Journal of ATRIAL FIBRILLATION

Vol-3 Issue-2 August-September, 2010

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Ranolazine for Atrial Fibrillation: Too Good to be True?

Joseph J. Gard, MD, Samuel J. Asirvatham, MD

Department of Internal Medicine, Mayo Clinic, Rochester, MN, USA, Division of Pediatric Cardiology, Department of Pediatrics and Adolescent Medicine, Mayo Clinic, Rochester, MN, USA

Introduction

Several management options for patients with symptomatic atrial fibrillation (AF) available today were not even in the realm of discussion two decades ago. These advances, however, have primarily involved invasive management options for patients with drug refractory arrhythmia. After the recognition that electrical isolation of the thoracic veins benefits patients with paroxysmal AF, a slew of more involved ablative techniques evolved. Major breakthroughs in antiarrhythmic therapy, however, have not paralleled this meteoric development of invasive techniques. The drive for invasive procedures has, in fact, been widely based on the lack of availability of simple, effective, and safe pharmacological options for AF. The introduction of dronedarone into clinical practice represented a recent addition to antiarrhythmic therapy options for use in the management of patients with AF. This agent is an analogue of amiodarone but devoid of the iodine moiety which allows its use without the well-recognized and dreaded organ toxicity associated with long-term use. Nevertheless, a significant need exists for a drug with limited side effects that can be used for symptomatic intermittent AF without the need for daily chronic use, fear of organ toxicity, and concern regarding proarrhythmia in patients with structural heart disease.

In this issue of JAFIB, Murdock et al. report their findings on using ranolazine, an antianginal agent, for the acute termination of AF in 35 patients. They performed a retrospective chart review involving two centers who had been independently using ranolazine as an “off-label” agent to convert recent onset AF to sinus rhythm. The study patients had AF between 3-48 hours, were not on any other antiarrhythmic agent, and received 2000 mg of ranolazine as a single dose. If AF terminated within 6 hours, its use was considered a success. There was a 71% (25/35) conversion rate of AF within a 6-hour timeframe. Importantly, 86% of these patients had structural heart disease and no major complications (1 patient with severe constipation), specifically, no proarrhythmia was noted. Based on these findings, the authors suggest further studies to determine if ranolazine can be a potential “pill-in-the-pocket” option for managing symptomatic AF. They note the success rate that they observed is comparable to what has been observed with propafenone or flecainide, the most frequently used pharmacological cardioversion of AF.

Why Ranolazine?

Ranolazine is an agent presently approved for use and is increasingly being utilized as an antianginal agent. The drug inhibits some late sodium-channel current and thus decreases calcium overload, the underlying mechanism for abnormal afterdepolarizations. Since early recurrences
of AF often involve arrhythmia arising from the pulmonary veins and triggered activity has been proposed as a likely mechanism for these arrhythmias, ranolazine is theoretically a candidate agent for AF. In a few small clinical studies, ranolazine has appeared to suppress AF. In the MERLIN trial, ranolazine was associated with reduction in several arrhythmias (atrial and ventricular) including new onset AF. Further, ranolazine is devoid of any known proarrhythmic potential and does not suppress sinus node or AV nodal function. Because of this, slow conduction would likely not result in organization of AF to chronic macroreentrant atrial tachycardias. Although not developed as an antiarrhythmic agent, ranolazine is not alone in taking this route to being a potential antiarrhythmic drug based on theoretical considerations and limited clinical data.

Prior to deciding whether ranolazine does, in fact, represent a safe effective agent for AF management, we must examine the present limitations with AF therapy as well as the limitations of the present report by Murdock et al.

1. Intermittent AF. Radiofrequency ablation is relatively successful often as a single procedure to manage patients with paroxysmal AF. These patients have frequently occurring, self-terminating episodes of arrhythmia that typically arise from the pulmonary veins, and electrical isolation of these veins is a largely effective and safe option for symptom management. These patients commonly have coexisting dyslipidemia or hypertension. HMG-CoA reductase inhibitors (statins) and inhibitors of the renin-angiotensin system (angiotensin-converting enzyme inhibitors and angiotensin II–receptor blockers) may reduce the risk of developing AF.

In patients with persistent or chronic AF, especially where cardioversion is ineffective, long-term drug therapy including rate control and anticoagulation approaches can be effective as well.

However, a unique set of patients are those who have intermittent AF but the episodes do not terminate spontaneously. Nevertheless, cardioversion (electrical or pharmacological) is effective in relieving the index episode, and recurrence may not occur for several months or years. For these patients, commitment to long-term daily drug therapy or immediate invasive procedures appears an inappropriate and inadequate management strategy. “Pill-in-the-pocket” as well as atrial defibrillator placement-based therapies were developed to target this patient population. However, atrial defibrillators are rarely used since the pain associated with shocks adversely impacts quality of life.

2. AF in the setting of structural heart disease. A major limitation with present therapies for AF involves problems with using pharmacologic agents in patients with structural heart disease. Class 1c agents (flecainide, propafenone, etc.), the most commonly used drugs in patients with normal hearts, are contraindicated with significant structural heart disease because of the potential of inducing proarrhythmic, malignant ventricular arrhythmia. AF, however, frequently occurs in the setting of structural heart disease including congestive heart failure, valvular disease, and coronary artery disease. Drug treatment options are limited for this patient population. Amiodarone is commonly used, but long-term accumulation of the drug and induction of organ toxicity (pulmonary, hepatic, skin, etc.) essentially rule out this drug for use in younger patients. Dofetilide can also be used as AF management in structural heart disease. Unfortunately, the drug’s exquisite dependence on normal renal function and effects on ventricular repolarization make it difficult to use this agent in sick patients who are at risk for renal dysfunction, etc. Dronedarone with its recent approval is a major new option for managing AF in patients with structural heart disease. However, this agent does have effects on sinus and AV nodal function (this effect may be beneficial in managing symptoms as well) and needs to be used on a daily basis indefinitely.

Ranolazine, if found to be effective in larger, future studies, is potentially an attractive agent for these patient populations based on the lack of observed proarrhythmia and the absence of major side effects.

3. Pulmonary vein arrhythmogenecity. Presently available antiarrhythmic agents increase refractoriness, slow cardiac conduction, or, in some instances, suppress enhanced automaticity. The recent understanding of the unique role of the pulmonary and other thoracic veins has, in turn,
resulted in the need for agents that may be specifically useful in suppressing triggered arrhythmias from the thoracic veins that result in recurrence of AF. Although it is much too early to know whether ranolazine is such an agent, it may be that discussion of such agents begins to fill this void in our antiarrhythmic drug therapy armamentarium.

Too Good to be True?

The authors acknowledge major limita tions in their study that are worth reiterating.

Their study is an uncontrolled, non-placebo-controlled retrospective chart review. The need for placebo control has been well emphasized since the nature of paroxysmal AF involves self termination of arrhythmia in a majority of patients. Although the authors compare their data with historical placebo conversion rates, the type of patients including the duration of arrhythmia, prior episodes, and comitant illnesses may have been quite different. Thus, in addition to a placebo arm, controlling also in a prospective fashion for well-recognized predictors of successful therapy for AF is essential. The authors did not seek or obtain IRB approval for their study, and they state that this was not required because of the retrospective chart review nature of their study. Future trials with high-dose ranolazine will require careful patient consent and institutional approval given the lack of efficacy or safety data with high-dose use, especially in the arrhythmia population. Another issue that requires clarification but is limited by their study design has to do with why ranolazine would be specifically effective for acute cardioversion. The theoretical basis for studying this agent in AF involves its potential ability to prevent early recurrence from triggered pulmonary vein arrhythmia. Why, therefore, should this agent be useful in terminating existing AF? Does this suggest that in some patients the continued persistence of AF reflects the persistence of a focal triggered arrhythmia?

This report by Murdock et al. does generate considerable thought and is potentially an important hypothesis-generating report. With this and other recent retrospective data, there is likely enough evidence to warrant carefully controlled studies before we know whether ranolazine is the promised drug or is just too good to be true.

References


www.jafib.com 5 Aug-Sep, 2010 | Vol 3 | Issue 2
Electrophysiological Changes of the Atrium in Patients with Lone Paroxysmal Atrial Fibrillation

David K. Murdock, MD, James A Reiffel, MD, Jeff Kaliebe, MT, CCRC, German Larrain, MD

aCardiovascular Associates of Northern Wisconsin, bCARE Foundation, Inc., cAspirus Wausau Hospital, dCo- lumbia University

Abstract

Background: The “Pill-in-Pocket” (PIP) is an approach to atrial fibrillation (AF) where oral anti-arrhythmic agents at 75% to 100% of the normal daily dose, given as a single dose, is used to convert recent-onset AF. Pro-arrhythmic risk has limited this approach to patients without structural heart disease (SHD). Ranolazine is an anti-anginal agent, which inhibits the abnormal late Na+ channel current resulting in decreased Na+/Ca++ overload. This inhibits after-depolarizations and reduces pulmonary vein firing, which have been implicated in the initiation and propagation of AF. Ranolazine increases atrial refractoriness and has no known pro-arrhythmic affects. Ranolazine is routinely given to patients with SHD. The ability of Ranolazine to terminate AF in man has not been described but if useful could be a safer PIP agent with application in the presence or absence of SHD. We describe our experience using oral Ranolazine to convert new or recurrent AF.

Method: 2000 mg of ranolazine was administered to 35 patients with new (16 patients) or recurrent (19 patients) AF of at least 3 but not greater than 48 hours duration. Clinical features, echocardiographic data, and SHD were noted. Success was defined as restoring sinus rhythm within 6 hours of Ranolazine.

Results: All but 4 patients had some form of SHD. Twenty-five patients were in the hospital, 5 were in the office, and 5 were at home at the time Ranolazine was administered. Twenty-five of 35 patients converted to sinus rhythm. No pro-arrhythmic effects, hemodynamic instability, adverse rate effects, or perceived intolerance were noted. The 71% conversion rate was comparable to other reported PIP protocols and much higher than reported placebo conversion rates.

Conclusions: High dose oral Ranolazine shows utility as a possible safe agent to convert new or recurrent AF. Larger placebo-controlled studies would appear to be warranted.

Key Words: Atrial fibrillation, ranolazine, conversion, anti-arrhythmic therapy, anti-arrhythmic agents.

Introduction

Paroxysmal atrial fibrillation (AF) frequently requires intervention to restore sinus rhythm.1-2 Transthoracic electrical cardioversion is the most effective method for terminating AF.3 Anti-arrhythmic agents may be used in some patients to convert them to normal sinus rhythm.4-13 Pro-arrhythmic concerns have limited the usefulness of anti-arrhythmic therapy in the un-monitored...
setting. As has, in some patients, bradycardic concerns and concerns about the potential transition of AF to atrial flutter with a rapid ventricular response when class IC or IA agents are used. However, in properly chosen patients, those without structural heart disease (SHD), high dose oral anti-arrhythmic agents (usually 75 to 100% of the normal daily dose of propafenone or flecainide given as a single oral dose) may effectively and safely convert 70-80% of patients with recent-onset, new or recurrent, AF in an outpatient setting. This may be at home, unmonitored, in patients at lowest risk or in those who have previously shown both efficacy and tolerance with this approach. This “Pill-in-Pocket” approach has allowed these patients to effectively treat themselves on an “as needed” basis when AF occurs without the need to immediately seek medical attention or use anti-arrhythmic therapy on a chronic basis.

