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Ablation for Atrial Fibrillation

An Evidence-Based Analysis

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The Medical Advisory Secretariat is part of the Ontario Ministry of Health and Long-Term Care. The mandate of the Medical Advisory Secretariat is to provide evidence-based policy advice on the coordinated uptake of health services and new health technologies in Ontario to the Ministry of Health and Long-Term Care and to the healthcare system. The aim is to ensure that residents of Ontario have access to the best available new health technologies that will improve patient outcomes.

The Medical Advisory Secretariat also provides a secretariat function and evidence-based health technology policy analysis for review by the Ontario Health Technology Advisory Committee (OHTAC).

The Medical Advisory Secretariat conducts systematic reviews of scientific evidence and consultations with experts in the health care services community to produce the *Ontario Health Technology Assessment Series.*

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Abbreviations

AAD	Antiarrhythmic drug
AF	Atrial fibrillation
AFL	Atrial flutter
AVNRT	Atrioventricular nodal re-entrant tachycardia
CPVI	Circumferential pulmonary vein isolation
CTI	Cavotricuspid isthmus
ICE	Intracardiac echocardiographic (guided mapping)
IVC	Inferior vena cava
LA	Left atrium
RCT	Randomized controlled trial
RFA	Radiofrequency ablation
PVI	Pulmonary vein isolation
PV-LAJ	Pulmonary vein-left atrial junction
SPVI	Segmental pulmonary vein isolation
SR	Sinus rhythm
SVC	Superior vena cava
SVT	Supraventricular tachycardia
VT	Ventricular tachycardia

Executive Summary

Objective

To review the effectiveness, safety, and costing of ablation methods to manage atrial fibrillation (AF). The ablation methods reviewed were catheter ablation and surgical ablation.

Clinical Need

Atrial fibrillation is characterized by an irregular, usually rapid, heart rate that limits the ability of the atria to pump blood effectively to the ventricles.

Atrial fibrillation can be a primary diagnosis or it may be associated with other diseases, such as high blood pressure, abnormal heart muscle function, chronic lung diseases, and coronary heart disease. The most common symptom of AF is palpitations. Symptoms caused by decreased blood flow include dizziness, fatigue, and shortness of breath. Some patients with AF do not experience any symptoms.

According to United States data, the incidence of AF increases with age, with a prevalence of 1 per 200 people aged between 50 and 60 years, and 1 per 10 people aged over 80 years. In 2004, the Institute for Clinical Evaluative Sciences (ICES) estimated that the rate of hospitalization for AF in Canada was 582.7 per 100,000 population. They also reported that of the patients discharged alive, 2.7% were readmitted within 1 year for stroke.

One United States prevalence study of AF indicated that the overall prevalence of AF was 0.95%. When the results of this study were extrapolated to the population of Ontario, the prevalence of AF in Ontario is 98,758 for residents aged over 20 years.

Currently, the first-line therapy for AF is medical therapy with antiarrhythmic drugs (AADs). There are several AADs available, because there is no one AAD that is effective for all patients. The AADs have critical adverse effects that can aggravate existing arrhythmias. The drug selection process frequently involves trial and error until the patient's symptoms subside.

The Technology

Ablation has been frequently described as a "cure" for AF, compared with drug therapy, which controls AF but does not cure it. Ablation involves directing an energy source at cardiac tissue. For instance, radiofrequency energy uses heat to burn tissue near the source of the arrhythmia. The purpose is to create a series of scar tissue, so that the aberrant electrical pathways can no longer exist.

Because the pulmonary veins are the predominant source of AF initiation, the primary goal of ablation is to isolate the pulmonary veins from the left atria through the creation of a conduction block.

There are 2 methods of ablation: catheter ablation and surgical (operative) ablation. Radiofrequency energy is most commonly used for ablation. Catheter ablation involves inserting a catheter through the femoral vein to access the heart and burn abnormal foci of electrical activity by direct contact or by isolating them from the rest of the atrium. The surgical ablation is performed minimally invasively via direct visualization or with the assistance of a special scope for patients with lone AF.

Review Strategy

In March 2006, the following databases were searched: Cochrane Library International Agency for Health Technology Assessment (first quarter 2006), Cochrane Database of Systematic Reviews (first quarter 2006), Cochrane Central Register of Controlled Trials (first quarter 2006), MEDLINE (1966 to February 2006), MEDLINE In-Process and Other Non-indexed Citations (1966 to March 1, 2006), and EMBASE (1980 to 2006 week 9). The Medical Advisory Secretariat also searched Medscape on the Internet for recent reports on trials that were unpublished but that were presented at international conferences. In addition, the Web site Current Controlled Trials (www.controlled-trials.com) was searched for ongoing trials investigating ablation for atrial fibrillation. Search terms included: radiofrequency ablation, catheter ablation and atrial fibrillation.

Summary of Findings

Sixteen RCTs were identified that compared ablation methods in patients with AF. Two studies were identified that investigated first-line therapy for AF or atrial flutter. Seven other studies examined patients with drug-refractory, lone AF; and the remaining 7 RCTs compared ablation plus heart surgery to heart surgery alone in patients with drug-refractory AF and concomitant heart conditions.

First-line Catheter Ablation for Atrial Fibrillation or Atrial Flutter

Both studies concluded that catheter ablation was associated with significantly improved long-term freedom from arrhythmias and quality of life compared with medical therapy. These studies included different patient populations (those with AF in one pilot study, and those with atrial flutter in the other). Catheter ablation as first-line treatment is considered experimental at this time.

Catheter Ablation Versus Medical Therapy in Patients With Drug-Refractory, Lone Atrial Fibrillation

In this review, catheter ablation had success rates (freedom from arrhythmia) that ranged from 42% to 90% (median, 74%) in patients with drug-refractory, lone AF. All 3 of the RCTs comparing catheter ablation to medical therapy in patients with drug-refractory, lone AF found a significant improvement in terms of freedom from arrhythmia over a minimum of 12 months follow-up ($P<.05$).

Ablation Plus Heart Surgery Versus Heart Surgery Alone in Patients With Atrial Fibrillation

It is clear that patients with drug-refractory AF who are undergoing concomitant heart surgery (usually mitral valve repair or replacement) benefit significantly from surgical ablation, in terms of long-term freedom from AF, without substantial additional risk compared to open heart surgery alone. This group of patients represents about 1% of the patients with atrial fibrillation, thus the majority of the burden of AF lies within the patients with lone AF (i.e. those not requiring additional heart surgery).

Conclusion

Catheter ablation appears to be an effective treatment for patients with drug-refractory AF whose treatment alternatives are limited. Ablation technology is continually evolving with increasing success rates associated with the ablation procedure.

Objective

To review the effectiveness, safety, and costing of ablation methods to manage atrial fibrillation (AF). The ablation methods reviewed were catheter ablation and surgical ablation.

Background

Clinical Need: Target Population and Condition

Atrial fibrillation is a highly prevalent chronic condition. In Ontario, the prevalence is about 1.1% of the population aged over 20 years. The prevalence will continue to increase as the population ages. (1)

The results of the North American Society of Pacing and Electrophysiology (2) prospective ablation registry indicated high success rates for ablation for atrioventricular (AV) nodal tachycardia (96%), accessory pathway (94%), and atrial flutter (86%). Due to the high success rate of ablation, there are few, if any, randomized controlled trials (RCTs) comparing the effectiveness of ablation to other treatments in patients with these arrhythmias. Since the effectiveness of ablation for these arrhythmias has been established, and the therapy for these arrhythmias is common practice in Ontario, this review will focus primarily on the effectiveness of ablation for AF.

