### *Rate versus Rhythm Control*

There is ongoing debate about whether rate control or rhythm control is the more effective approach to managing atrial fibrillation (AF), and which method of management — pharmacological, procedural, or surgical — is the appropriate first-line therapy. Major studies (summarized in **Table 1** below), have produced results that the field does not consider universally definitive, partly because of the diverse study protocols used in these studies (see Table 1), and partly because they have not enrolled all of the different types of patients who have AF.

TABLE 1: BASIC CHARACTERISTICS OF RATE VERSUS RHYTHM CONTROL TRIALS								
Trial	Patients (n)	Mean age (years)	Mean follow-up (years)	Inclusion criteria	Primary outcome	Patients reaching primary outcome		
						Rate control	Rhythm control	P - value
PIAF (2000)	252	61.0	1.0	Persistent AF	Symptomatic improvement	60.8%	55.1%	0.32
AFFIRM (2002)	4060	69.7	3.5	Paroxysmal or Persistent AF; 65 years or older with risk of stroke or death	All-cause mortality	25.9%	26.7%	0.08
RACE (2002)	522	68.0	2.3	Persistent AF or flutter for less than a year; 1-2 cardioversions over 2 years and oral anticoagulation	Composite of multiple outcomes	17.2%	22.6%	0.11

STAF (2003)	200	66.0	1.6	Persistent AF < 4 weeks	Composite of multiple outcomes	10.0%	9.0%	0.99
HOT CAFÉ (2004)	205	60.8	1.7	First clinically overt persistent AF between ages 50-75.	Composite of multiple outcomes	1.0%	3.9%	>0.71
AF-CHF (2008)	1376	66	3.1	Left ventricular ejection fraction ≤35% symptoms of congestive heart failure	Cardiovascular death	25%	27%	0.59
J-Rhythm (2009)	823	64.7	1.6	Paroxysmal AF	Composite of multiple outcomes	22.0%	15.3%	0.012

Data in this table are from the European Society of Cardiology (ESC) 2010 guidelines.<sup>17</sup>

### *Anti-arrhythmic Drugs Versus Catheter Ablation*

In the decades since catheter ablation for AF was first reported, technologies and techniques have evolved, especially for those patients who have paroxysmal AF and minimal heart disease.<sup>18</sup> A recent systematic review suggests that there is less arrhythmia after catheter ablation than with anti-arrhythmic drugs,<sup>19</sup> but differences in the characteristics of patients given different treatments, and the inclusion of retrospective studies (which are inherently unreliable) raise doubts about this conclusion. Additionally, the studies considered in this systematic review tended to not enroll the elderly, patients with heart failure, coronary artery disease, or patients with increased risk of stroke. Finally, most of the studies considered in the systematic review did not capture data after one year.

There are ongoing studies that will further explore the comparative effectiveness of catheter ablation and drug therapy. Among these is the Catheter Ablation versus Anti-Arrhythmic Drug Therapy for Atrial Fibrillation (CABANA) study<sup>20</sup> and the Catheter Ablation versus Standard conventional Treatment in patients with Left ventricular dysfunction and Atrial Fibrillation (CASTLE) trial. The CABANA trial will compare catheter ablation to conventional anti-arrhythmic drug therapy in patients with untreated or incompletely treated AF warranting therapy,<sup>21</sup> and will measure outcomes (i.e. quality of life, disability due to stroke, hospitalization, and cardiovascular death).<sup>22</sup> The Castle trial will compare catheter-based radio-frequency ablation and conventional treatment, and will measure mortality and morbidity.<sup>23</sup> Both trials will address research gaps identified by prior studies.

### *Management of Stroke and Thromboembolic Risk*

Prevention of stroke and thromboembolic events is one of the main therapeutic goals in treating and managing AF. When recommending antithrombotic therapy, however, clinicians must weigh bleeding risk against stroke risk. There is a wide variety of options, including vitamin K antagonists, aspirin, other antiplatelet agents, dabigatran and apixaban, and non-pharmacological options. Current evidence does not identify the best protective strategy for a given patient, and, there continues to be enough variation in treatment and management approaches that it is difficult to determine optimal antithrombotic therapy for clinical practice or for the management of patients enrolled in clinical trials.

Presently, clinical practice guidelines recommend vitamin K antagonists (VKAs) such as warfarin based on CHADS<sub>2</sub> risk score. However, VKAs increase the risk of severe bleeding, and warfarin in particular has many characteristics that make clinical treatment challenging, including the need for frequent monitoring, drug and food interactions, and a long onset and offset of action.<sup>24</sup> These challenges have spurred development of alternative agents such as dabigatran,<sup>25</sup> and rivoroxiban, which were recently approved by the FDA, and apixaban<sup>26</sup> which, at the time of this writing, has gained priority review by the FDA.