Many cases of AF appear to originate and be propagated from ectopic activity originating at the junction of the left atrium and the pulmonary veins. The mechanisms responsible for the abnormal impulse activity have been the source of several investigations. Triggered activity may be particularly important.

Ranolazine is an anti-anginal agent, which inhibits the normal and abnormal late Na+ channel current in the ventricle and the peak Na+ channel current in the atrium. By this inhibition, it affects intracellular calcium handling, producing an energy sparing effect. Ranolazine induces post repolarization refractoriness in atrial tissue and is a potent inhibitor of after depolarizations produced by a number of mechanisms, an effect that could reduce pulmonary vein firing. As such, ranolazine should prove to be particularly useful in the treatment of AF. Indeed, in the Holter monitor data from the MERLIN trial, ranolazine was associated with a reduction in the incidence of several arrhythmias, including new episodes of AF. We have extended these observations to show that ranolazine can be successfully employed as an anti-arrhythmic agent and can be particularly useful in AF.

Since ranolazine is devoid of known pro-arrhythmic effects, is well tolerated, is not an inducer of sinus node dysfunction or atrial flutter, and can be given to patients with SHD, it could prove to be an ideal agent for the “Pill-in-Pocket” approach to AF if it were effective in converting patients with AF to sinus rhythm. Indeed, in preliminary observation from a single center, we described the safety and feasibility of using ranolazine for this purpose in a limited number of patients. The purpose of this report is to significantly expand upon that experience with data from more than one center and including several additional patients with and without SHD. This was a retrospective analysis of our experience using ranolazine for this purpose. Institutional review board approval is not required for retrospective chart review.

Study Population

Thirty-five patients with a known duration of AF of greater than 3 hours but less than 48 hours encountered in our clinical practices had been treated with oral ranolazine in an attempt to convert their AF. Each patient had been informed that this was an “off label” use of ranolazine and its ability to convert him/her to sinus rhythm was unknown but that its safety profile in patients with SHD made it appear to be a reasonable consideration. In 2009, the investigators, learning of each other’s use of ranolazine in this manner, decided to do a retrospective chart review of their combined experience. The age and gender was noted for each patient. Echocardiographic data, and other cardiac test results, when available, including left ventricular anatomy and function, left atrial size, presence or absence of ischemic disease was gathered. Also any other associated cardiovascular disorder such as hypertension or diabetes was noted. The history of the AF problem (first recognized episode or recurrent) was also determined for each patient. Finally, the location of the first ranolazine treatment (home, office, hospital) was noted.

The treatment with ranolazine consisted of the administration of 2000 mg of ranolazine. In 34 patients this was given as a single dose. One patient received a 1000 mg dose followed by a second 1000 mg 2 hours later. This dosage represented 100% of the usual maximum daily dose for angina. The treatment was deemed successful if the interval between administration of ranolazine and conversion of AF to sinus rhythm was 6 hours or less. Each patient in the hospital or office was also observed for side effects, such as symptomatic hy-
Potension (systolic blood pressure <100mm Hg), symptomatic bradycardia after restoration of sinus rhythm, dyspnea, presyncope, syncope, or conversion to atrial flutter or atrial tachycardia. Patients at home when they took the ranolazine were later questioned for adverse side effects. In addition all patients were questioned regarding any worsening of the symptoms related to AF and possible side effects associated with ranolazine such as constipation, light headedness or nausea.

Patients were excluded from consideration of this approach if they were on any other anti-arrhythmic agent other than beta or calcium channel blockers, had a history of second- or third-degree atrioventricular block, or bradycardia–tachycardia syndrome (unless paced).

Results

Table 1 describes the clinical characteristics of the patients included in this study and the setting in which ranolazine was administered. Echocardiographic data was available on all but 1 patient. Note that the majority of patients had SHD (86%) and left atrial enlargement (69%). The one patient without echocardiographic data had a normal electrocardiogram, no history of SHD, nor any reason to suspect it.

Note: most patients were in the hospital when ranolazine was administered including all patients with new onset AF. In the hospitalized patients, AF was not present at the time of admission but occurred during the course of treatment for other issues. One hospitalized patient was recruited immediately after he had failed electrical cardioversion for new AF. In 5 patients with a history of recurrent AF, the AF occurred in the outpatient setting and the patients called our facilities with recurrent palpitations. These patients were seen in the office where the AF was confirmed by an electrocardiogram. Five patients with well-tolerated paroxysmal AF were at home when ranolazine was administered. Each of these patients had demonstrated that they were aware of their arrhythmia because of palpitations but were hemodynamically stable (i.e., without symptoms such as dyspnea, presyncope, or syncope) during the episodes.

Twenty-five of 35 patients with new or recurrent AF converted to sinus rhythm within 6 hours of ranolazine administration. Ranolazine was very well tolerated in this setting. No patient experienced any cardiovascular side effects or worsening of AF symptoms. One patient experienced severe...

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<tr>
<td>Characteristic</td>
<td>Total Patients (100%)</td>
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<tr>
<td>Age</td>
<td>72 ± 7</td>
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<tr>
<td>Sex</td>
<td>22 (63)</td>
</tr>
<tr>
<td>Female</td>
<td>13 (37)</td>
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<tr>
<td>Type of A-Fib</td>
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<tr>
<td>Initial</td>
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<tr>
<td>Paroxysmal</td>
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<td>LVEF (%) ≤45%</td>
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<td>No</td>
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<tr>
<td>Type of SHD:</td>
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<tr>
<td>CAD</td>
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<tr>
<td>MVP</td>
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<td>LVH</td>
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<td>AS</td>
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<td>Concomitant Conditions</td>
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<td>HTN</td>
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<td>Diabetes</td>
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<td>CHF</td>
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<td>COPD</td>
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<td>Pacemaker</td>
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<td>Marfan’s Syndrome</td>
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<td>None</td>
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<td>5 (14)</td>
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constipation lasting about 36 hours each time he used ranolazine. Six patients with recurrent AF continue to use ranolazine on a “pill in pocket” basis. One other patient stopped using it after its initial effectiveness abated and now has persistent AF.

Discussion

We found that 2000 mg of oral ranolazine, when administered as a single oral dose, was reasonably effective and Ranolazine was very well tolerated. Twenty-five of 35 patients with new or recurrent AF converted to sinus rhythm within 6 hours of dose administration. The conversion rate we observed with ranolazine was similar to the 6 to 8 hour conversion rates previously reported with high dose oral “pill in pocket” propafenone or flecainide10-13 and higher than the 39% placebo 8-hour conversion rate noted by Capucci et al.13 In none of our patients was ranolazine associated with any worsening of the symptoms from AF prior to conversion or did any adverse cardiovascular effects develop. Although is likely that some of these patients would have converted spontaneously without ranolazine, the high rate of conversion strongly suggests that ranolazine was instrumental in the conversion process. These results are in agreement with other reported observations with this agent. Ranolazine has been shown to suppress AF in a few, mostly small, clinical studies25, 30, 32 none of which, however, studied pharmacologic conversion as the therapeutic goal. In a canine study, ranolazine prolonged atrial refractory periods in a use dependent manner, which should give it anti-fibrillatory effects.26 Additionally, ranolazine is an inhibitor of triggered activity which may be important mechanism underlying to initiation and potentiation of AF.19-23, 25-28 Finally the time course of the observation is consistent with our prior experience in which we reported that ranolazine begins to have significant anti-arrhythmic effects within a few hours of administration.21 Our current report adds important additional information to the developing profile of ranolazine as a clinically useful and relevant anti-arrhythmic agent.

Limitations

The small number of patients in our report cannot be assumed to reflect the certain reproducibility of our observations, although there is no basic or clinical data on which to question them. Additionally, this was a real life experience with ranolazine. Like all real life clinical decision making regarding anti-arrhythmic therapy, we gauged the effectiveness of ranolazine based upon the observed clinical response. Additional data from a continuous ECG monitoring protocol would be of interest. In addition, because our experience was not placebo controlled, the number of patients who may have converted spontaneously within the 6 hours period is unknown. Indeed it seems very likely that some would have,10-13 But our conversion rates approximate that with class IC agents which have been proven to result in higher and more rapid conversion rates than placebo.34 This observation serves as a useful pilot study demonstrating the feasibility of this approach.

In Summary

We found that high dose oral ranolazine (2 grams) was very well tolerated and shows promise as an anti-arrhythmic agent that can be useful in facilitating the conversion of AF. This has implications for a possible broad “pill-in-pocket” approach using ranolazine. Given the apparent electrophysiologic safety of ranolazine and the ability to use it in patients with SHD where current class I agents used as “pill in the pocket” therapy cannot be used, such an option could have enormous clinical and economically implications. Further investigations are warranted to explore this novel use for this medication.

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cainide versus verapamil for acute conversion of paroxysmal atrial fibrillation or flutter to sinus rhythm, Am J Cardiol 63 (1989), pp. 693–696.
Use of Ivabradine in Postural Orthostatic Tachycardia Syndrome

Jamil-Copley S, MRCP, Nagarajan DV, MRCP, Baig MK, MD, FRCP, FESC, FACC

Trent Cardiac Centre, Nottingham university hospitals, Nottingham.

Abstract

Postural orthostatic tachycardia syndrome (POTS) is characterized by inappropriate increase in heart rate on assuming upright position from a supine position without a necessary drop in blood pressure. Etiology of this condition is complex and multifactorial. Autonomic dysfunction, hypovolemia, hyper responsiveness of beta adrenergic receptors with associated elevations of plasma norepinephrine levels have been implicated as underlying pathophysiologic mechanisms. Beta blockers have previously been used to treat this condition. Ivabradine which selectively inhibits If ion current in the sino atrial node, has been reported to be useful in patients with POTS. We present one further such case of POTS successfully treated by Ivabradine.

Case report

A previously fit twenty-five year old staff nurse was referred to the cardiology clinic with recurrent pre-syncopal and syncopal episodes over 18 months. Her symptoms were described as a sharp pain felt on the left side of the head followed by palpitations in her chest. Immediately following these she would feel light-headed and then collapse, losing consciousness for a few seconds. Her past medical history included essential hypertension for which she took Ramipril and Bisoprolol. She denied smoking or recreational drug use and consumed minimal alcohol. There was no family history of relevance.

Clinical examination revealed her to be euthyroid and well. She was in sinus tachycardia with a heart rate of 100bpm and a blood pressure of 140/80mmHg whilst seated, rising to 160/90 on standing. Her heard sounds were normal and there were no carotid bruits or signs of heart failure. Respiratory, Abdominal, and Neurological examination were unremarkable.