Normal Heart Rhythm (Sinus Rhythm)

In a normal heart, the electrical pathway flows from the right atrium to the left atrium, which causes the muscles of the atria to contract and allows blood to be pumped from the atria to the ventricles. The sinoatrial (SA) node (at the junction of the superior vena cava and the high right atrium) initiates the electrical pathway. The electrical current flows to the AV node (located in the lower part of the atria wall near the ventricles). The AV node is the only electrical connection between the atria and the ventricles. The purpose of the AV node is to control the transmission of the electrical current to allow the atria to contract completely and the ventricles to fill, before the electrical signal continues to the bundle of His which causes the contraction of the ventricles. Arrhythmias occur when there is a problem with the flow of electrical current through the heart.

Atrial Fibrillation

Atrial fibrillation is characterized by an irregular, usually rapid, heart rate. In 1962, Moe (3) published his hypothesis that AF is caused by multiple, interlacing, re-entrant wavelets of electrical activity. He demonstrated through a computer model that interlacing waves of activity could sustain arrhythmia. Complex approaches were developed to interrupt the wavelets; however, it was not until the mid-to-late 1990s that researchers were able to identify that the pulmonary veins were the prime initiating focus of AF. (4)

During AF, electrical charges are generated from other parts of the atria than the SA node, causing rapid and irregular contractions of the atria, which in turn limit the ability of the atria to pump blood effectively to the ventricles. The ventricles are unable to fill to their full capacity between contractions, which means that blood is ineffectively being pumped through the body. Atrial fibrillation may spontaneously revert to sinus rhythm, or a patient may require an intervention (such as electrical cardioversion) to convert back to sinus rhythm.

Atrial fibrillation can be a primary diagnosis or it may be associated with other diseases, such as high blood pressure, abnormal heart muscle function, chronic lung diseases, and coronary heart disease. The most common symptom of AF is palpitations. Symptoms caused by decreased blood flow include dizziness, fatigue, and shortness of breath. Some patients with AF do not experience any symptoms.

Atrial fibrillation can be paroxysmal or sustained. Patients with paroxysmal AF may or may not have underlying heart disease. Patients with sustained AF are more likely than those with paroxysmal AF to have an underlying cardiovascular problem (e.g., rheumatic heart disease, coronary artery disease, or hypertension) or hyperthyroidism. Heavy or binge-drinking alcohol consumption is also associated with AF.

Strokes are a complication associated with AF. The rapid contractions or quivering of the atria can cause blood to stagnate inside the atria with the formation of blood clots, which, if dislodged, can cause strokes. (5) The risk of stroke is dependent on the presence of other risk factors including age, previous history of stroke, left ventricular ejection fraction, and valvular heart disease. Patients with AF may have a 5-fold increased risk for stroke compared to age-matched controls. (6) This risk can be managed with the use of anticoagulant drugs.

According to United States data, (6) the incidence of AF increases with age, with a prevalence of 1 per 200 people aged between 50 and 60 years, and 1 per 10 people aged over 80 years. In 2004, the Institute for Clinical Evaluative Sciences estimated that the rate of hospitalization for AF in Canada was 582.7 per 100,000 population. They also reported that of the patients discharged alive, 2.7% were readmitted within 1 year for stroke. (7)

The United States prevalence study of AF by Go et al. (8) indicated that the overall prevalence of AF was 0.95%. When the results of this study were extrapolated to the population of Ontario, the prevalence of AF in Ontario is 98,758 for residents aged over 20 years. Table 1 provides the prevalence by age and gender (derived from results of Go et al.).

Table 1: Prevalence of Atrial Fibrillation in Ontario (People Aged Over 20 Years)*†

Age, Years	Male Pop., Ontario	Prevalence of AF, Males, %	Male Pop. With AF	Female Pop., Ontario	Prevalence of AF, Females, %	Female Pop. With AF
20–55	3,150,671	0.2	6,301	3,142,169	0.1	3,142
55–59	321,378	0.9	2,892	327,284	0.4	1,309
60–64	245,170	1.7	4,168	257,743	1.0	2,577
65–69	209,528	3.0	6,286	227,175	1.7	3,862
70–74	184,793	5.0	9,240	211,736	3.4	7,199
75–79	136,095	7.3	9,935	185,008	5.0	9,250
80–84	79,366	10.3	8,175	128,184	7.2	9,229
≥ 85	47,608	11.1	5,285	108,876	9.1	9,908

* AF indicates atrial fibrillation; pop., population.
† Derived from Go et al. (8)

Atrial Flutter

In atrial flutter (AFL), the left and right atria are stimulated rapidly and regularly, causing a rapid heart rate. The rapid yet regular heart rhythm is due to a constant reentrant system in the right atrium. Patients can have symptoms (which are similar to those of AF), or they may be asymptomatic. Patients may also have chronic AFL or occasional bouts of AFL lasting from hours to days. Atrial flutter can be isthmus-dependent or non-isthmus dependent. Patients with isthmus-dependent AFL have a large re-entrant circuit

in the right atrium (involving isthmus tissue between the tricuspid valve annulus and the inferior vena cava). Usually re-entry occurs in a counterclockwise motion up the atrial septum and the down the lateral wall of the right atrium. Non-isthmus-dependent flutters occur elsewhere in either the left or right atria (however, left AFLs are uncommon). (9)

Other Supraventricular Tachycardia (Excluding Atrial Fibrillation and Atrial Flutter)

Supraventricular tachycardia (SVT) may be more accurately described as regular narrow QRS tachycardia because these tachycardias are not isolated to the atria and may involve ventricular tissue. These tachyarrhythmias are characterized by rapid heart rhythms with normal (narrow) QRS intervals. Supraventricular tachycardia is separated into 3 categories: atrioventricular nodal re-entrant tachycardia (AVNRT), reciprocating tachycardia, and atrial tachycardia.

Atrioventricular Nodal Re-entrant Tachycardia

AVNRT is characterized by paroxysmal, regular, rapid heart through due to re-entry through abnormal pathways around the AV node. Rarely, the abnormal pathway can be within the AV node (intranodal).

Reciprocating Tachycardias

Reciprocating tachycardias involve the accessory pathways. Accessory pathways refer to abnormal muscular connections between the atria and ventricles. Typically, the electrical activation is from the atria to the ventricles through the AV node, then returning through the accessory pathway to the atria. Rarely, the conduction is in the opposite direction (ventricles to atria).

Atrial Tachycardia

Atrial tachycardia is characterized by a rapid, regular atrium rhythm usually due to intra-atrial re-entry or an ectopic atrial focus. This is the least common form of narrow QRS tachycardia. It is a “true” SVT, because the arrhythmia is isolated to the atria. There are various causes of atrial tachycardia including atrial irritation due to pericarditis, inflammation of the pericardium, the fibrous sac that surrounds the heart; and drug or chemical toxicity.

Ventricular Tachycardia

Ventricular tachycardia (VT) occurs when there are more than 3 successive beats of ventricular origin at a rate greater than 120 beats per minute. There are no normal-looking QRS complexes. The rhythm is usually regular, but on occasion it may be modestly irregular. Ventricular tachycardia is usually associated with coronary artery disease. Patients who have VT in the absence of coronary artery disease may have other cardiac abnormalities, including cardiomyopathy, mitral valve prolapse, valvular heart disease, or QT interval prolongation. (10) Ventricular tachycardia rarely occurs in the absence of structural heart disease.