### *Surgery versus Catheter Ablation*

There has been little research comparing surgery and catheter ablation, due in part to the low volume of surgical procedures performed each year, the increasing popularity of catheter ablation, and difficulties and challenges inherent in randomizing patients to surgical over non-surgical alternatives.<sup>a</sup> Some literature suggests, however, that surgery for AF may have advantages. For one, the ability to fully visualize and access the heart makes it easier to ensure appropriate lesion sets are made and are made completely. Surgery allows for real time testing of those lesions, and also provides an opportunity for exclusion or excision of the left atrial appendage, which may reduce risk of stroke. However, the atrial fibrillation catheter ablation versus surgical ablation treatment (FAST) trial found fewer episodes of left atrial arrhythmia one year after minimally invasive surgical ablation than after catheter ablation. The patients enrolled in this study had hypertension, a dilated left atrium, were refractory to drug treatment or had previously unsuccessful catheter ablation. On the other hand, the adverse event rate was higher with surgical ablation.<sup>27</sup>

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<sup>a</sup> Success rates of 30% to 90% have been reported, depending on procedure performed, type of atrial fibrillation, and size of the atrial chambers. Principal risks appear to be those associated with open chest procedures in general, such as nosocomial infection.

## RESEARCH DESIGN RECOMMENDATIONS

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The recommendations below are directed to researchers attempting to design prospective studies that address the comparative effectiveness of alternative treatments for atrial fibrillation. They are designed to provide clear, actionable recommendations for clinical researchers that will improve the quality and relevance of the trial results for decision making by patients, providers and payers.

However, we lack an understanding of many aspects of AF disease, treatment and outcomes. This limits the ability to design studies that will provide all of the information needed by patients, payers, and other end users. Because of this, we have added a section on “priority research” that describes research that is urgently needed. We encourage the AF research community to focus on this research. In the interim, we offer the following recommendations:

**RECOMMENDATION 1: Clinical trials should include patients typical of those who have AF, including the elderly and patients with a history of heart failure, coronary artery disease, diabetes, and renal impairment.**

Description: Future trials should not exclude patients on the basis of age, a history of heart failure, CAD or diabetes. Sufficient numbers of patients with these characteristics should be enrolled in order to have enough statistical power to compare the effectiveness of the study interventions in these subgroups. Alternatively, separate adequately powered studies should be conducted focusing on one or more of them. Future trials should also define “elderly” as 75 years of age and older, following the CHADS<sub>2</sub> stroke risk assessment tool.<sup>28</sup> Researchers should explicitly justify their decision to exclude any of the subgroups mentioned in the recommendation.

Rationale: AF is a disease of aging, and AF patients with heart failure, coronary artery disease, diabetes, renal impairment, and other co-morbidities represent a substantial proportion of the patients seen in routine clinical practice. However, such patients are often excluded from AF clinical trials. Evidence based on studies that exclude these subgroups is of little benefit to patients, providers and payers.

Implementation: The potential pool of study subjects is large, and many AF patients have the comorbidities of interest (heart failure, coronary artery disease and diabetes). Nevertheless, the number of patient subgroups that can be studied in any given trial is limited because enrolling these subgroups in sufficient numbers to answer the study question has a substantial impact on trial size. For example, comparing the outcomes of patients with and without heart failure within a study comparing one intervention to another (or to placebo) will nearly double the size of the trial, and examining additional subgroups within that study will further increase the size of the trial, meaning that researchers must carefully consider which subgroups they wish to study. They should also specify these subgroups before beginning the trial to avoid results that are spuriously significant (Type I errors).

A more feasible way to compare patient subgroups may be to design studies of a single intervention that are conducted solely for this purpose. To ensure that enrollees are like those in the general population of patients with AF, enrollees for such a study should be randomly selected from all patients at the participating center(s) or they should be consecutively enrolled. The patient subgroup(s) to be compared must be specified before the study begins, and power calculations should be performed to ensure that enough patients are enrolled to detect clinically meaningful differences between subgroups as statistically significant. If the patients enrolled in the study received different treatments,

investigators should report the proportion of patients that received these treatments as part of an effort to describe the patient population, but they should not use this information to attempt to determine whether one treatment is more effective than another. The fact that patients in such a study are not randomly assigned to treatment precludes this comparison. Investigators should also avoid the temptation to perform any other statistical testing that was not planned before the study began unless those tests are designed to generate hypotheses for future research, and are reported as such.