Her Echocardiogram and electrocardiogram were both normal. Holter monitor revealed sinus tachycardia which was, at times, associated with the patient’s symptoms. She proceeded to a tilt table test, including GTN provocation. During this she was found to again have a sinus tachycardia of 146bpm with tilting but no reproduction of symptoms. As she was leaving the tilt table room she collapsed in association with a sinus tachycardia but no drop in her blood pressure. She was admitted to hospital and was noted to collapse on the ward several times a day in association with a sinus tachycardia on the cardiac monitor. There was no detectable abnormality in her blood pressure during the collapses. A CT scan of the brain was found to be normal. She was started on Ivabradine 5 mg twice daily following which her symptoms improved. She had a mean heart rate around 90 beats per minute whilst on Ivabradine. The patient was seen in clinic three weeks later where she was noted to be feeling well with no further syncopal episodes.
Conclusion

Our present case would add to the existing body of evidence for use of Ivabradine in POTS. Randomized control trials are required to look into the efficacy of this new treatment for a relatively complex medical condition.

References

Introduction

Atrial fibrillation (AF) is the most common arrhythmia encountered by caregivers for the elderly. A plethora of new, mostly invasive techniques have evolved to treat patients who remain symptomatic from this arrhythmia despite attempts at pharmacological therapy. The most widely-used of these new techniques is radiofrequency ablation, but in selected patients, special types of pacemaker, cryoablation, and surgical maze therapy may be of benefit.

In this article, we review the significance of these new techniques for the elderly population. After a brief summary of the relevant epidemiological and pathological bases for classifying AF and the basis for clinical decision-making in terms of who is likely to benefit most from these procedures, we then provide a description of the techniques, anticipated success rates, and complications associated with AF ablation to guide the primary caregiver in counseling patients with symptomatic AF. Because of the relative novelty of ablation in the elderly and very elderly, risk benefit analysis when counseling these patients can be challenging. Reports assessing ablation for AF in the geriatric population have recently become available. A brief overview of non-ablation invasive management strategies, including pacemakers, defibrillators, and the surgical maze procedure is then included.

The evidence for PV isolation

Approximately five million patients in the United States have AF, and this number is expected to double to 10 million over the next 30 years. Being a signature disease of the elderly, it has a prevalence of about 5% in people aged 65 years and older and affects approximately 10% of those 80 years old. Current estimates state that by the year 2050, 12 to 15 million people in the United States will be affected by AF. This is not surprising since the ATRIA trial (2001) found that beginning at 50, the prevalence of AF almost doubles with each decade of life; increasing from 0.5% at age 50 to 59 years to 5% to 7% or greater in those aged 70 to 79 years. Even more relevant, the Framingham Heart Study found that the arrhythmia may be an independent risk factor for death with a relative risk of about 1.5 for men and 1.9 for women after adjustment for known risk factors.

Although aging is the major risk factor for developing AF, other reversible factors must be ruled out before targeting age alone as the culprit, e.g., myocardial infarction, valvular disorders, status post cardiac surgery, pericarditis, alcohol use (“holiday heart”), pneumonia, pulmonary embolism, hyperthyroidism, structural, caffeine, pheochromocytoma, chest tumor, stroke, and other forms of SVT in the setting of Wolff-Parkinson-White Syndrome.
The current guidelines for managing AF focus on control of heart rate and rhythm, along with prevention of thromboembolism. Non-valvular AF increases the risk of ischemic stroke by approximately five-fold and causes an estimated 15% of all strokes in the United States. In people 80 to 89 years old, this proportion is even higher, approximately 24%. Oral anticoagulants are highly effective in preventing AF-related stroke, but since the oldest patients are likely to have the highest risk for hemorrhage on warfarin, prescribing anticoagulation is a dilemma that clinicians face, especially for the geriatric population.

Another matter of contention is the issue of rate-control versus rhythm-control. The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial pinned these treatment strategies against each other, only to find no significant difference in mortality. Additionally, symptom management and the need for pharmacologic therapy are being increasingly challenged with invasive electrophysiologic techniques that abolish the need for drugs and rid patients of symptoms.

Classification

The term “lone atrial fibrillation” has been used to describe AF that occurs in the absence of demonstrable underlying cardiac disease or history of hypertension. Lone AF occurs in approximately 3% of patients with AF. Patients with lone AF over the age of 61 have an increased risk of stroke and death.

AF may also be classified as paroxysmal AF or non-paroxysmal (chronic) AF. Paroxysmal AF may last from a few seconds to several weeks. In the strictest sense, paroxysmal AF patients experience episodes that terminate spontaneously within seven days and usually within 24 hours; 68% presenting with AF of less than 72 hours duration spontaneously converted to sinus rhythm. Approximately 40% of all cases of AF are paroxysmal. Non-paroxysmal, on the other hand, refers to AF that lasts longer than seven days and requires cardioversion for termination. Finally, the term permanent (or chronic) AF is use to describe AF that has been present for more than seven days and cannot be consistently terminated with cardioversion.

Pathogenetic basis for invasive AF management

AF is in a sense two separate diseases rolled in one. One disease represents triggering of AF often from one of the thoracic veins, and the second disease is one of changes that occur in the atrial myocardium itself, and ablation approaches often require more then pulmonary vein isolation alone.
cardium itself that enables the persistence of AF in a given patient. Aging results in several changes in the electrophysiology of the atrium, including increases in the refractory period, prolongation of conduction times, and fibrosis, thus creating the substrate for persistent AF [Figure 1].

Hypertension, which is common in the elderly, does increase atrial and pulmonary venous stretch and may contribute to the increase in trigger-mediated AF in the elderly, as well.

Electrical Remodeling

Electrical remodeling occurs when repeated episodes of rapidly firing atrial foci result in marked shortening of the atrial refractory period and the loss of the normal lengthening of atrial refractoriness at slower heart rates. These rapidly firing foci are usually found in or near the pulmonary veins, which are electrically active structures with a sleeve of syncytial myocardium that extends from the atrium into the vein. Additionally, other thoracic veins other than the pulmonary vein can serve as potential triggers. The smooth muscle that lines these thoracic veins is electrophysiologically distinct from the endocardium proper. This venous muscle has a shorter effective refractory period and is capable of more rapid discharge than the endocardium. Additionally, myocardium has been known to extend into the vein of Marshall and into the superior vena cava, again acting as a foci for generating irregularly firing potentials. Such foci may mimic the appearance of AF on the surface electrocardiogram, or more commonly, it may degenerate into or trigger classic AF after a brief burst of ectopic activity.

Clinical assessment prior to invasive management

While the diagnosis of AF is usually straightforward, specific features are important to evaluate when counseling patients on the appropriateness. The clinical profile that correlates best with benefit from invasive management is the patient who has paroxysmal AF and minimal or no underlying structural heart disease. Symptoms may include palpitations, fatigue, or unexplained episodic ventricular rates may give rise to palpitations, and the marked irregularity results in unpredictable ventricular filling and may result in fatigue or exertional dyspnea.

Figure 2: Typical electrocardiogram of AF illustrating the common reasons or symptoms seen in patients. Periods of rapid ventricular rates may give rise to palpitations, and the marked irregularity results in unpredictable ventricular filling and may result in fatigue or exertional dyspnea.
shortness of breath that has been correlated with electrocardiographic documentation of AF [Figure 2].

General Management

While the focus of this review is invasive management strategies for the elderly patient with AF, in the next few paragraphs, we briefly outline the present guidelines for anticoagulation and for choosing between rate-control versus rhythm-control strategies in elderly patients with AF.

Anticoagulation

In the ACC/AHA/ESC Guidelines for Management of Patients with Atrial Fibrillation, patients with a CHADS2 score of 1 may be treated with either aspirin or warfarin, while patients with a CHADS2 score of 0 should receive aspirin alone. Warfarin reduces the risk of stroke by about 68% and mortality by 33%. Aspirin, on the other hand, reduces strokes by 21%. Since optimal anticoagulation occurs between International Normalized Ratios of 2.0 to 3.0, low fixed-dose warfarin has been shown to be ineffective in preventing strokes.

For patients over 65 years who were treated with warfarin for the first time, the incidence of major hemorrhage was 13.1 per 100 person-years for patients over 80 years of age, and 4.7 for those less than 80 years old. The risk of hemorrhage was highest in patients with CHADS2 scores greater than 3, exactly the patients who would appear to be most in need of anticoagulation to prevent thromboembolism. Current studies are underway that weigh the risks and benefits of direct, competitive thrombin inhibitors for the use of anticoagulation in AF. Dabigatran has been recently studied and shown to result in hemorrhagic stroke less often than warfarin and so may be a drug that is safe and an effective alternative to warfarin. Further investigation is needed, however, and for now warfarin remains the most effective drug to prevent stroke in elderly patients at risk with AF.

Rate versus Rhythm

For those patients in whom no reversible cause is found for AF, a management strategy for minimizing symptoms and thromboembolic phenomenon must be chosen [Figure 3]. Rate control refers to control the ventricular rate in order to preserve adequate hemodynamics by either pharmacologic or non-pharmacologic means. Rhythm control refers to an active attempt to keep the patient in sinus rhythm as much as possible, whether it is through the use of anti-arrhythmic drugs (e.g. amiodarone, propafenone, sotalol), DC cardioversion, percutaneous ablation, or even sometimes surgery. The AFFIRM trial compared the efficacy in regards to mortality of both management strategies and found no significant differences in mortality or quality of life in patients assigned to a rate-control strategy versus a rhythm-control strategy.

Rhythm control was associated with a statistically insignificant trend toward higher mortality, and hospital admissions were more frequent in this group. Additionally, follow-up investigations of the AFFIRM trial showed that there was modest improvement in six-minute walk distances with the rhythm-control arm and that there was no difference in cognitive function between the study arms. The study has shown that less emphasis should be placed on the path of management and more should be placed on regaining functionality.

Elderly, minimally symptomatic patients will likely benefit greatly more from rate control rather than rhythm control, while those who are maximally symptomatic may do better with rhythm control whether by non-pharmacologic or pharmacologic means. Unfortunately, drug therapy is ineffective for long term treatment of AF with a 60% failure rate over a two-year treatment period. As such, we will focus on the non-pharmacologic invasive strategies that contribute to both rate and rhythm control and discuss the success, complications, and post-procedure management.

Ablation for AF: What is it and for whom should we recommend it?

Having established that rate control with anticoagulation is a completely valid option for managing AF, we need to consider which patients we would still recommend an invasive procedure. Patients who continue to exhibit symptoms despite pharmacological therapy represent the only present indication for AF ablation. Specifically, AF ablation should not be recommended with the idea of decreasing mortality or decreasing stroke risk since there is no data to support such contentions.
Some patients remain symptomatic with palpitations because rate control is not possible or there are intolerable side effects associated with AV nodal blocking drugs. For such patients, AV node ablation and permanent pacemaker implantation should be considered. Another large group of patients have symptoms, however, including fatigue despite rate control, and they have failed pharmacological attempts to maintain sinus rhythm. For these patients, “focal” ablation targeting the triggers and possibly modifying the substrate responsible for AF may be appropriate. 