Existing Treatments Other Than Technology Being Reviewed

Currently, the first-line therapy for AF is medical therapy with antiarrhythmic drugs (AADs). There has been extensive research conducted as to whether it is better to manage a patient’s heart rate (i.e., slow the heart rate) or manage a patient’s heart rhythm. Cordina & Mead {Cordina, 2005 2285 /id} published a Cochrane systematic review describing the evidence regarding pharmaceutical management of patients with AF and AFL. They reviewed 2 RCTs comparing rhythm control versus rate control medications and found that neither was superior to the other in terms of preventing mortality. They did note, however, that the drugs used to control rhythm were associated with higher hospitalization and adverse event rates. The

long-term pharmaceutical treatment of AF is associated with a failure rate of 50% at 1 year and up to 84% at 2 years. (12)

There are several AADs available because there is no one AAD that is effective for all patients. The AADs have critical adverse effects that can aggravate existing arrhythmias. The drug selection process frequently involves trial and error until the patient's symptoms subside. Table 2 outlines some of the drugs used to maintain sinus rhythm in patients with AF.

Table 2: Typical Dosages of Drugs Used To Maintain Sinus Rhythm in Patients With Atrial Fibrillation*

Drug	Daily dosage	Potential adverse effects
Amiodarone	100–400 mg	Photosensitivity, pulmonary toxicity, polyneuropathy, gastrointestinal symptoms, bradycardia, torsades de pointes (rare), hepatic toxicity, thyroid dysfunction
Disopyramide	400–750 mg	Torsades de pointes, heart failure, glaucoma, urinary retention, dry mouth
Dofetilide	500–1000 mcg	Torsades de pointes
Flecainide	200–300 mg	Ventricular tachycardia, congestive heart failure, enhanced atrioventricular nodal conduction
Procainamide	1000–4000 mg	Torsades de pointes, lupus-like syndrome, gastrointestinal symptoms
Propafenone	450–900 mg	Ventricular tachycardia, heart failure, enhanced atrioventricular nodal conduction
Quinidine	600–1500 mg	Torsades de pointes, gastrointestinal symptoms, enhanced atrioventricular nodal conduction
Sotalol	240–320 mg	Torsades de pointes, heart failure, bradycardia, exacerbation of lung disease

*Adapted from Fuster et al. (13)

Another mechanism for restoring sinus rhythm is through electrical cardioversion. Electrical cardioversion involves applying an electrical shock to the heart to convert an abnormal heart rhythm back to a sinus rhythm. This technique is frequently successful in the short term; however, it has limited sustainability over time. (14) Mead et al. (15) published a Cochrane systematic review comparing electrical cardioversion to rate control therapy. Based on the results of 3 controlled studies (N = 927), they concluded that mortality rates between the electrical cardioversion and rate control therapy groups were equivalent. They found a trend toward more strokes in the electrical cardioversion group; however, the electrical cardioversion group also reported significantly higher quality of life scores at 2-year follow-up.

Ablative Methods for Atrial Fibrillation

Because the pulmonary veins are the predominant source of AF initiation, the primary goal of ablation is to isolate the pulmonary veins from the left atria through the creation of a conduction block. Patients who have had persistent AF for a long time may require additional ablation lesions; however, this subgroup has not been characterized.

There are various approaches to ablation that take into consideration what tissue should be ablated and how to access the tissue. The research on what tissue should be ablated is continually evolving. However, there is general consensus that AF is induced by triggers in the pulmonary veins in more than 85% of

cases. (4;16;17)

Segmental pulmonary vein ablation isolates the pulmonary veins from the left atrium by applying discrete lesions at the ostial region of the pulmonary veins. Circumferential pulmonary vein ablation encircles all of the pulmonary veins by creating linear lesions in the left atrial myocardium outside the pulmonary vein ostia. In addition to circumferential pulmonary vein isolation, a connecting lesion to the mitral annulus and the cavotricuspid lesions are performed to limit the development of postablation left and right AFL respectively.

Ablative methods have been frequently described as a "cure" for AF, (18-20) compared with pharmaceutical therapy, which controls the AF but does not cure it. Ablation involves directing an energy source at cardiac tissue. For instance, radiofrequency energy uses heat to burn tissue near the source of the arrhythmia. A probe with an electrode at its tip is guided to the area of heart of interest. Then energy is transmitted to the area. This destroys the selected heart muscle cells in a very small area. The aim is to create scar tissue so that an electrical current can no longer be conducted through the area.

One of the primary concerns with ablation is accidentally ablating the normal conduction system, thereby producing heart block. If this occurs, a patient may require a pacemaker. This is a relatively rare occurrence, which is outlined in detail in the section on complications of this review.

There are 2 methods of ablation: catheter ablation or surgical (operative) ablation. Both are described in detail below. The energy source used to cause the ablation is variable. Currently, radiofrequency energy is most commonly used to cause the ablation. Cryoablation, microwave, and ultrasound energy are alternatives to radiofrequency energy that are still considered experimental.

Catheter Ablation

Catheter ablation involves inserting a catheter through the femoral vein to access the heart and burn abnormal foci of electrical activity by direct contact or by isolating them from the rest of the atrium. Tremendous precision is required to create the lesions and avoid inadvertently transferring energy to adjacent tissues.

Surgical (Operative) Ablation

The surgical ablation is performed minimally invasively via direct visualization or with the assistance of a special scope for patients with lone AF. It is more often performed via direct visualization when patients are undergoing additional surgical procedures. In 2003, Doll et al. (21) reported that there was a high risk of esophageal perforation during surgical ablation with unipolar probes. Because of this increased risk, the energy source currently used is mostly bipolar and contained by the 2 jaws of the energy device, hence the elimination of energy dispersal and adjacent tissue damage (Personal communication, November 2005).

Cut and Sew (Cox Maze) Surgery

Cut and sew surgery for AF does not use an energy source. Instead, small lesions are cut in the heart and then sewn together to create scar tissue to limit the electrical conduction pathways. The most common cut and sew technique is the Cox maze procedure.

The Cox maze procedure was the first successful nonpharmalogical technique used to treat AF. The procedure was first applied by Cox et al. in 1987. (22) There are 4 variations of the procedure, each attempting to be less invasive, complex, and time-consuming. The first Cox maze procedure involves

open heart surgery. It is associated with high risk and complication rates, especially in patients with concomitant heart conditions. However, over time, the Cox maze procedure has been refined. There are several other surgical techniques described in the literature; nonetheless, the Cox maze is the most widely reported technique.

A systematic review published by Khargi et al. (23) in 2005 found that there was no difference in postoperative sinus rhythm conversion rate or 30-day mortality rate in patients treated for AF with the Cox maze procedure compared with those treated with ablation plus radiofrequency energy or cryoablation. This systematic review was a thorough review of the literature that included 3,832 patients. However, all of the studies reviewed were cohort studies; there were no randomized or non-randomized comparison studies. It is also important to note that 98.4% of the patients underwent concomitant surgery for other heart conditions (usually mitral valve repair or replacement); thus, this systematic review cannot make any conclusions regarding the Cox maze procedure versus catheter ablation in patients with lone AF.

Energy Sources

Radiofrequency

- Radiofrequency ablation (RFA) is a procedure where high-frequency energy is directed at cardiac tissue. Radiofrequency ablation uses heat to burn tissue near the source of the arrhythmia. Radiofrequency is the most commonly used energy for ablative procedures at this time.