**RECOMMENDATION 2: Information that is meaningful to patients and providers, including information about how patients feel and function, should be collected from all patients enrolled in clinical studies.**

Description: In addition to the usual information (age, gender, etc.), researchers should collect and report the following characteristics for their study population:

- AHA/ACC/HRS classification (% paroxysmal, persistent, permanent)<sup>29</sup>
- Comorbidities (including heart failure, coronary artery disease and diabetes)
- Current medications taken for AF and other conditions
- Prior medications taken to control heart rhythm and AF symptoms
- Timing of past procedures for AF (cardioversions, catheter ablation, surgical procedures)
- Time since patient-reported symptom onset
- Date of EKG-confirmed AF diagnosis
- Disease-specific quality of life (QOL) at baseline as measured on Canadian Cardiovascular Society Severity of Atrial Fibrillation (CCS-SAF) Scale<sup>30</sup>
- Ability to perform activities of daily living (ADLs) at baseline

Rationale: When reporting clinical trials, researchers often do not describe study populations in a comprehensive and consistent manner. They frequently do not report relevant patient characteristics, and commonly use terms, such as “difficult-to-treat,” that do not identify a specific subgroup of patients. Providers are commonly unable to match the characteristics of their AF patients with the characteristics of patients in the clinical trials. Some of this is due to the exclusion of typical patients from clinical trials (see Recommendation #1) and some is due to a lack of knowledge of the clinical importance of and/or patient interest in particular characteristics (see Recommendation #3). We propose collecting the above information partly because of this lack of standardization. Describing study subjects will help ensure comparability across trials, and improve translation and dissemination of results.

The list above is compiled from input from our TWG and ESAG as well as interviews with patients and providers. Some, such as comorbidities, past procedures and medications, are routinely collected but are listed because they were strongly supported by our stakeholders. Others, such as the timing of past procedures and time since diagnosis are not routinely collected, but are extremely important to patients and providers who are attempting to make treatment decisions without adequate information. Common questions include: “How long should I wait between treatments?” “Is my likelihood of responding to treatments dependent on the length of time I’ve had AF?” “I have diabetes. Does that change my response to treatment?” Ensuring this type of data is collected and reported in all trials begins to help answer some of these questions.

Inclusion of QOL data allows patients who have paroxysmal AF who may be affected by symptoms differently, may be newly diagnosed or who have lived with atrial fibrillation for years to make informed

decisions about their choice of treatment. Describing study subjects consistently will help ensure comparability across trials and improve translation of results.

The current AHA/ACC/HRS AF classification system has been in use for several decades. Many of our stakeholders felt that it was outdated and that a new classification system should be developed. We agree, and address this later (see Priority Recommendation #3). However, those same stakeholders urged that the current system be routinely used until a new system replaces it.

Implementation: Most of these characteristics can be self-reported and recorded remotely (over the phone, by mail, or e-mail) or at an initial study visit. Some are already collected as part of the standard history and physical. An EKG-confirmed AF diagnosis is a common requirement for study entry. The CCS-SAF Scale is a published, non-proprietary instrument that is easily administered.<sup>30</sup>

**RECOMMENDATION 3: Researchers should report outcomes by time since diagnosis in future clinical trials of catheter ablation and surgical procedures for atrial fibrillation.**

Description: Researchers should report patient outcomes by time since diagnosis, defined as date of EKG-confirmed AF diagnosis, using months as the unit of measure during the first year after diagnosis, and full years as the unit of measure after that.

Rationale: Although EKG-confirmed diagnosis of AF is a common requirement for study entry, most studies do not report outcomes by time since diagnosis. This has hampered our ability to understand disease progression and its attendant changes in burden of disease, which leaves patients and providers without the knowledge needed to make appropriate treatment choices. This is particularly true of the timing of interventions. How quickly should AF patients who return to AF after cardioversion be placed on rate/rhythm control medications and when should more definitive treatments be added? Some experts believe that there is an “AF burden” placed upon the myocardium that is time-dependent. Greater knowledge of these timing questions will improve decision-making by both patients and providers.

Implementation: Expressing results in terms of time since diagnosis affects the statistical analysis of the data. Researchers can express results as time (since diagnosis) to an event. Kaplan-Meier or Cox’s proportional hazards analyses naturally lend themselves to such analyses. Should researchers choose to conduct analyses of the number of events per year since diagnosis, they should treat time as a continuous variable. There is insufficient evidence to use any given time as a cut point to categorize the disease in temporal terms like “early” or “late.”

**RECOMMENDATION 4: Trials of catheter ablation and surgical procedures should follow patients for at least to five years to assess recurrence.**

Description: Both symptomatic and asymptomatic recurrence should be assessed. The former can be assessed using simple patient self-reports. The latter requires periodic follow-up at office visits or remote technology.