**AV Junction Ablation and Pacemaker Placement**

When patients do not respond to drug therapy, AV junction ablation combined with permanent pacemaker implantation can be considered. Additionally, the procedure can be used in persistent, drug-refractory AF and systolic dysfunction. This procedure eliminates the posterior atrial inputs to the AV node and essentially produces complete heart block, with a slow junctional escape rhythm, for those patients whose ventricular rate is difficult to control. With pacemaker dependence, the patient is likely to have decreased symptoms and have an improved quality of life. Furthermore, control of the rapid ventricular rate has been also associated with decreased risk of the development of tachycardia-mediated cardiomyopathy. Nonetheless, AV node ablation has been shown to have a neutral effect on overall survival.

**Focal Ablation**

Focal ablation refers to the identification and ablation of rapidly firing atrial foci located usually in the thoracic veins. During the foci isolation procedure, a mapping catheter is placed into the area of interest, and characteristic abnormal electrical findings are seen on the intracardiac tracing. The foci is then ablated and...
essentially electrically disconnected from the atria. The thoracic veins include the pulmonary veins, vein of Marshall, or the superior vena cava. While pulmonary vein isolation is the most common type of ablation for AF, the isolation of the thoracic veins is usually reserved for those patients who have paroxysmal AF associated with a structurally normal heart and frequent atrial ectopy.\textsuperscript{11, 27, 28}

In the elderly, diastolic disease, valvular dysfunction, possibly fibrotic atria, etc., all contribute to the cause of AF and require ablation of the specific atrial substrate. Substrate modification is based on the principle that ablation can 1) compartmentalize the muscle mass of the atria, containing fibrillatory spread and 2) reduce the muscle mass necessary to sustain fibrillation.\textsuperscript{31, 32}

Ablation targeting the thoracic veins and other triggers for AF may be insufficient in the elderly because of these changes in the atrial substrate. More recent ablation paradigms involve attempts to modify the substrate with linear ablation in the left and right atria and in some instances targeting the retroatrial ganglionated plexuses so as to globally modify the atrial substrate.\textsuperscript{29, 33}

**Pacemakers**

Pacemakers are not a first-line or standalone therapy for AF. Nevertheless, there are some instances where pacemakers may benefit elderly patients with AF.\textsuperscript{12}

- Some patients with AF have tachy-brady syndrome with underlying significant sinus node dysfunction. The symptoms for these patients may in fact be the bradyarrhythmia and chronotropic incompetence readily amenable to pacemaker therapy.\textsuperscript{34}
• As described above, following AV node ablation, permanent ventricular pacing is required.

• Special types of pacemakers called antitachycardia devices [Figure 5] may be considered in some symptomatic patients. These devices are not helpful in preventing or treating AF; however, they can be quite effective in treating atrial flutter.

• In general, pharmacological therapy with agents such as flecainide or propafenone may be reasonably effective in controlling AF but are poor in terms of preventing or treating atrial flutters. For such patients, a combined approach of pharmacological therapy and an antitachycardia pacemaker may be considered.\textsuperscript{12}

**Defibrillators**

Atrial defibrillators are implanted cardiac devices that “shock” the patient automatically out of AF. These devices may be attractive in patients with rare recurrences of AF but who typically require cardioversion to minimize the surprise factor and pain associated with defibrillator therapy. The device can be programmed to administer therapy only at night or when “commanded” by the patient or physician. Despite these options, because of the discomfort with therapy and the fact that AF is not being prevented, very few patients at the present time are treated in this fashion.\textsuperscript{35-37}

### Surgical Procedures: Maze and Mini-Maze

The Maze III operation is a classic ablation procedure that abolishes the macro-reentry responsible for AF\textsuperscript{38} The 15-year success rate of the Maze III operation has been reported to be as high as 97% for AF associated with other cardiac conditions. This procedure, although it is successful, is not widely adopted because of the need to perform extensive incisions and suturing of the atria, which results in lengthy procedures with increased aortic cross-clamp times. The procedure is usually performed during other open-heart surgery, such as mitral valve replacement. The Mini-Maze procedure was developed in an effort to establish feasibility and decrease complications [Figure 6]. Multiple studies have been done using different variations of the principle developed by Dr. James Cox.\textsuperscript{38} He established a lesion pattern that included encircling the pulmonary vein lesion, the left atrial isthmus with attendant coronary sinus lesion, and the right atrial isthmus lesion. High-Intensity Focused Ultrasound is currently being investigated in Europe as a potential source of epicardially-initiated ablation. It does so by causing cells to oscillate and to destroy themselves through the heat generated by friction, and may do without damaging the coronary arteries.

**Figure 5:** Electrocardiogram of typical atrial flutter. Antiarrhythmic agents are generally more effective for atrial fibrillation than atrial flutter. In such cases, combined approaches using membrane active drugs for AF and either ablation or antitachycardia pacemaker-based therapy for atrial flutter can be useful.
In summary, the classical open surgical cut-and-sew maze procedure remains the most invasive technique available to maintain sinus rhythm. However, the morbidity associated with this procedure precludes widespread use except in patients who are already having an open cardiac surgical procedure for other reasons. Newer variants of this classic procedure, including thoracoscopic and limited maze procedures appear to be less invasive. However, at present, success rates in the long term are limited.\textsuperscript{39,40}

**How Successful is AF ablation?**

When counseling patients, it should be emphasized to them that AF ablation is not a long term cure for AF, especially in patients with more persistent forms of this disease. Typically, 60% to 70% of patients can be expected to be symptom free with or without adjunctive antiarrhythmic therapy and with approximately 10% to 40% requiring a second ablation procedure for full benefit.\textsuperscript{16,23,41-45}

When comparing the efficacy of AV junction ablation with focal ablation\textsuperscript{29} AV node ablation is more definitive, especially with near 100% relief from palpitation as a symptom. Nevertheless, a majority of elderly patients with paroxysmal AF may anticipate benefit with symptom-relief and without the need for permanent pacing when the focal ablation approaches described above are utilized.\textsuperscript{1,9}
What are the complications with AF ablation? Are they more likely in the elderly?

Catheter ablation is generally a safe and effective procedure. However, given the invasive nature and requirement for placing electrode-tipped catheters into the heart, complications do occur.\(^{46}\)

Some complications are considered relatively minor and are germane to all invasive cardiac procedures, including bleeding, infection, cardiac perforation potentially requiring epicardial drainage, and vascular complications.

The more serious complications of AF ablation include stroke and TIA as a result of coagulum or thrombus formation during left atrial ablation\(^{47}\) and pulmonary vein stenosis.\(^{48}\) Because ablation is done near the pulmonary veins, 4% to 10% of patients may develop narrowing of the pulmonary vein. This may be asymptomatic, but some patients, particularly those with severe multivessel stenosis, may have significant shortness of breath, hemoptysis, cough, and chest pain. In these cases, percutaneous pulmonary vein angioplasty may be required to resolve symptoms.\(^{13, 49-53}\)

Another rare but potentially life-threatening complication of AF ablation involves the occurrence of left atrial esophageal fistula formation. Here, a direct fistulas connection between the left atrium and the esophagus is created. Patients may experience odynophagia, endocarditis, and air embolization producing stroke-like syndromes. Prompt recognition and surgical treatment is essential to save life.\(^{54}\)

The risk for these serious complications appear to be significantly reduced with present techniques to minimize energy delivery in the left atrium and the use of adjunctive imaging resources, such as intracardiac ultrasound to guide ablation therapy.\(^{55}\)

Although some studies have demonstrated that patients older than 75 years of age especially those with concomitant congestive heart failure have a higher risk of ablation-related complications.\(^{49}\)

With appropriate care in patient selection, age alone should not be considered a contraindication to recommending invasive options in patients with symptoms despite medical therapy.

Clinical Approach to AF Ablation in the Elderly

In our practice, just as with younger patients, when counseling the elderly for AF ablation, we stress the fact that this is potentially a quality of life improving technology and procedure. In other words, we emphasize that the procedure is not done to prevent stroke or prevent death but rather to help with symptomatic AF. If the elderly patient is symptomatic despite attempts at rate control and possibly a trial of one or more antarrhythmic agents, we recommend radiofrequency ablation. Although this approach is similar to the one we use in younger patients, with the elderly, we typically give the option of AV node ablation and pacemaker insertion if rate control could not be achieved with pharmacological agents or rate control ameliorated symptoms of palpitation, however, the drugs could not be tolerated.

With regard to the invasive ablation approach, in the elderly, with paroxysmal AF, we typically perform pulmonary vein isolation and cavotricuspid isthmus ablation. Should there be other venous triggers of AF identified, these are mapped and ablated as well (superior vena cava, vein of Marshall). For persistent AF, left atrial linear lesions are also performed. Special care to avoid collateral damage especially to the esophagus is made with limiting ablation lesions in the posterior left atrium and ablating only as much as is required to diminish the local atrial electrograms. During the procedure, meticulous attention should be given to anticoagulation, and fluid management is essential in elderly patients, specifically over anticoagulation with increased risk of vascular access and pericardiac bleeding and avoidance of prerenal failure exasperating the often coexisting mild renal insufficiency in the elderly.\(^7\)

Summary

Invasive management for symptomatic AF in the elderly is an important consideration to potentially improve quality of life. When the primary caregiver needs to counsel an elderly patient with AF on appropriate management strategies, the following steps should be undertaken:

1. Determine the appropriate choice for antico-
agulation.

2. An attempt at rate control to alleviate symptoms.

3. Consider rhythm control strategy with a pharmacological agent when patients remain symptomatic despite rate control.

4. Consider AV node ablation if rate control is not possible pharmacologically or is associated with intolerable side effects.

5. For those patients who remain symptomatic despite the above measures, AF ablation should be considered along with possible adjunctive pacemaker-based therapy.

Elderly patients should not be excluded from invasive therapy, as with appropriate caution these procedures can be performed with acceptable risk and a relatively high chance of alleviating symptoms. Patients, however, should be made aware that ablation is being offered purely for symptom-reduction since there is no evidence to support invasive therapy purely to decrease mortality or to decrease stroke risk.

References


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Is AF Ablation Cost Effective?

William Martin-Doyle, BA\textsuperscript{a}, Matthew R. Reynolds, MD, MSc\textsuperscript{b,c}

\textsuperscript{a}University of Massachusetts Medical School, Worcester, MA, \textsuperscript{b}Beth Israel Deaconess Medical Center, \textsuperscript{c}Harvard Clinical Research Institute, Boston, MA

Abstract

The use of catheter ablation to treat AF is increasing rapidly, but there is presently an incomplete understanding of its cost-effectiveness. AF ablation procedures involve significant up-front expenditures, but multiple randomized trials have demonstrated that ablation is more effective than antiarrhythmic drugs at maintaining sinus rhythm in a second-line and possibly first-line rhythm control setting. Although truly long-term data are limited, ablation, as compared with antiarrhythmic drugs, also appears associated with improved symptoms and quality of life and a reduction in downstream hospitalization and other health care resource utilization. Several groups have developed cost effectiveness models comparing AF ablation primarily to antiarrhythmic drugs and the model results suggest that ablation likely falls within the range generally accepted as cost-effective in developed nations. This paper will review available information on the cost-effectiveness of catheter ablation for the treatment of atrial fibrillation, and discuss continued areas of uncertainty where further research is required.