Cryoablation

- Cryoablation catheters apply very cold temperatures to the target tissue over an extended period, resulting in injury to the tissue. There are a few claims of benefits of cryoablation over RFA. The manufacturers of the cryoablation systems claim that compared with RFA, cryoablation is pain-free for catheter ablation and it can be performed without causing permanent damage to the underlying structure of the heart. (24-27)

Microwave

- The device for microwave energy appears similar to those for RFA and cryoablation. Microwave ablation uses high-frequency electromagnetic radiation. This electromagnetic radiation causes rapid oscillation of the water molecules in the atrial tissue, thereby producing heat, which causes thermal injury to the tissue and leads to conduction block. The proposed difference between radiofrequency and microwave energy is that microwave energy does not cause endocardial surface charring and has greater tissue penetration than does radiofrequency energy, increasing the likelihood of conduction block. (28)

Ultrasound

- This new form of energy for ablation of the heart uses focused ultrasound to deliver energy to atrial tissue which results in deep heating and conduction block. Ultrasound energy is a new technology that is not yet licensed for use in Canada.

Regulatory Status

Radiofrequency Ablation

Nine centres in Ontario are performing RFA: St Michael's Hospital, Hamilton General Hospital, Ottawa Heart Institute, University Health Network, Southlake Regional Health Centre, London Health Sciences Centre, Sunnybrook Health Sciences Centre, Kingston General Hospital, and the Hospital for Sick Children.

Four manufacturers are licensed by Health Canada to distribute RFA technology: Biosense Webster (A Johnson & Johnson Company); Medtronic Inc.; St Jude Medical, Daig Division; and Boston Scientific Corporation. It is important to note that some of the electroanatomic mapping devices incorporate ablation catheters into a mapping system. Also, these manufacturers distribute either probes for catheter ablation, or probes for surgical ablation, or both.

Cryoablation

The manufacturer CryoCath (Montreal, Quebec) has 2 devices licensed by Health Canada for the cryoablation of cardiac arrhythmias: Freezor (licence #34934, class 4 device) and SurgiFrost Surgical CryoAblation System (licence #62488, class 4). Six health centres in Ontario (Sunnybrook Health Sciences Centre, St. Michael's Hospital, Hospital for Sick Children, London Health Sciences Centre, Toronto General Hospital, and Ottawa Heart Institute) have cryoablation systems. There are 12 centres that have CryoCath ablation systems in Canada (6 in Ontario, 5 in Quebec, 1 in Alberta). These products are also used throughout Europe and the United States.

The products licensed for cryoablation by Health Canada are indicated for VT and AVNRT. They are not indicated for AF. However, there is a new technology developed by CryoCath that is specifically designed to treat AF. This product is not licensed by Health Canada yet; however, CryoCath has made a submission to Health Canada.

Microwave Ablation

There is no Canadian Classification of Health Interventions code for ablation of complex cardiac arrhythmias with microwave energy. A clinical expert from Ontario reported that ablation with microwave energy is experimental and is not used in clinical settings in Ontario (Personal communication, November 2005). There are no manufacturers of microwave ablation licensed by Health Canada to distribute the technology for cardiac ablation.

Ultrasound Ablation

No manufacturers of ablation systems using ultrasound energy are licensed by Health Canada to distribute their system.

Literature Review on Effectiveness

Objective

The aim of this health technology policy assessment was to assess the effectiveness, in terms of freedom

from recurrence of arrhythmia and complication rates, of ablation for the treatment of AF. Ablation methods investigated were catheter ablation and surgical ablation.

Questions Asked

- Is ablation effective in treating patients with AF compared with pharmaceutical treatment, in terms of freedom from arrhythmia, mortality, and improvement in quality of life?
- What is the complication rate associated with ablation?
- If superior to pharmaceutical treatment, which ablation method is most effective and cost-effective?

Methods

Outcomes of Interest

- Freedom from arrhythmia/symptomatic improvement
- Incidence of stroke and other complications
- Mortality/survival
- Quality of life

Inclusion criteria

- Systematic reviews of RCTS, meta-analyses of RCTs, and RCTs
- > 20 patients included in the study
- Studies reported in English
- Studies with follow-up of at least a mean of 6 months
- Studies that reported baseline characteristics of patients in treatment groups (such as age, gender, duration of symptoms, left ventricular ejection fraction, etc.)
- Studies that reported at least one of the aforementioned outcomes of interest

Exclusion criteria

- Studies that included pacing therapy as a part of the treatment
- Studies including patients who had previous ablation procedures
- Studies including children (patients < 18 years)
- Non-human studies
- Studies in a language other than English
- Non-randomized studies, prospective case series, case reports, retrospective studies, editorials, and letters

Databases and Search Strategy

- Search date: March 1, 2006
- Databases: Cochrane Library International Agency for Health Technology Assessment (first quarter 2006), Cochrane Database of Systematic Reviews (first quarter 2006), Cochrane Central Register of Controlled Trials (first quarter 2006), MEDLINE (1966 to March 2006), MEDLINE In-Process and Other Non-indexed Citations (1966 to March 2006), and EMBASE (1980 to 2006 week 9)

The Medical Advisory Secretariat also conducted Internet searches of Medscape for recent reports on trials that were unpublished but presented at international conferences. In addition, the Web site Current Controlled Trials (www.controlled-trials.com) was searched for ongoing trials on ablation for AF.

The detailed literature search strategy is shown in Appendix 1.

Results of Literature Review

The results of the North American Society of Pacing and Electrophysiology prospective ablation registry (2) indicated high success rates for ablation for AV nodal tachycardia (96%), accessory pathway (94%), and AFL (86%). Due to the high success rate of ablation, there are few, if any, RCTs comparing the effectiveness of ablation to other treatments in patients with these arrhythmias.

Since the effectiveness for these arrhythmias has been established, this review will focus primarily on the RCTs investigating the effectiveness of ablation for AF. The results of the literature review have been separated into 3 sections:

- First-line catheter ablation therapy for patients with AF or AFL.
- Ablation for patients with drug-refractory AF that do not require additional heart surgery.
- Ablation for patients with drug-refractory AF that require heart surgery.

Summary of Existing Health Technology Assessments

CCOHTA (Canadian Coordinating Office of Health Technology Assessment), 2002: Radiofrequency Catheter Ablation for Cardiac Arrhythmias: A Clinical and Economic Review (29)

The Canadian Coordinating Office of Health Technology Assessment searched the literature from 1985 to November 2001 looking for evidence on the clinical efficacy and cost-effectiveness of catheter RFA. They concluded that catheter ablation is associated with good procedural success rates for atrial tachycardias, but that there was insufficient evidence on the long-term efficacy and cost-effectiveness of catheter ablation. They also noted that data on the short- and long-term clinical success of catheter ablation for AF and VT were still emerging.

ASERNIP-S (Australia Safety and Efficacy Register of New Interventional Procedures – Surgical), 2004: Intraoperative Ablation for the Treatment of Atrial Fibrillation (30)

The Australia Safety and Efficacy Register of New Interventional Procedures – Surgical compared intraoperative surgical ablation to cardiac surgery alone and the Maze III procedure (which is the current gold standard surgical treatment for AF). They concluded that intraoperative surgical ablation was at least as effective as cardiac surgery alone, but they recommended that an RCT comparing intraoperative surgical ablation to cardiac surgery alone was necessary to measure long-term survival and the stroke rate among these patients.

NICE (National Institute for Clinical Excellence), 2004: Interventional procedures overview of microwave ablation for atrial fibrillation as an associated procedure with other cardiac surgery (31)

The National Institute for Clinical Excellence reported that there appeared to be evidence that microwave ablation for AF with concomitant surgery was effective, but that the evidence was limited. The 1 RCT they identified was small and only reported follow-up for 12 months, so they could not comment on the long-term effectiveness of microwave ablation in these patients.

They identified 6 studies that met their inclusion criteria: 1 RCT, 2 prospective comparison studies, and 3 case series. The RCT (Schuetz et al., 2003 (32)) is included in the tables below. The other 5 studies did not meet the inclusion criteria for this report. Since the publication of this NICE overview, no additional RCTs investigating microwave ablation were identified that met the inclusion criteria for this report.