Rationale: Very few studies have followed patients beyond two years, and current monitoring protocols differ in duration and methods of follow-up. Since catheter and surgical ablation are relatively new procedures, most previous studies focused on efficacy and followed patients for only one or two years. Information about how effective AF treatments are in the face of this progressive disease is, therefore,

sparse. In 2008, the UK National Institute for Health Research (NIHR) Health Technology Assessment Program pointed to “uncertainties around longer-term effects” of radiofrequency catheter ablation,<sup>31</sup> and in 2009, the Agency for Healthcare Research and Quality (AHRQ) noted longer follow-up was “needed before more reliable inferences [could] be made concerning the longer term efficacy.”<sup>32</sup> The absence longer-term data makes it difficult for patients to weigh their treatment options and for payers to know the most effective course of action.

**Implementation:** Studies of catheter ablation and other surgical procedures routinely follow patients for one to two years as part of their basic protocol. In extending that follow-up period to at least five years, researchers should use a simple patient self-report system. Patients enrolled in a study should be given clear guidance in their post operative counseling as to the mechanisms for reporting any symptomatic recurrence to their treating physician. The treating physician should have clear guidance on reporting these outcomes in the same manner as other outcomes are reported. In addition, all patients should be queried about symptomatic recurrence preferably every six months after the first year, but no less often than annually. This should continue for at least five years. A simple mail or phone contact is sufficient to collect this information. Although costs will obviously rise in longer trials, they can be minimized by using simple, standard processes currently in place.

In addition to collecting data on symptomatic recurrence, all AF studies should track patients using scheduled heart rhythm recordings every six months in order to detect asymptomatic recurrence. This can be done during routine office visits or using remote technology.

Ideally, all patients enrolled in a trial should be followed for five years, but resource constraints may prohibit this. In this case, a percentage of the original enrollees should be randomly chosen for longer follow-up. The percentage should be chosen to ensure that there is sufficient statistical power to perform any comparisons previously specified by the investigators. These considerations will limit the number of comparisons that researchers can make.

Five year follow-up is feasible. Tzou et.al,<sup>33</sup> followed 120 of 123 patients who were free of AF one year after pulmonary vein isolation catheter ablation in a five-year observational study. All patients had transtelephonic monitoring at 3 to 6 months and 12 months and at least yearly contact thereafter. Hussein et.al<sup>34</sup> are following 831 patients after pulmonary vein isolation catheter ablation in 2005 in their AF registry. After ablation, patients were given an event recorder to monitor for arrhythmias during the first 3 months, and recorded on a weekly basis and whenever symptomatic. Additional event recorder monitoring was obtained beyond the 3-months period if patients had atrial tachyarrhythmia within with arrhythmia. Patients had 24-hour Holter recordings done at 3, 6, and every 6 months thereafter. Follow up visits were scheduled at 3, 6 and 12 months post ablation and yearly thereafter when possible. More frequent follow-ups were scheduled for patients who experienced symptoms, arrhythmia recurrence, or complications from the procedure. Patients who have been treated for AF patients have disease processes that make frequent physician visits routine, and involving primary care physicians in assessing recurrence at these routine office visits will help minimize those costs.

**RECOMMENDATION 5: Researchers should measure and report quality of life as an outcome in all clinical trials of atrial fibrillation using a recommended disease-specific instrument.**

**Description:** Researchers should use the Canadian Cardiovascular Society Severity of Atrial Fibrillation (CCS-SAF) Scale to measure disease-specific quality of life. Quality of life should be determined at baseline and at one, two, and five years. Other instruments may also be appropriate for consideration

in addition to or in place of the CCS-SAF, though use of another instrument should be justified in the study protocol.

Rationale: AF can dramatically affect patient QOL, and both patients and clinicians have emphasized that symptoms and quality of life are highly relevant in making clinical decisions about various treatments options. On average, QOL among AF patients is significantly worse than for individuals of the same age and sex.<sup>1</sup> AF treatments themselves can also negatively affect QOL. Use of QOL measures in future clinical trials will help provide patients and providers with information that would be useful to factor into decisions about what treatment is appropriate for them.<sup>35</sup>

The Canadian Cardiovascular Society Severity of Atrial Fibrillation (SAF) Scale is a published, non-proprietary, “simple semiquantitative scale that approximates patient-reported subjective measures of QOL in AF.”<sup>30</sup> It has been in use since 2008 and has been validated against the SF-36 generic QOL questionnaire and the AFSS (University of Toronto Atrial Fibrillation Severity Scale) disease-specific questionnaire.<sup>30</sup> We recommend the SAF Scale because of its simplicity and because, as a disease-specific instrument, it will be more sensitive to changes in patient status than general instruments.