Background

The direct costs of treating atrial fibrillation in the United States have been estimated at $6.7 billion,\textsuperscript{1} a figure which is likely to grow with the large expected increases in the prevalence of AF.\textsuperscript{2} As one component of AF treatment, the use of catheter ablation to treat atrial fibrillation is growing rapidly.\textsuperscript{3-4} However, catheter ablation to treat AF is a relatively young and evolving technology, first described in 1998,\textsuperscript{5} is associated with significant up-front costs, and carries a risk of procedural complications. As previous reviews on the cost-effectiveness of AF ablation have noted, healthcare decision makers currently have only limited information to guide them on whether the use of AF catheter ablation represents good value.\textsuperscript{6-8} Cost-effectiveness analysis attempts to assess this value by quantifying the incremental changes in both cost and effectiveness involved with use of a new technology compared to the current standard of care, with results commonly expressed in units of cost per quality-adjusted life year.\textsuperscript{9} This review aims to summarize the available information on the cost-effectiveness of catheter ablation for the treatment of atrial fibrillation, and to identify continued areas of uncertainty where further research is required.

Clinical Evidence in Support of AF Ablation

In clinical studies conducted to date, AF ablation has generally been found to result in higher success rates (as measured by freedom from AF) compared to AADs, with less frequent but potentially more serious adverse events, as described elsewhere.\textsuperscript{10-13} A 2009 meta-analysis of 63 clinical studies on AF ablation completed through 2007(10) reported ablation success rates of 57% (single-procedure, off AAD therapy), 71% (multiple procedure, off AAD), and 77% (multiple procedure, AAD or unknown AAD), with major complications occurring in 4.9% of patients. Re-
ported success rates for the treatment of paroxysmal AF are generally higher than for persistent AF, and while overall success rates are relatively high, there has been wide variation in results from study to study.\textsuperscript{14}

While these figures appear promising when compared to the lower success rates typically achieved with AADs, especially in patients who have already failed one or more AADs, the limitations of the current clinical evidence base are widely recognized. Few RCTs comparing AF ablation to AADs have been conducted, and studies to date have generally been relatively small and of short duration, with few studies reporting follow-up longer than 12 months. Perhaps most importantly, while freedom from AF is the most common endpoint used in trials to date, it remains to be determined by randomized controlled trials whether ablation reduces the risk of stroke or mortality, as suggested by one nonrandomized study.\textsuperscript{15} These uncertainties in the clinical evidence base naturally lead to uncertainties in health economic assessments, which have used varied assumptions about long term ablation efficacy and the benefits of sinus rhythm maintenance.

**AF Ablation and Quality of Life**

AF has significant negative effects on quality of life in the majority of patients.\textsuperscript{16-17} In both randomized and nonrandomized studies of ablation which have measured QOL as an outcome, AF ablation has resulted in large improvements in quality of life.\textsuperscript{17-20} In one randomized controlled trial comparing AF ablation to AADs as first line therapy for paroxysmal AF, ablation resulted in statistically significant differences versus AADs on five of eight subscales of the SF-36 after 6 months, with the largest differences observed in the physical functioning and role-physical subscales, and significant differences also noted on the general health, social functioning, and bodily pain subscales.\textsuperscript{19} However, these studies have generally been limited by short follow-up duration and high rates of crossover.

While there is abundant evidence about the negative impact of AF on QOL and increasing evidence supporting the positive QOL impact of ablation, until recently there had been no available data on how those QOL changes translate into health state utility values, a fact noted by the authors of the first AF ablation cost-effectiveness analyses.\textsuperscript{21-22} Health state utility values range from 0 to 1 and are required to calculate quality-adjusted life years (QALYs) associated with a given health state – QALYs are simply the product of utility scores and life expectancy, summed over time.\textsuperscript{25} To address this lack of data on health state utilities in AF, the authors of the most recent AF ablation cost-effectiveness analysis,\textsuperscript{24} calculated the utilities of AF patients at baseline, and after successful conversion to NSR via AAD or ablation using previously validated methods for deriving utility scores from SF-12 or SF-36 questionnaires.\textsuperscript{25, 26} Based on analysis of several AF cohorts, the authors reported a mean baseline utility value of 0.725 for patients in AF, and a change in utility for successful sinus rhythm maintenance of +0.065.

**AF Ablation Costs and Cost Effectiveness**

**AAD treatment costs and hospitalizations**

Hospitalization accounts for roughly half the medical costs associated with AF.\textsuperscript{1-27-30} Compared with rate control, rhythm control using AADs is associated with higher costs, partially due to higher rates of hospital admissions required to adjust medications.\textsuperscript{31-32} One study explored this relationship between AAD use and hospitalization cost, and found that medical costs among AF patients pursuing a rhythm control strategy rose dramatically with increasing numbers of recurrences, primarily driven by hospitalization costs.\textsuperscript{27} A recent meta-analysis of RCTs comparing AF ablation to AADs found that ablation is associated with significantly lower rates of hospitalization for cardiovascular causes than AADs, with a rate ratio of 0.15.\textsuperscript{33} One potential economic rationale for the use of AF ablation as opposed to AAD therapy, therefore, is that despite higher initial costs of ablation, there may be lower long-term follow-up and hospitalization costs resulting from ablation’s higher efficacy in maintaining normal sinus rhythm. Better documentation of this idea is needed.

**Cost of AF Ablation**

Six studies to date have evaluated the total costs associated with pursuing an AF ablation treatment strategy, as shown in Table 1. Weerasooriya
### Table 1

<table>
<thead>
<tr>
<th>Reference</th>
<th>Location, perspective</th>
<th>Type of AF, patient characteristics</th>
<th>Analysis type</th>
<th>Currency, year</th>
<th>Time horizon</th>
<th>Discount rate</th>
<th>Comparator Therapy</th>
<th>Cumulative cost of ablation over time horizon</th>
<th>Cumulative cost of comparator therapy over time horizon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weera-soruya et al., 2003(34)</td>
<td>France, healthcare system</td>
<td>Paroxysmal, AAD failures</td>
<td>Model based on resource data from retrospective ablation cohort</td>
<td>EUR, 2001</td>
<td>5 years; 10 years</td>
<td>5%</td>
<td>AADs</td>
<td>5 years: €6,730 10 years: €8,291</td>
<td>5 years: €7,194 10 years: €12,760</td>
</tr>
<tr>
<td>Chan et al., 2006(21)</td>
<td>U.S., societal</td>
<td>All types AF, at low and moderate risk of stroke, 55 y.o. &amp; 65 y.o. cohorts</td>
<td>Model based on published literature and Medicare data</td>
<td>USD, 2004</td>
<td>Patient lifetime</td>
<td>3%</td>
<td>Rate control (RC); Amiodarone</td>
<td>Moderate stroke risk / 55 y.o.: $59,380</td>
<td>Moderate stroke risk / 55 y.o.: RC: $50,509; Amiod: $55,795</td>
</tr>
<tr>
<td>Khaykin et al., 2007(35)</td>
<td>Canada, healthcare system</td>
<td>Paroxysmal, average patient based on resource utilization patterns in Canada and France</td>
<td>Model based on published literature, CARAF registry, and Canadian price weights</td>
<td>CAD, 2005</td>
<td>5 years</td>
<td>3%</td>
<td>AADs, RC, AC (weighted average)</td>
<td>Range of $16,278 to $21,294, with annual cost of $1,597 to $2,132.</td>
<td>Range of $4,176 to $5,060 annually</td>
</tr>
<tr>
<td>Rodgers et al., 2008(22) / McKenna et al., 2009(36).</td>
<td>U.K., healthcare system</td>
<td>“Predominantly paroxysmal”, refractory to ≥1 AADs base CHADS =1</td>
<td>Model based on published literature and ablation costs from 1 UK cardiologist</td>
<td>GBP, 2006</td>
<td>Patient lifetime</td>
<td>3.5%</td>
<td>Amiodarone</td>
<td>£26,027</td>
<td>£15,367</td>
</tr>
<tr>
<td>Khaykin et al., 2009(37)</td>
<td>Canada, healthcare system</td>
<td>Paroxysmal, symptomatic, first-line</td>
<td>Model based on resource data from RAAFT pilot study</td>
<td>CAD, 2005</td>
<td>1 year; 2 years</td>
<td>3%</td>
<td>AADs</td>
<td>1 year: $12,283 2 years: $15,303</td>
<td>1 year: $6,053 2 years: $14,392</td>
</tr>
<tr>
<td>Reynolds et al., 2009(24)</td>
<td>U.S., healthcare system</td>
<td>Paroxysmal, refractory to ≥1 AADs, male, 60 y.o. without severe structural heart disease</td>
<td>Model based on published literature, FRACTAL registry, Medicare data, and ablation costs at authors' institution</td>
<td>USD</td>
<td>5 years</td>
<td>3%</td>
<td>AADs</td>
<td>$26,584</td>
<td>$19,898</td>
</tr>
</tbody>
</table>

AADs = antiarrhythmic drugs; AC = anticoagulation; AF = atrial fibrillation; Amiod = Amiodarone; CAD = Canadian dollars; CARAF = Canadian Registry of Atrial Fibrillation; EUR = Euros; FRACTAL = The Fibrillation Registry Assessing Costs, Therapies, Adverse events and Lifestyle; GBP = British Pound; NSR = normal sinus rhythm; RAAFT = Randomized Trial of RFA versus AAD as First-Line Treatment of Symptomatic Atrial Fibrillation; RC = rate control; USD = U.S. dollars
et al. 24 first described the cost of AF ablation in 118 consecutive patients treated at a single center in France. The authors estimated that over a five year period, the cumulative cost of the ablation strategy reached €6,730 (in 2001 euros), similar to the five-year cost of €7,194 incurred with an antiarrhythmic drug strategy. The majority of costs of the ablation strategy were incurred upfront with the ablation procedure, and annual treatment costs after that point were higher among AAD patients; the authors note that after five years the costs associated with a pharmacologic strategy were higher than with ablation, and that costs continued to diverge after that point.

As part of a US cost-effectiveness model of AF ablation versus rate control or AADs, Chan et al. [21] compared lifetime costs in hypothetical 55 year-old and 65-year-old patient cohorts at moderate or low risk of stroke. Lifetime costs were calculated as somewhat higher for patients undergoing ablation, and ranged from $43,036 to $59,380 for ablation, compared to ranges of $24,540 to $50,509 for rate control, and $38,425 to $55,795 for amiodarone (all in 2004 US dollars). The authors estimated the initial cost of AF ablation as $16,500, and assumed lower costs thereafter for successfully treated ablation patients than for AAD-treated patients.

Khaykin and colleagues 35 subsequently estimated the costs of AF catheter ablation in Canada compared to the cost of rate control or AAD treatment. This model also relied on published literature and data on AF healthcare utilization patterns in Canada and France, and estimated that over a five-year time horizon the costs of AF ablation would slightly exceed those of medical therapy, ranging from $16,278 to $21,294 with an annual cost of $1,597 to $2,132, compared to an annual cost of medical therapy ranging from $4,176 to $5,060 (in 2005 Canadian dollars). The paper concluded that costs of ablation and AAD therapy would be equal after 3.2 to 8.4 years of follow-up, or with 3% discounting applied, after 4.5 to 10.8 years of follow-up.