NICE, 2005: Interventional procedures overview of radiofrequency ablation for atrial fibrillation as an associated procedure with other cardiac surgery (33)

In this assessment, NICE reported that there was adequate evidence to support the use of surgical ablation in association with other cardiac surgery. They included 7 studies in their review, including 1 small RCT. The RCT by Deneke et al. (34) is included in this review and discussed in greater detail further in this review. NICE concluded that surgical ablation is one of only several energy sources that can be used in ablation of AF, and that surgical ablation was easier to perform than the Cox maze procedure. They concluded that there was a lack of consensus regarding the optimal lesion set to ablate.

NICE, 2005: Interventional procedures overview cryoablation for atrial fibrillation as an associated procedure with other cardiac surgery (35)

The NICE review of cryoablation for AF included 3 non-randomized studies and 3 case series. They concluded that there is limited but promising evidence that cryoablation is an effective and safe energy source for ablation in patients with atrial fibrillation undergoing other cardiac surgery.

Summary of Studies Identified to be Included in the Medical Advisory Secretariat Review

Table 3 outlines the number and type of studies included in this review. A thorough quality assessment of the studies is included in the sections reporting the results of the studies, and the GRADE quality assessment tables are listed in Appendix 2. For the purposes of this review, long-term success is defined as the number of patients who did not suffer from a recurrence of arrhythmia within a minimum of 6 months from treatment onset.

Table 3: Quality of Evidence of Included Studies*

Study Design	Level of Evidence	Number of Eligible Studies
Large RCT *(N ≥ 100), systematic reviews of RCT	1	6
Large RCT unpublished but reported to an international scientific meeting	1(g)†	
Small RCT	2	10
Small RCT unpublished but reported to an international scientific meeting	2(g)	0
Non-RCT with contemporaneous controls	3a	0
Non-RCT with historical controls	3b	0
Non-RCT presented at international conference	3(g)	0
Surveillance (database or register)	4a	0
Case series (multisite)	4b	0
Case series (single site)	4c	0
Retrospective review, modeling	4d	0
Case series presented at international conference	4(g)	0

* RCT indicates randomized controlled trial.
† g indicates grey literature.

First-line Treatment for Atrial Fibrillation and Atrial Flutter

Two RCTs were identified that compared catheter ablation with radiofrequency energy to medical therapy

as first-line treatment in patients with AF (36) and AFL (37). When describing the quality of these studies it is important to note that blinding in these trials was not feasible. The overall quality of the evidence was moderate (Table 4). GRADE was also applied to these RCTs, and those results are listed in the Appendix 2. The pilot RCT by Wazni et al. (36) was a well-reported study; however, because it was a pilot study, the sample size was small. Despite this, Wazni et al. were still able to detect a significant reduction in the number of recurrences in the catheter ablation group compared with the medical therapy group. It is important to recognize that one of the studies included patients with AF and other included patients with AFL.

Table 4: Quality of Evidence: Studies Comparing Radiofrequency Ablation to Medical Therapy as First-line Treatment for Patients With Atrial Fibrillation or Atrial Flutter*

Study, Year	Adequate Sample Size?	Patients Randomized?	Clearly Defined Endpoints?	Treatment Arms Similar at Baseline?	Lost to Follow-up	Other Strengths/ Limitations	MAS Overall Assessment
Wazni, 2005 (36)	Unknown; pilot RCT: trial was open for 6 months regardless of sample size N = 70	Computer generated	Yes Recurrence of AF during the 1-year follow-up	Yes	4% (3 pts) lost; sensitivity analysis to assess impact of loss	No regulation of drug used in medical therapy arm	**Moderate-high quality** Well reported study; limitation is that it is a pilot study, not a true RCT
Natale, 2000 (37)	Unknown: did not report how sample size calculated N = 61	Not described	Yes Recurrence of AFL, QoL, hospitali-zation	Yes	16% (5 pts) in catheter ablation group did not receive catheter ablation: they were not accounted for	No regulation of drug used in medical therapy arm	**Moderate quality** Well reported study, concerns about sample size and the loss of patients in catheter ablation arm

* AF indicates atrial fibrillation; AFL, atrial flutter; MAS, Medical Advisory Secretariat; QoL, quality of life; pts; patients; RCT, randomized controlled trial.

Tables 5 and 6 show the characteristics of the studies, and Table 7 shows the outcomes. Wazni et al. reported the results of a pilot RCT comparing catheter radiofrequency ablation to medical therapy as first-line treatment in patients with symptomatic AF. Two patients in the medical therapy group and 1 patient in the catheter ablation group were lost to follow-up. Wazni and colleagues performed a sensitivity analysis that included the patients that were lost to follow-up (assuming worst outcomes, patient in catheter ablation group had recurrent AF and patients in medical therapy group were symptom-free at follow-up). The significantly higher freedom from arrhythmia rate in the catheter ablation arm was still observed (85% recurrence in catheter ablation arm, 41% recurrence in medical therapy arm, $P < .001$).

The RCT by Natale et al. (37) randomized patients with AFL either to undergo catheter ablation or to receive medical therapy. Similar to what Wazni et al. (36) found, the patients undergoing catheter ablation had significantly improved long-term success in terms of freedom from arrhythmia compared with patients receiving medical therapy (80% versus 36%, $P < .01$).
Both Wazni et al. and Natale et al. reported quality of life scores for the patients in their studies. They each found that quality of life was significantly improved in the patients undergoing catheter ablation compared with patients undergoing medical therapy. The complications reported in each study are listed

in Table 8. Neither Wazni et al. nor Natale et al. reported substantial long-term adverse effects among the patients undergoing catheter ablation.

In both studies, recurrence of arrhythmia was measured according to Holter monitor assessments (the monitor assesses an individual's heart rate over an extended period of time, usually 24 hours) at 3, 6, and 12 months after randomization, or if the patients reported being symptomatic between the follow-up intervals (Table 6).

Table 5: Characteristics of Studies Comparing Radiofrequency Ablation to Medical Therapy as First-line Treatment in Patients With Atrial Fibrillation or Atrial Flutter*

Study, Year	Condition	Treatment Arms	N	Mean (SD) Duration of Condition, Months	Mean (SD) Age, Years	Mean Follow-up, Months	Male, %	Mean (SD) LVEF	Mean (SD) Left Atrial Size, mm
Wazni, 2005 (36)	97% paroxysmal; 3% persistent	RF ablation	33	5 (2.0)	53 (8)	≥ 12	NR	0.53 (0.05)	41 (8)
	95% paroxysmal; 5% persistent	Medical therapy	37	5 (2.5)	54 (8)			0.54 (0.06)	42 (7)
Natale, 2000 (37)	Atrial flutter	RF ablation	31	NR	67 (8)	22 (SD, 11)	65	NR	NR
		Medical therapy	30		66 (11)		73		

* AF indicates atrial fibrillation; LVEF, left ventricular ejection fraction; NR, not reported; PVI, pulmonary vein isolation; RCT, randomized controlled trial; RF, radiofrequency; SVT, supraventricular tachycardia.

Table 6: Description of Follow-up in Studies Comparing Radiofrequency Ablation to Medical Therapy as First-line Treatment in Patients With Atrial Fibrillation or Atrial Flutter

Study, Year	How Arrhythmia Was Measured During Follow-up
Wazni, 2005 (36)	- A loop event-recorder was worn for 1 month for 1st month and 3rd month. - Patients were asked to record when they experienced symptoms. - Patients were monitored with 24 hour Holter monitoring before discharge, then at 3, 6, and 12 months. - Patients were called on a monthly basis to ask about symptoms.
Natale, 2000 (37)	- Follow-up at 3, 6, and 12 months with 24-hour Holter monitoring. - If arrhythmia is suspected, Holter monitoring outside follow-up schedule.