Implementation: Implementing this recommendation does not place an undue burden on researchers or study subjects. Quality of life can be measured at initial and follow-up study visits. These outcomes are best measured in blinded trials, inasmuch as the patients answers to questions about quality of life could be affected if they know what treatment they are receiving.

## PRIORITY RESEARCH RECOMMENDATIONS FOR AF

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**RECOMMENDATION 6: Create a national registry for atrial fibrillation in order to conduct studies and generate hypotheses and evidence about which therapies work best in which patients, at what point in their disease process.**

Description: A national registry for atrial fibrillation (AF) should include younger patients (i.e., those 30-40 years of age) and older patients (i.e., those of approximately 80 years of age), and those with common comorbidities, such as heart disease, coronary artery disease, hypertension and stroke. It should capture risk factors of diabetes and obesity. A national registry should include information about the clinician (generalist and specialist), and the circumstances (usual care, emergency) in which treatment occurs. It should capture variables that may characterize “standard” interventions and influence outcomes, including the level of operator experience, and extent of facility support (staff and equipment resources) for catheter ablation and surgical procedures, and the consumption of particular foods and dietary supplements. It should capture data on a broad array of outcomes, including patient-reported symptoms and QOL measures, congestive heart rate, stroke, anti-coagulant and anti-arrhythmic medications that patients must continue or resume, the side-effects of these medications, the number and length of hospitalizations, death rates, and other information that is of interest to patients, such as “time since diagnosis.”

The data collected should meet the needs of already planned and anticipated observational studies and protocols. Examples of possible studies include examination of the prevalence of asymptomatic recurrence and its effect on stroke risk; continued examination of potential benefits of restoring normal sinus rhythm; and an investigation of the relationship between symptoms and patient-reported quality of life (QOL) measures.

Rationale: The three primary reasons for a registry are that it will; (1) have data from more patients than are in the typical clinical trial and, therefore, be able to detect differences between treatments and patient subgroups that are clinically important but too small for most clinical trials to detect as statistically significant, (2) allow for collecting a broader array of data than is typically feasible in a clinical trial and, (3) allow for long-term tracking of patients.

Long-term tracking is needed because we lack an understanding of many aspects of AF disease, treatment, and outcomes. Most critical is our need to better understand the heterogeneity of treatment response. A national AF registry will give researchers an opportunity to conduct observational studies, identify differences in treatment response that might be associated with patient characteristics, and generate informed hypotheses for future large-scale clinical trials. In the words of one patient advocate:

*“[E]ach AF patient is an experiment of one. And there are so many combinations and permutations of things that contribute to the individual patient . . . with observational studies, we’ll be able to figure out how to really stratify patients into specific groups and understand what treatments work best in those unique combinations.”*

A registry will also address patient concerns and interests. Because we lack an understanding of disease progression and remodeling, we do not know the optimal timing of treatments. Patients, families and clinicians are concerned that if “AF begets AF,” then the more time a patient spends in AF the less likely

it is that a rhythm control intervention, specifically catheter ablation, will restore normal heart rhythm. They want to know how “time since diagnosis” will affect their outcomes. A registry should also examine common patient practices that currently lack evidence, such as certain foods and dietary supplements (for example, low sodium vegetable juice and fish oil) used at-home for treatment and prevention. Patients currently create their own regimens based on trial and error, sometimes at great cost in terms of time, money and safety. Tracking these practices will provide valuable insights.

Finally, a registry will allow for collection of data about adverse events, some of which may not occur frequently enough to be detected as statistically significant by even relatively large trials. This information will be valuable to patients, who not only want to know which treatment has the fewest such events, but who must also weigh their impact against the benefits of the various AF treatments.

Implementation: There is no comprehensive national registry for AF. Existing and planned registries have met with varying degrees of success, and focus on specific aspects of treating patients with AF. For example, the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study, which began in the 1990s and which continues to receive funding, focuses on warfarin use, and the larger Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) focuses on identifying “reasons and risk factors for non-receipt of anticoagulation (AC) therapy,” and “reasons why AF patients who are prescribed AC therapy do not take” it. The planned Safety of Atrial Fibrillation Ablation Registry Initiative (SAFARI) will focus on AF ablation.<sup>36, 37</sup> Finally, the RECORD AF Registry was established to evaluate the management and clinical outcomes of recently diagnosed atrial-fibrillation patients over one year, and the Atrial Fibrillation: Focus on Effective Clinical Treatment Strategies (AFFECTS) registry was designed to examine atrial fibrillation treatment by United States cardiologists in the context of the American College of Cardiology, American Heart Association, and European Society of Cardiology guidelines after recent landmark clinical trials<sup>38,39</sup>.