Rodgers et al. 22 evaluated the cost-effectiveness of AF ablation from the U.K. healthcare system perspective, in an analysis initially released as part of a NICE health technology assessment, and subsequently published in a peer reviewed journal. 36 Their cost assumptions for ablation and AADs included an ablation procedure cost of £9,810 and AAD costs of £186 in year 1, and then £32 per year thereafter (only generic amiodarone was modeled). Annual treatment costs were assumed to be equal for both the NSR and AF health states, at £646 per year – an assumption which does not factor in potentially higher long-term hospitalization costs associated with AAD adjustments. Based on these assumptions, for their base-case scenario the authors estimated lifetime costs of £26,027 for ablation and £15,367 for AAD treatment.

In 2009, Khaykin and colleagues 37 published an economic analysis of the RAAFT pilot study in Canada, comparing the costs of AF ablation to antiarrhythmic drugs as first-line therapy for the treatment of symptomatic paroxysmal AF. Following the first year of follow-up, costs were $12,283 in the ablation arm and $6,053 in the AAD arm (in 2005 Canadian dollars), and there was a significant difference in the rate of hospitalizations for AF favoring the ablation arm (9% vs. 54%). At the end of the two-year treatment period, costs for patients in the antiarrhythmic arm approached those of patients in the ablation arm, at $14,392 for AADs versus $15,303 for ablation. However, during the second year of the trial AAD patients were allowed to receive ablations. Since during the second year 18 of 37 AAD patients underwent ablations, this two-year AAD cost figure more accurately represents the cost of a delayed ablation strategy rather than a pure AAD strategy.

Most recently, Reynolds et al. 24 assessed the cost-effectiveness of AF ablation from the US healthcare system perspective, relying on data from the published literature and AF ablation costs and QOL outcomes at the authors’ own institution. Initial costs of ablation were estimated at $15,000, with annual follow-up costs of $1,300 in year 1 and $200 in later years if NSR was maintained. AAD-associated costs, based on resource utilization observed in the FRACAT registry, 27 were set at $4,000 per year for patients who were well on a first line drug and $3,500 per year for patients well on amiodarone. Addition or changes of an AAD in either the AAD or ablation arm were assumed to incur the cost of a telemetry admission at $5,000. Like the previous analyses, over a five-year time horizon, ablation was found to cost somewhat more than therapy with antiarrhythmic drugs ($26,584 versus $19,898, in US dollars), and the authors noted that
the initial higher costs of ablation were partly offset by lower long-term costs compared to AAD treatment over time.

**Cost-Effectiveness of AF Ablation**

Three studies,²¹ ²² ²⁴ have evaluated the cost-effectiveness of AF ablation, as described in Table 2. These studies evaluated cost-effectiveness using the commonly accepted metric of the incremental cost-effectiveness ratio (iCER) [⁹], which is measured in units of cost per quality-adjusted life year (QALY). All three studies used a Markov decision analytic model approach, and model inputs relied mainly on published literature, supplemented by previously unpublished cost information and other assumptions when necessary. There are various important differences between the structures and assumptions of these models, including the target AF patient population considered, the choice of comparator treatment, the differential risk of stroke / mortality assumed between NSR and AF states, the differential health state utility assumed between NSR and AF states, and the time horizon. The general structure of the three models and description of evaluated target patient populations are shown in Table 2.

The study by Chan et al. in 2006 was the first to evaluate the cost-effectiveness of AF ablation.²¹ This model evaluated the cost-effectiveness of AF ablation compared to both rate control and AAD (amiodarone) treatment over a lifetime time horizon in three patient cohorts: a 55 year-old AF

### Table 2

<table>
<thead>
<tr>
<th>Item</th>
<th>Chan et al., 2006(21)</th>
<th>Rodgers et al., 2008(22) / McKenna et al., 2009(36)</th>
<th>Reynolds et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of AF considered</td>
<td>All types AF</td>
<td>“Predominantly paroxysmal”, refractory to ≥1 AADs</td>
<td>Paroxysmal AF, refra</td>
</tr>
<tr>
<td>Patient characteristics</td>
<td>Three cohorts considered: Age 55 / moderate stroke risk Age 65 / moderate stroke risk Age 65 / low stroke risk</td>
<td>Average age: 52.80% male Base-case stroke risk: CHADS₂ =1</td>
<td>Age: 60 Male No severe structural heart disease</td>
</tr>
<tr>
<td>Location</td>
<td>United States</td>
<td>United Kingdom</td>
<td>United States</td>
</tr>
<tr>
<td>Perspective</td>
<td>Societal</td>
<td>Healthcare system</td>
<td>Healthcare system</td>
</tr>
<tr>
<td>Analysis type</td>
<td>Markov model</td>
<td>Markov model</td>
<td>Markov model</td>
</tr>
<tr>
<td>Sources used for model inputs / assumptions</td>
<td>Published literature and Medicare data</td>
<td>Published literature and ablation costs from 1 UK cardiologist</td>
<td>Published literature, FRACTAL registry, Medicare data, and ablation costs at authors’ institution</td>
</tr>
<tr>
<td>Time horizon</td>
<td>Patient lifetime</td>
<td>5 years; Patient lifetime</td>
<td>5 years</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>All groups on warfarin depending on stroke risk; if NSR achieved, warfarin→ aspirin after 6 months NSR</td>
<td>Anticoagulation equivalent between groups: 64% on warfarin, 27% aspirin, 9% no anticoagulation</td>
<td>Anticoagulation equivalent between groups</td>
</tr>
<tr>
<td>Comparator therapy</td>
<td>Rate control (RC) or AAD (amiodarone)</td>
<td>AAD (amiodarone)</td>
<td>AAD: Sotalol / flecainide first-line; amiodarone second-line; rate control / anticoagulation (RC/AC) for treatment failures</td>
</tr>
<tr>
<td>Treatment strategy if NSR not maintained (Markov process)</td>
<td>Ablation: Average 1.3 ablations/patient in 1st 12 months. Patients in AF &gt;12 months after ablation shifted to anticoagulation only. RC / AAD: Patients in AF maintained on initial treatment strategy (RC / AAD).</td>
<td>Average 1.3 ablations/patient in 1st 12 months. Patients in AF post-AAD or in AF &gt;12 months after ablation shifted to anticoagulation only.</td>
<td>Ablation: Ablation 1→AAD1→ Ablation 2→AAD2→RC/AC AAD: AAD1→AAD2→RC/AC</td>
</tr>
</tbody>
</table>
patient cohort at moderate stroke risk, a 65 year-old cohort at moderate stroke risk, and a 65 year-old cohort at low stroke risk. The primary goal of this study was to determine what reduction in stroke risk would be necessary for AF ablation to be cost-effective compared with either rate control or antiarrhythmic drug strategies. Therefore, the authors considered a range of reductions in stroke and mortality following conversion to normal sinus rhythm, which was assumed to be achieved by a higher percentage of ablation patients than by patients following any other strategy. In contrast, due to a lack of available data on health state utilities in AF, the authors assumed utility changes near zero following successful conversion to NSR.

For the patient cohorts evaluated, the Chan model calculated an incremental cost-effectiveness ratio (iCER) of ablation versus rate control of $28,700/QALY for 55 year-old patients at moderate risk of stroke, $51,800/QALY for 65 year-old moderate stroke risk patients, and an unfavorable $98,900/QALY for 65 year-old low stroke risk patients, as shown in Table 3. These results were based on as-

### Table 3

AF Ablation Cost-Effectiveness Analyses: Findings in QALYs, Costs, and Incremental Cost-Effectiveness Ratios

<table>
<thead>
<tr>
<th>Finding</th>
<th>Chan et al., 2006(21)</th>
<th>Rodgers et al., 2008(22) / McKenna et al., 2009(36)</th>
<th>Reynolds et al., 2009(24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>55 y.o., mod stroke risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ablation</td>
<td>14.26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comparator AAD: 13.81</td>
<td>AAD: 10.75 RC: 10.81</td>
<td>AAD: 11.02 RC: 11.21</td>
<td></td>
</tr>
<tr>
<td>Incremental QALYs vs. AAD: 0.45</td>
<td>vs. AAD: 0.31 vs. RC: 0.25</td>
<td>vs. AAD: 0.38 vs. RC: 0.19</td>
<td></td>
</tr>
<tr>
<td>Incremental QALYs vs. RC: 0.31</td>
<td>0.42</td>
<td>1.37</td>
<td>0.13</td>
</tr>
<tr>
<td>Incremental QALYs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ablation Cumulative costs</td>
<td>$59,380</td>
<td></td>
<td>$26,016</td>
</tr>
<tr>
<td>Incremental QALYs</td>
<td>vs. AAD: not calculated vs. AAD: not calculated vs. AAD: not calculated</td>
<td>vs. AAD: not calculated vs. RC: $12,978 vs. AAD: not calculated vs. RC: $18,496</td>
<td>£10,664</td>
</tr>
<tr>
<td>Incremental cost-effectiveness</td>
<td>vs. AAD: not calculated vs. AAD: not calculated vs. AAD: not calculated</td>
<td>vs. AAD: not calculated vs. RC: $28,700/ QALY vs. AAD: not calculated vs. RC: $51,800/ QALY</td>
<td>£25,510/QALY (£20,831 to £27,745 for other CHADS2 scores)</td>
</tr>
<tr>
<td>Sensitivity analyses</td>
<td>Rate of stroke in AF (warfarin) Discount rate Reversion rate to AF post-ablation Ablation cost Utility of warfarin therapy Rate of hemorrhage on warfarin Efficacy of rate control</td>
<td>Utility of NSR vs AF Prognostic value NSR (stroke prevention)Time horizon Reversion rate to AF post-ablation</td>
<td>Utility of NSR vs AF Time horizon Utility of rate control Ablation cost</td>
</tr>
<tr>
<td>Probability that AF ablation</td>
<td>$50,000/QALY: 82%</td>
<td>$50,000/QALY: 40%</td>
<td>£20,000/QALY: 16.5%</td>
</tr>
<tr>
<td>Probability that AF ablation is</td>
<td>$100,000/QALY: 96%</td>
<td>$100,000/QALY: 78%</td>
<td>£20,000/QALY: 16.5%</td>
</tr>
<tr>
<td>cost-effective at assumed</td>
<td></td>
<td></td>
<td>£20,000/QALY: 98.1%</td>
</tr>
<tr>
<td>willingness-to-pay</td>
<td></td>
<td></td>
<td>£30,000/QALY: 68.6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>£30,000/QALY: 99.6%</td>
</tr>
</tbody>
</table>
sumptions favoring the ablation arm in terms of stroke and mortality risk: that 78% of ablation patients would be in NSR at the end of the first year, compared to approximately 36% and 58% of rate control and amiodarone patients, that patients in NSR would have stroke risks ranging from 0.5%-0.9% (depending on baseline stroke risk and treatment with warfarin or aspirin) compared to 0.7%-2.3% for patients in AF, and that patients experiencing a stroke would face a mortality risk of 8.2%-17.9%. Since the rate control strategy dominated the AAD strategy in this cost-effectiveness analysis (i.e., was associated with greater effectiveness at less cost), a comparison between the AAD and the ablation strategy was not made.