Table 7: Outcomes of Studies Comparing Radiofrequency Ablation to Medical Therapy as First-line Treatment in Patients With Atrial Fibrillation or Atrial Flutter*

Study, Year	Condition	Treatment Arms	N	Long-term Success, %	Quality of Life	Complications
Wazni, 2005 (36)	AF	RF ablation	33	87	SF-36 Significant improvement between baseline and 6-month follow-up	No pts developed severe pulmonary vein stenosis; 2 pts had mild-moderate pulmonary vein stenosis.
		Medical therapy	37	37	SF-36 No significant improvement between baseline and 6-month follow-up	3 pts had onset of bradycardia.
Natale, 2000 (37)	AFL	RF ablation	31	80	Endicott, Quality of Life Enjoyment and Satisfaction Questionnaire Significant improvement in QoL 6 months and 12 months after treatment	No long-term adverse effects. 1 chest discomfort for 2 weeks postop, 1 hematoma at site of venous puncture (did not require intervention).
		Medical therapy	30	36	No significant difference in QoL within 6 months and 12 months of treatment	None reported.

* AF indicates atrial fibrillation; AFL, atrial flutter; NR, not reported; PVI, pulmonary vein isolation; pts, patients; QoL, quality of life; SF-36, Short-Form 36 (measure of quality of life).

Treatment for Drug-Refractory Atrial Fibrillation (With no Other Heart Condition Requiring Surgery)

Seven RCTs were identified that compared treatments for patients with drug-refractory, lone AF. Three RCTs compared drug therapy to catheter ablation with radiofrequency energy. The other 4 compared various ablation techniques. Table 8 outlines the quality of these studies. No studies were identified that met the inclusion criteria that included patients with drug-refractory AF who did not require additional heart surgery who were undergoing microwave ablation or cryoablation. Nor were any RCTs identified that investigated surgical ablation for patients who were not undergoing concomitant additional heart surgery.

Table 8: Quality of RCTs Investigating Ablative Techniques for Patients With Drug-Refractory Atrial Fibrillation That Do Not Require Additional Surgery for Other Heart Conditions*

Study, Year	Adequate Sample Size?	Randomization Process	Clearly Defined Endpoints?	Treatment Arms Similar at Baseline?	Lost to Follow-up	Other Strengths/ Limitations	MAS Overall Assessment
Oral, 2006 (38)	Yes, 30% difference in rate of arrhythmia at follow-up between the 2 groups N=146	Computer generated	Freedom from arrhythmia in the absence of drug therapy	Yes	None were lost	ITT analysis (53 pts in drug arm underwent ablation)	**High quality**
Stabile, 2005 (39)	Yes: 30% difference in rate of arrhythmia at follow-up between the 2 groups N=137	Computer generated	First atrial arrhythmia	Yes	3 pts (1 in treatment group) withdrew from the study ITT analysis	Well-defined sample	**High quality**
Krittayaphong, 2003 (40)	Unknown; no power calculation provided N = 30	Not described	Frequency of symptoms at 1, 3, 6 , and 12 months	Yes	1 pt (7%) in catheter ablation group lost; not accounted for in analysis	Small sample leading to conflicting results, randomizatio n not described	**Low quality**
Karch, 2005 (41)	Yes N = 100	Randomization code in sealed envelopes	Freedom from atrial tachycardias	Yes	None reported	Clear sample size explanation, RCT, clearly defined endpoints	**High quality**
Haissaguerre, 2004 (42)	No comment on how sample size was chosen N = 70	Not described	No	Yes	None reported	No sample size calculation, no endpoint reported	**Low-moderate quality**
Katritsis, 2004 (43)	Yes N = 52	Not described	Freedom from AF, subjective symptomatic improvement	Yes	None reported	Clear power calculation	**Moderate-high quality**
Wazni, 2003 (44)	No comment on how sample size was chosen N = 108	Not described	No	Yes	None reported	No sample size calculation, no endpoint reported	**Low quality**

* AF indicates atrial fibrillation; ITT, intention to treat; MAS, Medical Advisory Secretariat; QoL, quality of life; pt, patient; RCT, randomized controlled trial.

Catheter Ablation Versus Medical Therapy

Three randomized controlled trials were identified that compared catheter ablation with radiofrequency energy to medical therapy as treatment in patients with drug-refractory cardiac arrhythmias. (38-40)

Similar to the studies investigating first-line treatment for arrhythmias, blinding in these trials was not feasible. The studies included patients with drug-refractory, lone atrial fibrillation. Two of the RCTs were categorized as high quality (38;39) and the other low quality. (40) (Table 8)

The RCT by Oral et al (38) randomized 146 patients with chronic atrial fibrillation to receive catheter ablation with 3 months of drug therapy (amiodarone) or 3 months of drug therapy and cardioversion 6 weeks after randomization. Patients in the control group with recurrent AF were allowed to undergo cardioversion again within 3 months of first cardioversion. If AF developed more than 3 months after the first cardioversion patients were allowed to resume drug therapy or undergo ablation. All patients were given event monitors for 12 months and recorded their rhythm at least 5 days a week for 3 minutes or whenever they had symptoms of AF. At 12 months, all 77 patients randomized to receive ablation underwent the ablation procedure. In the control arm, 53 of 69 patients underwent the ablation procedure within the 12 month period following randomization. At 12 months, the results of the intent-to-treat analysis indicated that 74% of patients in the ablation group were free from arrhythmia, and 58% were free from arrhythmia in the control group (includes the patients who underwent ablation) (P=.05). Of the 53 patients in the control group that underwent ablation, 70% were free from arrhythmia at 12 months. At 12 months 3 patients (4%) were in sinus rhythm who did not undergo ablation and who were not using drug therapy.

In terms of complications, Oral et al reported that 5 patients (6%) in the ablation arm developed atrial flutter (mean of 139$\pm$123 days). All 5 patients underwent another ablation procedure to treat the atrial flutter. No other complications were reported in either treatment group.

It is important to note that the RCT by Oral et al was not designed to establish superiority of ablation over drug therapy. The control group was designed to control for confounding variables.

The RCT by Stabile et al. (39) randomized 137 patients to receive catheter ablation with drug therapy or drug therapy alone. Unlike patients in the Oral et al study, patients in the study by Stabile et al had paroxysmal or persistent AF, not chronic AF. Most patients were prescribed amiodarone, unless they had a history of side effects with this drug, in which case they were prescribed another AAD. A review of rate and rhythm control for AF by King et al. (45) reported "some investigators consider amiodarone to be the most effective agent for converting to sinus rhythm in patients who do not respond to other agents." After ablation and the initiation of drug therapy, patients had a 1-month blanking period (i.e., no AADs). About 34% of patients in the ablation group and 30% of patients in the drug therapy group were prescribed a drug that previously had not controlled their arrhythmia. Recurrence of arrhythmia (> 30 seconds of arrhythmia) was measured through a transtelephonic echocardiogram (ECG). Patients had a 30-second transtelephonic ECG every day for 3 months (after the blanking period). Standard ECG, Holter monitoring, and transthoracic ECGs were scheduled at 1, 4, 7, 10, and 13 months.

Stabile et al. indicated a 30% difference in the rate of atrial arrhythmia 1 year after randomization was a meaningful difference, and based their power calculations on this hypothesis. At 1 year, 56% of patients in the ablation group were free from arrhythmia compared to 9% of patients in the drug therapy only arm ($P < .001$) (Table 10).