Initial registry development efforts should focus on supporting, expanding, and connecting existing registries, performance measurement systems, and datasets. For example, large clinical trials such as the Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) study, sponsored by the National Institutes of Health (NIH) and expected to conclude in 2015, will produce a dataset that might be expanded into a registry. Manufacturers of catheter ablation equipment have datasets on new technologies that may warrant continued use as registries. Finally, professional cardiovascular societies have implemented performance reporting systems which collect some measures on anticoagulation, although they are not specific to AF.

Specialty societies with related registry experience such as the American College of Cardiology (ACC) and the Heart Rhythm Society (HRS) should be involved in the development of this registry. Patients and patient advocates are also supportive of establishing a national registry; their input and involvement should be actively sought, potentially through voluntary health organizations such as WomenHeart and StopAfib. Patients themselves are also likely to play a critical role in the success of a registry, directly contributing data on disease, treatment, and outcomes. Efforts should be made to ensure that the registry contains information from sites that are representative of all sites, not just those likely to obtain the “best” results.

**RECOMMENDATION 7: Develop a new AF classification system more relevant to both patients and clinicians for use as the basis of inclusion and exclusion criteria for future large-scale clinical trials.**

Description: The current atrial fibrillation (AF) classification system (see Introduction: Clinical Framework) is focused on the frequency, duration, and reversibility of AF episodes, aspects of AF that are less meaningful to patients and clinicians than symptoms, QOL, heart rate, and “time since diagnosis”. A new classification system is needed to develop inclusion and exclusion criteria for future large-scale clinical trials, as well as for electronic health record systems and coding rules used in submission of claims to payers.

Rationale: The current AF classification system does not sufficiently differentiate patients or characterize their disease in a way that facilitates the assessment of appropriate therapies. For example, patients with paroxysmal AF can have greatly different QOL, which strongly influences their treatment preferences, values, and choices. If patients are to make more informed treatment decisions, the study subjects in clinical trials and guidelines must be described in a way that makes it easy for patients to compare themselves and their situations. Additionally, if clinicians are to implement study findings more quickly and follow treatment guidelines more consistently, they must have decision support tools that allow them to best manage the AF patients they care for on a daily basis. Active, consistent, and rigorous use of an AF classification system meaningful to patients and clinicians as the basis for inclusion and exclusion criteria will help ensure comparability across trials, with the goal of improving translation and dissemination of results.

Implementation: A new classification system for AF will require significant work on the part of experts in the field. Resistance to change is a barrier. Data to support a new system could flow from the registry discussed above. Regardless of the data source, developers of a new classification system should ensure that this system is both valid and reliable, where validity is the degree to which the classification system measures what it is intended it to measure, and reliability is the consistency of the classification system.

There are three types of validity that researchers must demonstrate for the classification system; construct validity, content validity, and predictive validity. Demonstrating that a classification system has construct validity means that its results must vary with another measure of the health of patients with AF. For example, one might expect that dramatic decreases in health measured by a new system would also be reflected in poorer SF-36 scores or worsening abilities to perform activities of daily living. Demonstrating that the classification system has content validity requires testing its ability to include or represent all of the content of a particular construct. There is no easy way to determine content validity aside from expert opinion. Finally, if the classification system is to be used for prediction, one must demonstrate that it can, in fact, predict future outcomes. For example, clinicians and patients would like to know whether a relatively small worsening of AF as detected by the classification system means that they will continue to worsen.

Researchers should also demonstrate that the classification system has three kinds of reliability; test-retest reliability, inter-rater reliability, and internal consistency. To demonstrate test-retest reliability, the rating system should be administered to patients twice, and during a period of time short enough to ensure that their disease has not changed. There should be a high correlation between the classification obtained on the first administration and the second one. Because it is likely that some of the classification system will involve clinician judgment, the inter-rater reliability of the classification system must also be demonstrated. In other words, the classifications obtained by different clinicians should agree. Finally, the individual items that comprise the classification system should all measure the same

thing (in this case, the severity of AF). Determining this internal consistency requires computing a statistic known as Cronbach's alpha from, for example, the matrix of correlation coefficients of the individual items that comprise the classification system.

**RECOMMENDATION 8: Research should conduct RCTs that assess the impact of different post procedure anticoagulation strategies on stroke rates.**

Description: In studies of catheter ablation and surgical procedures for the treatment of AF, patients should be randomized post-operatively to arms that continue anticoagulation or discontinue anticoagulation at three months and six months, and follow all arms for 36 months to assess the risk of stroke.