Later authors took slightly different approaches to the structure of their cost-effectiveness analyses. Rodgers et al. evaluated the cost-effectiveness of AF ablation compared to AAD treatment with amiodarone, from the perspective of the UK healthcare system. The analysis modeled cost-effectiveness for a “predominantly paroxysmal” AF patient cohort with characteristics conforming to those reported in a case series of patients seen in UK clinical practice, including an average age of 52 and 80% male gender. Like the Chan et al. analysis, the UK group assumed some differential reductions in stroke and mortality following conversion to NSR, with the assumption that NSR is maintained more frequently in patients undergoing ablation, in 84% of ablation patients at one year, compared to 37% of amiodarone patients. However, Rodgers and colleagues also assumed that quality of life gains secondary to achieving NSR would translate into meaningful improvements in health state utility compared to patients in AF.

Unlike the Chan et al. analysis, Rodgers et al. did not include a rate control comparator arm in their analysis, and assumed that ablation patients had already failed at least one AAD, consistent with current recommendations that ablation be used as second-line treatment for rhythm control. The authors conducted their analysis over a range of patient cohorts with differential stroke risks based on CHADS2 score, taking a CHADS2 score of 1 as the base-case scenario. Over a 5-year time horizon, the authors derived an iCER for AF ablation compared to amiodarone of £25,510 per QALY for the base case scenario, ranging from £20,831 to £27,745 per QALY for patients with CHADS2 scores from 3 to 0. When extended to a lifetime time horizon, the calculated iCERs were significantly more favorable, at £7,780 per QALY for the base case, ranging from £7,763 to £7,910 per QALY.

Finally, Reynolds et al. evaluated the cost-effectiveness of AF ablation from the US healthcare system perspective, comparing ablation to antiarrhythmic drugs for the treatment of paroxysmal AF patients who had already failed one or more antiarrhythmic drugs. The target patient population selected for modeling was 60 year-old men without severe structural heart disease, to conform to the typical characteristics of ablation patients reported in the published literature. In contrast to the previous analyses, the authors assumed no difference in stroke risk or mortality between the NSR and AF health states. The authors instead chose to focus on differences in utility between NSR and AF health states to drive any calculated differences in incremental quality-adjusted life expectancy between ablation and AADs. Since data on health state utilities for AF patients were not previously available, the group calculated utility weights for the AF and NSR health states based on AF patient responses to SF-12 and SF-36 questionnaires, as described above, assigning utility values of 0.725 and 0.79 to the AF and NSR health states.

Also unlike previous authors, Reynolds and colleagues did not calculate cost-effectiveness beyond a five-year time horizon, given the lack of long-term clinical data on AF ablation, nor did they assume that AAD treatment and its associated costs would be continued in the AAD patient cohort following recurrence of AF, as assumed in a few prior analyses. The authors assumed 60% single procedure efficacy off drugs, a 25% redo ablation rate, and 90% efficacy after 2 procedures with or without adjunctive AAD treatment. The authors note that their assumptions were conservative given that individual series and RCTs have reported higher success rates with ablation of paroxysmal AF.

Using these conservative assumptions, the model resulted in an incremental cost-effectiveness ratio of $51,431 per QALY gained for AF ablation compared to antiarrhythmic drugs. It should be noted that this iCER is consistent with the findings of the previous two analyses, and that it approximately
equals the threshold value of $50,000/QALY that is frequently cited as acceptable in the United States.\textsuperscript{40} The authors further noted that should future clinical data demonstrate either stroke or mortality reduction following AF ablation, or that the freedom from AF and improved QOL achieved with ablation are maintained for longer than 5 years, then the cost-effectiveness of AF ablation would be even more favorable.

All three groups conducted sensitivity analyses to identify model variables with significant impact on their overall findings. A “tornado diagram” from the Reynolds et al. 2009 study\textsuperscript{24} is reproduced in Figure 1, which displays the ranges in iCER that result when the value of key assumptions is varied within plausible limits of uncertainty. These one-way sensitivity analyses identified the utility of ablation success, the time horizon of the analysis, the utility of rate control, and the cost of ablation as the variables with the most impact on the incremental cost-effectiveness ratio. The Rodgers et al. and Chan et al. groups identified similar variables as the largest sources of uncertainty in their models [Table 3]. The UK group’s sensitivity analysis reinforces the Reynolds et al. finding that the differential utility of NSR vs. AF is a key variable influencing cost-effectiveness, and in addition they identified the prognostic benefits of NSR for stroke risk reduction and the long-term reduction of risk of recurrent AF following ablation as other key variables with significant effects on cost-effectiveness.

In addition to this type of one-way sensitivity analysis, the UK group also conducted a value-of-information (VOI) analysis,\textsuperscript{22} to quantify the expected value of perfect information regarding various assumptions used in their model. The VOI analysis assigns a monetary value to the maximum amount a decision maker should be willing to pay for perfect information about areas of uncertainty. This analysis found that further research to more precisely determine the magnitude and duration of health state utility changes in patients following ablation and AAD treatment would be of the

---

**Figure 1:** Incremental Cost-Effectiveness: AF ablation vs. AAD from Reynolds et al., 2009.\textsuperscript{(24)} Reproduced with permission. Tornado diagram displaying the results of key 1-way sensitivity analyses on the iCER for ablation compared with AAD therapy. The base-case result is denoted by the vertical line, and the changes to the iCER by varying individual parameters within plausible limits (shown in parentheses) are shown in the horizontal bars.
Using Monte Carlo simulation, both the UK study and the Chan et al. study\textsuperscript{21} also evaluated the probability of cost-effectiveness at certain assumed values for willingness to pay. The Chan et al. study found that ablation was most likely to be cost-effective in younger AF patients at moderate stroke risk (55 year-old, moderate risk cohort), with an 82\% probability of being cost-effective at a willingness to pay of $50,000/QALY, and a 96\% probability at $100,000/QALY. Rodgers and colleagues found that the probability of being cost-effective was highly dependent on both time horizon and assumed willingness to pay. In the 5-year, base-case (CHADS2=1) analysis, the probability of cost-effectiveness for AF ablation at willingness to pay values of £20,000/QALY and £30,000/QALY only reached 16.5\% and 68.6\%. However, when the time horizon was extended to the patients’ lifetimes, the corresponding probabilities of being cost-effective reached 98.1\% and 99.6\% \[Table 3\].

Discussion

Studies evaluating the costs associated with catheter ablation have generally found that ablation is somewhat more costly than AAD treatment short-term, with estimates varying from country to country and depending on the time horizon and specific comparator drug. However, the higher rates of NSR achieved by ablation compared to AADs appear to offset these upfront costs by reducing the long-term costs of repeat hospitalizations and other care associated with AAD treatment. A recent meta-analysis of RCTs does suggest that ablation reduces the rate of hospitalizations compared with AADs,\textsuperscript{33} et al. but more research is needed in this area.

Three studies have evaluated the cost-effectiveness of AF ablation compared to rhythm control or antiarrhythmic drug strategies in selected AF populations. Results of these analyses indicate that compared to AAD therapy, ablation treatment results in improved quality adjusted life expectancy at somewhat higher cost, and that AF ablation is likely to be a cost-effective treatment option for appropriately selected patients. Notably, in all analyses conducted to date, incremental cost-effectiveness ratios for AF ablation in selected populations were close to the value of $50,000 per QALY that is typically considered acceptable in the United States, as well as to the £20,000–£30,000 per QALY cost-effectiveness threshold applied in the United Kingdom.\textsuperscript{41}

The assumptions used to construct cost-effectiveness models have a noteworthy impact on determining which patients might be the most cost-effective candidates for ablation. If one assumes that the major health benefits for ablation over alternative treatments are reductions in stroke and mortality risk, as in the Chan et al. model, then ablation will appear most cost-effective in patients with at least a moderately elevated risk of stroke. If, however, QALY gains following ablation are driven primarily by improvements in symptoms and quality of life associated solely with maintenance of sinus rhythm, then the optimal ablation candidate from a cost-effectiveness standpoint is somewhat different. Under this set of assumptions, cost-effectiveness is most likely in patients with lower baseline quality of life scores \(i.e.\) patients highly symptomatic from their AF who lack major comorbid conditions, since impaired quality of life due to other health problems might be less likely to respond to ablation.

Limitations of Current Studies

Current cost-effectiveness analyses rely heavily on data from completed randomized trials of AF ablation. This restricts the AF population in which cost-effectiveness can be reasonably estimated to the primary subjects of AF ablation trials to date: relatively young, symptomatic paroxysmal AF patients treated second line, following AAD failure. In addition, many key assumptions in these cost-effectiveness models are based on sparse evidence, resulting in significant uncertainty about the true value of these parameters and therefore the cost-effectiveness of AF ablation. Perhaps most importantly, it is not yet known whether AF ablation will reduce the risk of stroke and mortality when compared to alternative therapies. Another key uncertainty is whether freedom from AF and improved quality of life are maintained long-term after initially successful ablations; there is little systematic long-term evidence of cure in ablated patients. In addition to the lack of long-term efficacy data, there have been no large long-term cost collection studies in these patients. Analyses suggesting that ablation is cost equivalent to medical
therapy are therefore contingent on the uncertain assumption that ablation efficacy is maintained long term. In addition, since data on the safety and efficacy of AF ablation have primarily been generated at leading treatment centers, it is also unclear whether the clinical results of AF ablation in real-world clinical practice (where operator experience and procedure volume may be lower) are as favorable as were modeled in these cost-effectiveness studies. These limitations all introduce significant uncertainty into the evaluation of the cost-effectiveness of AF ablation.

Future directions in AF ablation Cost Effectiveness Analysis

Data on the efficacy of AF ablation in reducing stroke and mortality and improving quality of life over the long term is needed. The Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation Trial (CABANA), a randomized controlled trial comparing AF ablation to rate control or AAD medication, began enrolling patients in August 2009. CABANA has been designed with a planned enrollment of 3,000 AF patients who will be followed for a minimum of two years, and the trial will prospectively gather data on mortality, stroke, and other clinical outcomes in a broad AF patient population, addressing many of the limitations of the current clinical evidence base. CABANA will also collect data on health economic and QOL outcomes. Completion of CABANA is expected in 2015. In addition to CABANA, other recently completed and ongoing clinical trials studying AF ablation in a range of settings can be expected to inform future cost-effectiveness analyses of AF ablation in additional patient groups. Going forward, these trials should help address the questions of whether AF ablation is both clinically appropriate and cost-effective, not only in currently recommended AF populations, but also when used in other settings, including as first-line therapy, in persistent AF, and in patients with comorbidities such as congestive heart failure.

Until such data is available, cost-effectiveness models extrapolating from the currently available clinical data suggest that AF ablation is a cost-effective treatment option for those selected AF patients for whom ablation is endorsed by current consensus guidelines.