Three patients withdrew from the RCT by Stabile et al. One patient in the ablation group refused to continue, and 2 patients in the drug therapy only group refused to continue (1 of these patients refused to use the telephonic ECG monitor). These patients were, however, included in the overall analysis of results.

The RCT by Krittayaphong et al. (40) randomized 29 patients to receive either catheter ablation or amiodarone. Patients could not have received amiodarone in the past to be eligible for the study.

Krittayaphong et al. reported that, on average, patients in the catheter ablation group had failed 1.7 (SD, 0.6) drugs, compared with patients in the amiodarone group who had failed 1.9 (SD, 0.7) drugs. (*P* value is not significant.)

Krittayaphong et al. found a 21% recurrence rate of arrhythmia in the catheter ablation group and a 60% rate of recurrence in the amiodarone group at 1 year (*P* = .02). Despite this result, they did not report a significant difference in the frequency of AF episodes per month between the 2 groups at 1 year (*P* = .335). There was a significant decrease in the frequency of AF episodes between baseline and 1-year follow-up in the catheter ablation group, but not in the amiodarone group. These conflicting results are most likely due to the small sample size (N = 29), which means that the study was probably not powered sufficiently to detect differences between the groups.

Krittayaphong et al. (40) also reported outcomes for quality of life using the Short-Form 36 quality of life scale. They reported a significant improvement in the general health score in the catheter ablation group compared with the medical therapy group (*P* = .007), but there was no significant difference between groups in the physical fitness score (*P* = .7).

The results of the 3 RCTs are consistent in that they each reported that catheter ablation was more effective at maintaining freedom from arrhythmia than medical therapy alone in patients with lone, drug-refractory AF. It is important to note that the patients in the Oral et al study all had chronic AF, and the patients in the other 2 studies had paroxysmal or persistent AF. Due to this heterogeneity it is not possible to combine the results in a meta-analysis, nonetheless the results are consistent across the 3 studies.

Comparison of Various Catheter Ablation Techniques

Four RCTs were identified that compared various ablation techniques. (41-44) All of the studies reported long-term freedom from AF after treatment. None of the studies included quality of life as an outcome measure. The quality of the studies is outlined in Table 8. Appendix 2 has the GRADE quality assessment results for these RCTs.

All of the RCTs compared different ablative techniques (Table 9). The GRADE results varied from moderate to low quality (see Appendix 2). The problem with 2 of the RCTs (42;44) is that they were likely were not adequately powered to detect a significant difference between the treatment groups should one have existed. From the statistical comparisons reported in these 2 trials (Table 9) and the relative risk calculated for GRADE the results do not identify one technique as a significantly superior technique compared with the others.

Table 9: Description of Procedures Performed in the Studies of Ablation Techniques in Patients With Drug-Refractory Atrial Fibrillation That Do Not Require Additional Surgery*

Study, Year	Procedure	Mapping Device Used in Procedure	Description of Ablation
Oral, 2006 (38)	CPVI + drug therapy	CARTO	Left and right pulmonary veins were encircled 1-2 cm from the ostia Additional ablation lines were created in the posterior left atrium and along the mitral isthmus
	Amiodarone (cardioversion if necessary)	N/A	
Stabile, 2005 (39)	Left atrium ablation, with PVI + drug therapy	CARTO	Trans-septal approach Ablation lines > 5mm from the ostia of PVs, circumferential PVI
	Amiodarone, unless intolerant	N/A	
Krittayaphong 2003 (40)	Left atrium ablation with PVI	CARTO	Trans-septal puncture (via femoral vein) Lines—circular line isolating the ostia of the PVs, and a line connecting this circular line with the mitral annulus Linear ablation between tricuspid valve ring and IVC, from SVC to IVC, and horizontal linear ablation line at the mid-right atrium
	Amiodarone	N/A	
Karch, 2005 (41)	SPVI	LASSO	Left atrium was accessed by double trans-septal puncture
	CPVI	CARTO	Left atrium was accessed by single trans-septal puncture
Haissaguerre, 2004 (42)	CPVI + CTI	LASSO	All pts had PVI and CTI ablation—to achieve bidirectional conduction block Trans-septal puncture, right femoral vein, quadripolar catheters 1 cm from ostium in PVs
	CPVI + linear ablation of mitral isthmus	LASSO	Mitral isthmus ablation performed between the left inferior PV and the lateral mitral annulus
Katritsis, 2004 (43)	Superior PV ablation	LASSO	LSPV disconnection followed by additional disconnection of the RSPV in case of AF recurrence within 3 months
	4 PV ablation	LASSO	Disconnection of all 4 PVs followed by repeat four-PV procedure in failures
Wazni, 2003 (44)	PV-LAJ + CTI ablation	LASSO	CTI block was performed under anatomic and electrogram guidance Bidirectional conduction block
	PV-LAJ	LASSO	Ablation was extended to the PV antrum in front of the tube-like portion of the PVs

* CPVI indicates circumferential pulmonary vein isolation; CTI, cavotricuspid isthmus; LSPV, left superior pulmonary vein; PV, pulmonary vein; PVI, pulmonary vein isolation; PV-LAJ, pulmonary vein-left atrial junction; RSPV, right superior pulmonary vein; SPVI, segmental pulmonary vein isolation.

Table 10 compares the outcomes of the studies investigating ablative techniques for patients with drug-refractory AF who did not require additional heart surgery. The long-term success rates cited by Karch et

al. (41) included some patients who had undergone a second ablation procedure (4 in segmental PVI group, and 6 in the circumferential PVI group).

Katrisis et al. (43) found no significant difference in long-term success in patients with drug-refractory AF undergoing pulmonary vein isolation of 3 pulmonary veins (excluding right inferior PV) or all 4 pulmonary veins. None of these patients were taking AADs at the time that long-term success was determined. In the studies by Krittayaphong et al. (40) and Wazni et al., (44) it was unclear whether the patients were receiving additional AADs, and this makes it difficult to ascertain the true effect of the ablative technique.

Table 10: Description of Procedures Performed in the Studies of Ablation Techniques in Patients With Drug-Refractory Atrial Fibrillation That Do Not Require Additional Surgery*

Study, Year	Procedure	No. of Patients	Mean (SD) Follow-up, Months	Mean (SD) Fluoroscopy Time, Minutes	Mean (SD) Ablation Time, Minutes	Long-term Success‡ Without Drug Therapy, %	Long-term Success‡ With Drug Therapy. %	Long-term Success‡ Unclear Drug Therapy in Ablation Group, %
Oral, 2006 (38)	CPVI + medical therapy	77	>12	NR	96 (77)	—	74	—
	Medical therapy	69		N/A	N/A	—	58 *P*<.05	—
Stabile, 2005 (39)	LA ablation + medical therapy	68	18 (range, 14–23)	25 (10)	193 (66)	—	56	—
	Medical therapy	69		N/A	N/A	—	9 *P* < .001	—
Krittayaphong, 2003 (40)	LA ablation	14	> 12	118.1 (30.3)	211.6 (27.5)	—	—	78.6
	Medical therapy	15		N/A	N/A	—	—	40 *P* = .02
Karch, 2005 (41)	SPVI	50	> 6	72 (26)	52 (30)	66	—	—
	CPVI	50		45 (21)	72 (19)	42 *P* < .01	—	—
Haissaguerre 2004 (42)	CPVI + CT	35	7 (3)	34 (17)	36 (11)	74	—	—
	CPVI + LA	35		44 (26)	58 (22)	83 *P* = NS	—	—
Katritsis, 2004 (43)	Superior PVI	27	> 12	22.2 (6.8)	8.9 (1.4)	59	—	—
	4 PVI	25		62.0 (10.3)	25.6 (3.7)	68 *P* = NS	—	—
Wazni, 2003 (44)	PV-LAJ + CTI ablation	49	13.3 (6.3)	NR	NR	—	—	86
	PV-LAJ	59	12.9 (5.4)	NR	NR	—	—	90 *P* = NS

* CPVI indicates circumferential pulmonary vein isolation; CT, cavotricuspid isthmus; LA, left atrium; NS, not significant; PV-LAJ, pulmonary vein-left atrial junction; SPVI, segmental pulmonary vein isolation.
‡ Long-term success defined as freedom from atrial fibrillation (sinus rhythm) at mean follow-up.