Rationale: There are no broadly accepted guidelines on the use of anticoagulant follow catheter ablation or surgical procedures. Some proponents, both clinicians and patients, believe a successful treatment that results in normal heart rhythm is essentially a "cure" and, as a result, long-term oral anticoagulation is no longer necessary. Supporting (but not proving) this point of view is that surgery allows for concomitant exclusion of the left atrial appendage, which is thought to significantly reduce stroke risk.

After catheter ablation or surgery, some AF patients who no longer experience AF symptoms may decide to stop anticoagulation. Although the desire stop anticoagulation appears to motivate many AF patients to undergo these procedures in the first place, stopping their medication may place them at risk. Clinicians acknowledge this practice of discontinuing anticoagulation, while simultaneously acknowledging the lack evidence to support it.

While observational studies will add to the knowledge base around stroke risk following anticoagulation discontinuance after catheter ablation or a surgical procedure, it will not provide sufficient evidence for making treatment decisions. A randomized trial is needed.

Implementation: Anticoagulant strategies were specified in all protocols of catheter ablation and surgical procedures that we reviewed. Most require use of anticoagulants for a prespecified period of time and then allow treating physicians to make decisions as to continuance. We recommend defining the protocol for the life of the trial by establishing specific arms for different strategies. We propose three strategies—continuance of anticoagulants for the life of the protocol or discontinuing anticoagulants at either three months or six months. Other strategies may be appropriate if justified. This addition to current protocols could affect enrollment as some patients agree to these procedures for the express purpose of discontinuing anticoagulants. However, appropriate counseling as to the lack of knowledge concerning the benefits or lack thereof from these procedures should minimize this difficulty.

## REFERENCES

1. Calkins H, Berger R. Atrial Fibrillation: The latest management strategies. New York: Johns Hopkins; 2010.
2. Wolf PA, Dawber TR, Thomas HE, Jr., Kannel WB. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: The Framingham study. *Neurology* 1978;28:973-7.
3. Chugh SS, Blackshear JL, Shen WK, Hammill SC, Gersh BJ. Epidemiology and natural history of atrial fibrillation: clinical implications. *Journal of the American College of Cardiology* 2001;37:371-8.
4. Atrial Fibrillation. (Accessed July 27, 2011, at <http://www.stroke.org/site/PageServer?pagename=afb>.)
5. Jahangir A, Lee V, Friedman PA, et al. Long-term progression and outcomes with aging in patients with lone atrial fibrillation: A 30-year follow-up study. *Circulation* 2007;115:3050-6.
6. Smith D, Lip GY, Lane DA. Impact of symptom control on health-related quality of life in atrial fibrillation patients: The psychologist's viewpoint. *Europace* 2010;12:608-10.
7. Knight B. Practical Rate and Rhythm Management of Atrial Fibrillation. In: Heart Rhythm Society; 2010.
8. Fuster V, Ryden LE, Cannom DS, et al. 2011 ACCF/AHA/HRS Focused Updates Incorporated Into the ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in partnership with the European Society of Cardiology and in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *J Am Coll Cardiol* 2011;57:e101-98.
9. Go AS. The ACTIVE pursuit of stroke prevention in patients with atrial fibrillation. *New Engl J Med* 2009;360:2127-9.
10. Fang MC, Go AS, Chang Y, Borowsky L, Pomernacki NK, Singer DE. Comparison of risk stratification schemes to predict thromboembolism in people with nonvalvular atrial fibrillation. *Journal of the American College of Cardiology* 2008;51:810-5.
11. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: The euro heart survey on atrial fibrillation. *Chest* 2010;137:263-72.
12. Ad N, Henry L. Historical Summary and Current State of the Maze Surgical Procedure. Falls Church, VA: Inova Heart and Vascular Institute; 2008 June.
13. Knight Be. Practical Rate and Rhythm Management of Atrial Fibrillation; 2010.
14. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Annals of Internal Medicine* 2007;146:857-67.
15. Stewart S, Hart CL, Hole DJ, McMurray JJ. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. *American Journal of Medicine* 2002;113:359-64.
16. Wattigney WA, Mensah GA, Croft JB. Increased atrial fibrillation mortality: United States, 1980-1998. *American Journal of Epidemiology* 2002;155:819-26.
17. Camm AJ, Kirchhof P, Lip GYH, et al. Guidelines for the management of atrial fibrillation: The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *European Heart Journal* 2010;31:2369-429.
18. Verma A. Atrial-fibrillation ablation should be considered first-line therapy for some patients. *Current Opinion in Cardiology* 2008;23:1-8.
19. Calkins H, Reynolds MR, Spector P, et al. Treatment of atrial fibrillation with antiarrhythmic drugs or radiofrequency ablation: two systematic literature reviews and meta-analyses. *Circulation, Arrhythmia, and Electrophysiology* 2009;2:349-61.
20. M. OR. STOP-AF and CABANA: Trials show effectiveness of ablation over drugs in AF. In: heartwire: WebMD.
21. In: U.S. Department of Health and Human Services.
22. Cleland JG, Coletta AP, Buga L, Ahmed D, Clark AL. Clinical trials update from the American College of Cardiology meeting 2010: DOSE, ASPIRE, CONNECT, STICH, STOP-AF, CABANA, RACE II, EVEREST II, ACCORD, and NAVIGATOR. *European Journal of Heart Failure* 2010;12:623-9.
23. Marrouche NF, Brachmann J, on behalf of the C-AFSC. Catheter Ablation versus Standard Conventional Treatment in Patients with Left Ventricular Dysfunction and Atrial Fibrillation (CASTLE-AF) - Study Design. *Pacing and Clinical Electrophysiology* 2009;32:987-94.
24. Lip GY, Andreotti F, Fauchier L, et al. Bleeding risk assessment and management in atrial fibrillation patients: a position document from the European Heart Rhythm Association, endorsed by the European Society of Cardiology Working Group on Thrombosis. *Europace* 2011;13:723-46.

25. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *New Engl J Med* 2009;361:1139-51.
26. Connolly SJ, Eikelboom J, Joyner C, et al. Apixaban in patients with atrial fibrillation. *New Engl J Med* 2011;364:806-17.
27. Boersma LVA, Castella M, van Boven W, et al. Atrial Fibrillation Catheter Ablation Versus Surgical Ablation Treatment (FAST). *Circulation* 2011.
28. <Altman 2010 Swiss Med Weekly-Use of the CHADS2 risk score in afib patients.pdf>.
29. ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): Developed in Collaboration With the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation* 2006;114:e257-e354.
30. Dorian P, Guerra PG, Kerr CR, et al. Validation of a New Simple Scale to Measure Symptoms in Atrial Fibrillation: The Canadian Cardiovascular Society Severity in Atrial Fibrillation Scale. *Circulation: Arrhythmia and Electrophysiology* 2009;2:218-24.
31. Rodgers M, McKenna C, Palmer S, et al. Curative catheter ablation in atrial fibrillation and typical atrial flutter: systematic review and economic evaluation. *Health Technology Assessment* 2008;12:iii-iv, xi-xiii, 1-198.
32. Terasawa T, Balk EM, Chung M, et al. Systematic review: comparative effectiveness of radiofrequency catheter ablation for atrial fibrillation. *Annals of Internal Medicine* 2009;151:191-202.
33. Tzou WS, Marchlinski FE, Zado ES, et al. Long-Term Outcome After Successful Catheter Ablation of Atrial Fibrillation. *Circulation: Arrhythmia and Electrophysiology* 2010;3:237-42.
34. Hussein AA, Saliba WI, Martin DO, et al. Natural history and long-term outcomes of ablated atrial fibrillation. *Circulation Arrhythmia and Electrophysiology* 2011;4:271-8.
35. Pedersen SS, Kupper N. Representing the patient perspective in the treatment of atrial fibrillation. *Europace* 2010;12:305-6.
36. ORBIT-AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation). (Accessed August 1, 2011, at <http://www.mplsheart.org/study/orbit-af-outcomes-registry-better-informed-treatment-atrial-fibrillation.>)
37. Al-Khatib SM, Calkins H, Eloff BC, et al. Planning the Safety of Atrial Fibrillation Ablation Registry Initiative (SAFARI) as a Collaborative Pan-Stakeholder Critical Path Registry Model: a Cardiac Safety Research Consortium "Incubator" Think Tank. *American Heart Journal* 2010;159:17-24.
38. Camm AJ, Breithardt G, Crijns H, et al. Real-Life Observations of Clinical Outcomes With Rhythm- and Rate-Control Therapies for Atrial Fibrillation: RECORDAF (Registry on Cardiac Rhythm Disorders Assessing the Control of Atrial Fibrillation). *Journal of the American College of Cardiology* 2011;58:493-501.
39. Reiffel JA, Kowey PR, Myerburg R, et al. Practice Patterns Among United States Cardiologists for Managing Adults With Atrial Fibrillation (from the AFFECTS Registry). *The American Journal of Cardiology* 2010;105:1122-9.

## APPENDIX A

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