References


Supraventricular Ectopic Activity: When Excessive it is not all Benign!

Tuan Le Nguyen MBBS, FRACP\(^a\), Liza Thomas MBBS, FRACP, PhD\(^b\)

\(^a\)Electrophysiology Fellow, Liverpool Hospital, Sydney, Australia, \(^b\)Conjoint Associate Professor, Liverpool Hospital and University of NSW, Sydney, Australia

**Introduction**

Stroke is a significant cause of mortality and disabling morbidity. The major subtypes of stroke are divided into thrombo-embolic, haemorrhagic and cryptogenic, with each having different predisposing risk factors and management strategies. Atrial fibrillation (AF) is the commonest arrhythmia predisposing to thrombo-embolic stroke. The incidence of AF increases with age, affecting up to 5% in the elderly population.\(^1-2\) Electrophysiology studies have implicated that spontaneous atrial ectopic beats that originate in or near pulmonary veins adjacent to the left atrium, may initiate paroxysms of AF.\(^2-3\) Supraventricular ectopy can be a manifestation of hypertensive heart disease or other structural heart disease, resulting in left atrial enlargement and increased wall stress, that could be associated with subsequent development of AF.\(^4\)

Binici et al. in their recent article entitled “Excessive supraventricular ectopic activity and increased risk of atrial fibrillation and stroke” in Circulation 2010, had conducted a population based cohort study of Danish individuals from the Copenhagen Holtor study, evaluating the hypothesis that excessive supraventricular ectopy would predispose to a higher incidence of thrombo-embolic stroke, death and AF.\(^4\) The population sample consisted of 678 Caucasian subjects (41.4% females) aged 55-75 years (mean 64.5 ± 6.8 years), and who otherwise had no previous history of stroke or heart disease. The participants were followed up for up to 7 years (median of 6.3 years).

The enrolled subjects had 48 hour ambulatory Holtor monitoring whereby supraventricular arrhythmias were identified. The observed arrhythmias were divided into isolated supraventricular ectopic complexes (SVEC) and runs of ≥ 3 SVEC. There were no previous definitions to determine the frequency of “excessive” supraventricular ectopy; hence the investigators used an arbitrary cut-off value being the top 10th percentile for both frequency and length of the runs of SVEC. Excessive supraventricular ectopic activity (ESVEA) was thereby defined as ≥ 30 SVEC per hour or any episodic runs of ≥ 20 SVEC. In the 678 subjects recruited, 99 had ESVEA, 70 had SVEC > 30/hour and 42 had runs of ≥ 20 SVEC (13 had both).

At baseline, the ESVEA positive group were older (67.6 ± 6.3 years vs 63.9 ± 6.7 years; p < 0.0001), had higher systolic and diastolic blood pressure, and higher N-terminal prohormone B-type natriuretic peptide levels from multivariable logistic regression analysis.

The primary endpoint (a composite of thrombo-embolic stroke and death), was significantly higher in the ESVEA group on univariate analysis (p<0.0001), and remained significant in this group after adjustment of conventional risk fac-
tors: smoking, systolic blood pressure, diabetes mellitus, cholesterol, sex and age (Hazard ratio (HR) = 1.64; 95 % confidence interval [CI], 1.03-2.60; p=0.036). Furthermore, subjects with ESVEA had significantly more hospital admissions for AF, from both univariate and age/sex adjusted Cox regression models (p=0.011 and p=0.035 respectively). Episodes of SVEC, as a continuous variable, also correlated with a significant increase in the primary endpoint of stroke or mortality on univariate analysis (HR=1.46; 95% CI, 1.22-1.73; p<0.0001 for SVEC; HR=1.13; 95% CI, 1.05-1.21; p=0.0007 for runs of SVEC), whilst multivariate analyses was significant for SVEC only (HR 1.27; 95% CI, 1.05-1.53; p=0.013 for SVEC; HR=1.06; 95% CI, 0.98-1.15; p=0.14 for runs of SVEC).

The presence of ESVEA, SVEC and runs of SVEC showed a significantly higher risk of all cause mortality (secondary endpoint) on univariate analysis (HR=2.12; 95% CI, 1.30-3.47; p=0.003; HR=1.49; 95% CI, 1.24-1.79; p<0.0001; and HR =1.12; 95% CI, 1.03-1.21; p=0.006 respectively). However on multivariate analysis, only SVEC was significant, while ESVEA or runs of SVEC were non-significant. Strokes occurred in only 27 patients (10 patients with ESVEA and 17 patients without ESVEA) during follow-up, with only ESVEA being significantly higher in both univariate and adjusted models, while SVEC or runs of SVEC were non-significant.

One of the main limitations as outlined by the authors was that the cohort recruited only middle aged Caucasian subjects; hence these results may not be applicable to other age groups and ethnicities. There was also a potential underestimation of AF reporting, in particular those with asymptomatic AF. Possible hospital admissions for AF may have been prevented by outpatient treatment, especially if symptoms were not severe. Given the small patient numbers and low event rates, the study was possibly underpowered to show statistically significant results with the multivariate models.

**Discussion**

Excessive supraventricular ectopic activity was associated with significantly increased risk (>60%) of mortality and stroke. A 2.7 fold increase in rate of AF was also observed during follow up. A stepwise increase in the risk of the primary endpoint by 27% and risk of AF by 50% was noted for each increase of 10 SVEC per hour.

The association between paroxysmal atrial ectopy and stroke has been supported by several studies in the literature. Todo et al, retrospectively examined the Holter results from a Japanese cohort presenting with thrombo-embolic strokes. The results suggested more frequent SVEC in the groups with pre-existing AF and an undetermined aetiology for stroke. An early report from Engström et al, examined prospectively a cohort of “Men Born in 1914” registry from Sweden. This revealed a significant association between frequent SVEC and the development of ischaemic stroke, independent from other major cardiovascular risk factors. SVEC progressing to AF was further characterised by a small prospective study by Wallmann et al, who reported that patients with more frequent SVEC’s were at higher risk of developing AF (OR of 9.3, p = 0.01) than those with less frequent supraventricular ectopy. Left atrial size was also significantly larger in the group developing AF compared to those remaining in sinus rhythm.

Although a simple investigative tool, ambulatory Holter monitoring is generally insensitive in detecting occult supraventricular arrhythmias given the limited recording time. Implantable devices can be utilised for longer periods of continuous cardiac monitoring. Ziegler et al described supraventricular ectopy, detected from implantable pacemakers and defibrillators, occurring in 28% of subjects with previous thrombo-embolic cerebrovascular events [8]. Implantable loop recorders are being utilised in a current trial, the CRYSTAL AF trial, to prospectively evaluate the long term detection of AF following cryptogenic stroke [9].

The findings of the current study raises questions about consideration for early implementation of anti-arrhythmic therapy and anticoagulation in those with increased SVEC and other risk factors for thrombo-embolism from AF. Currently there are no studies that explore this clinical scenario. In addition, further investigations to correlate increased SVEC with parameters of atrial volumes and function would be beneficial. Echocardiographic studies have demonstrated that left atrial enlargement in those with chronic and paroxys-
mal AF predicted a higher incidence of stroke [10-11]. Even in those in sinus rhythm, increased left atrial volumes have been associated with increased incidence of stroke, AF and other cardiovascular events [12-13]. Therefore, combining left atrial volume and function with increased SVEC may provide useful prognostic information in individuals at risk of future onset of AF and stroke. In turn, this may facilitate earlier initiation of both anti-arrhythmic and anticoagulant treatment in the prevention of adverse cardiovascular outcomes.

References

Commentary on : New-Onset Atrial Fibrillation Predicts Long-Term Mortality After Coronary Artery Bypass Graft by El-chami et.al

Giovanni Filardo, PhD, MPH\textsuperscript{a,b,c,d}.

\textsuperscript{a}Institute for Health Care Research and Improvement, Baylor Research Institute, Dallas, TX, \textsuperscript{b}Department of Infectious Diseases, University of Louisville, Louisville, KY, \textsuperscript{c}Department of Epidemiology, University of North Texas Health Science Center School of Public Health, Fort Worth, TX, \textsuperscript{d}Department of Statistical Science, Southern Methodist University, Dallas, TX

Introduction

El-chami and colleagues\textsuperscript{1} report that new-onset post-operative atrial fibrillation (AF) is associated with a significant reduction in long-term survival (adjusted hazard ratio: 1.21; 95% confidence interval: 1.12 to 1.32; follow-up: mean 6 years, range: 0 to 12.5 years) for patients undergoing isolated coronary artery bypass grafting (CABG). Moreover, the authors suggest that patients with new-onset post-CABG AF discharged on warfarin experienced reduced mortality during follow-up (adjusted HR: 0.78, 95% CI: 0.66 to 0.92) when compared to those who were not discharged on warfarin.

Early studies appear to indicate that new-onset post-operative AF is a transient event with little impact on short or long-term outcomes.\textsuperscript{2-4} However, more recent studies show atrial fibrillation, following CABG surgery, to be associated with both increased immediate complications and costs,\textsuperscript{5} as well as poorer long term outcomes.\textsuperscript{6-8} El-chami and colleagues\textsuperscript{1} study provides further evidence regarding the detrimental effect of new-onset post-CABG AF on long-term survival, and more importantly, provides new data regarding the effectiveness of warfarin at discharge.

Current recommendations for management of post-cardiac surgery AF\textsuperscript{9,10} are based on the notion that post-operative new-onset AF is transient, of self-limited duration, and of minor impact on long term outcomes. Therefore, the current recommendations are not reflective of recent publications on this subject matter. The use of anticoagulant therapy, according to current recommendations, must be weighed against the potential risk of bleeding associated with recent major surgery,\textsuperscript{9} without regard to more current findings –findings, that implicate post-cardiac surgery new-onset AF, as a strong indicator of poorer long term outcomes. In this current context of uncertainty, El-chami and colleagues\textsuperscript{1} data provide critical motivation for developing new strategies for post-operative management. Their data stress: 1) that new-onset post-CABG AF (independent of the patient’s pre-operative risk profile) has a significant effect on survival; and 2) that among those patients who experience new-onset AF, those who were prescribed warfarin at discharge had improved survival. The positive findings regarding warfarin reported by El-chami et al.\textsuperscript{1} might however, suffer from possible intervention bias / selection bias (e.g. perhaps warfarin was prescribed to those patients who had better post-operative risk profiles –the statistical analysis was adjusted for pre-
operative risk factors) and did not address continual use of warfarin during the follow-up period. However, these findings do emphasize the critical role played by in-hospital and post-discharge management of new-onset AF in improving long-term survival in CABG patients, and highlighted the critical need for further research in this field.

The increasing age and risk profile of the population undergoing CABG\textsuperscript{11} will result in increased incidence of new-onset post-operative AF. Reducing the burden of this serious and common post-operative adverse outcome has become a public health priority. Research, such as El-chami and colleagues’, that investigates the effectiveness of existent / new preventive and therapeutic strategies is critical for improving long-term outcomes for the over 125,000 people in the United States and more than 1.5 million people worldwide that undergo CABG\textsuperscript{12} each year.

References