The RCTs measured recurrences of arrhythmia using electrocardiography and/or Holter monitoring at various points throughout the follow-up period (Table 11). Stabile et al. reported that their success rate for

the ablation group (56%) may have been lower than other previously reported studies because they had 30-second transtelephonic ECG measurements daily for 3 months. They suggested that this daily measurement was more likely to detect asymptomatic recurrences compared to discrete measurements every few months.

Table 11: Description of Follow-up in Studies of Ablation Techniques in Patients With Drug-Refractory Atrial Fibrillation That Do Not Require Additional Surgery*

Study, Year	How Arrhythmia Was Measured During Follow-up
Oral, 2006 (38)	- Patients monitored heart rate >5 days/week for 3 minutes for 1 year - Follow-up visits scheduled with clinician at 3, 6, 12 months—patients had ECG and completed a questionnaire at each visit
Stabile, 2005 (39)	- Patients had a 30-second transtelephonic ECG every day for 3 months (after the blanking period). - Standard ECG, Holter monitoring and transthoracic ECGs were scheduled at 1, 4, 7, 10 and 13 months.
Krittayaphong, 2003 (40)	- Patients were followed-up at 1, 3, 6 and 12 months after surgery. - At each visit, the following information was collected: frequency of symptoms, 12-lead ECG, 24-hour ambulatory ECG monitoring, quality of life assessments, and complications or adverse effects.
Karch, 2005 (41)	- 7-day Holter monitoring at 6 months.
Haissaguerre, 2004 (42)	- Patients were hospitalized for 1 day at 1, 3, 6, and 12 months after surgery for transthoracic echocardiography, ambulatory monitoring and stress testing.
Katritsis, 2004 (43)	- Patients had a monthly clinical assessment. - Ambulatory ECG monitoring at 1, 3, and 12 months.
Wazni, 2003 (44)	- A loop recorder was used to measure events in the first and third month after surgery - 3, 6, 12 months Holter monitoring

* ECG indicates electrocardiogram.

Table 12 provides a summary of the characteristics of all the studies and their success rates (freedom from arrhythmia).

Table 12: Characteristics of Patients Included in Drug-Refractory, Lone Atrial Fibrillation Studies*

Study, Year	Treatment	N	Atrial Fibrillation Condition, %	Age, Mean (SD)	Duration of AF, Mean (SD), Years	No. of Failed Drugs, Mean (SD)	Follow-up, Months, Mean	Freedom From Arrhythmia, %
Oral, 2006	CPVI + medical therapy	77	Chronic: 100	55 (9)	5 (4)	2.0 (1.2)	>12	66
	Medical therapy	69	Chronic: 100	58 (8)	4 (4)	2.1 (1.2)	>12	34
Stabile, 2005 (39)	LA ablation ± medical therapy	68	Paroxysmal: 62 Persistent: 38	62.2 (9)	5 (4)	NR	18 (range, 14–23)	56
	Medical therapy	69	Paroxysmal: 72 Persistent: 28	62.3 (10.7)	7 (6)			9
Krittayaphong, 2003 (40)	LA	15	Paroxysmal: 73 Persistent: 27	55.3 (10.5)	5 (5)	1.7 (0.6)	> 12	79
	Medical therapy	15	Paroxysmal: 60 Persistent: 40	48.6 (15.4)	4 (5)	1.9 (0.7)		40
Karch, 2005 (41)	SPVI	50	Paroxysmal: 92 Persistent : 8	61 (54–65)	4 (2–7)	NR	> 12	66
	CPVI	50	Paroxysmal: 86 Persistent: 14	59 (52–64)	5 (3–7)			42
Haissaguerre, 2004 (42)	CPVI ± CTI	35	Clinical episodes ≥ 1 hour	53 (8)	NR	3.1 (1.1)	> 6	74
	CPVI ± LA	35		53 (9)		3.4 (1.1)		83
Katritsis, 2004 (43)	Superior PVI	27	Paroxysmal: 100	54 (9)	NR	NR	7 (SD, 3)	59
	4 PVI	25		50 (10)				68
Wazni, 2003 (44)	PV-LAJ ± CTI ablation	49	Paroxysmal: 61 Persistent: 12 Permanent: 27	54 (11)	6 (4)	3.2 (1.2)	13 (SD, 6)	86
	PV-LAJ	59	Paroxysmal: 58 Persistent: 8 Permanent: 34	55 (11)	5 (3)	3.1 (1.3)	13 (SD, 5)	90

* CPVI indicates circumferential pulmonary vein isolation; CT, cavotricuspid isthmus; LA, left atrium; NR, not reported; NS, not significant; PV-LAJ, pulmonary vein-left atrial junction; SPVI, segmental pulmonary vein isolation.

Complications

The complications reported by each of the RCTs of ablative techniques in patients with drug-refractory AF are outlined in Table 13. One of the major risk factors associated with AF is the risk of stroke. Among 491 patients who underwent catheter ablation, 2 had strokes. (One patient had a stroke immediately after the procedure, and it is unclear when the other patient had a stroke during the follow-up period.) Three patients had transient ischemic attacks. (The timing of the transient ischemic attacks is unclear.) There were no procedural-related deaths reported in any of the 7 RCTs. The study by Karch et al. (41) reported more complications than any of the other studies, but it is unclear why this is. It could be that complications were under-reported in the other studies.

Table 13: Complications Reported in the Studies of Ablation Techniques in Patients With Drug-Refractory Atrial Fibrillation That Do Not Require Additional Surgery*

Study, Year	Treatment Arms	N	Complications
Oral, 2006 (46)	CPVI + medical therapy	77	5 pts with atrial flutter
	Medical therapy + cardioversion	69	No complications reported associated with treatment
Stabile, 2005 (39)	LA ablation + medical therapy	68	- No PV stenosis was reported. - 1 pt suffered from a stroke during ablation (patient died 9 months later of a brain haemorrhage) - 1pt with transient phrenic paralysis - 1 pt with pericardial effusion requiring pericardiocentesis
	Medical therapy	69	- 1 pt transischemic attack - 2 pts with cancer (1 death) - 1 pt sudden cardiac death
Krittayaphong, 2003 (40)	LA	15	- 1 pt suffered from a stroke immediately after the procedure - 1 pt had a minor complication (groin hematoma)
	Medical therapy	15	- Side effects of amiodarone include nausea, sinus node dysfunction and hypothyroidism
Karch, 2005 (41)	SPVI	50	- Re-ablation in 8 pts - Procedure-related complications: -- 5 pts with pericardial effusion (no further information regarding the management of the pericardical effusion provided) --1 pt with transient ischemic attack -- 6 pts with PV stenosis > 50% - No deaths reported
	CPVI	50	- Re-ablation in 12 pts - Procedure-related complications: -- 22 pts with pericardial effusion (no further information regarding the management of the pericardical effusion provided) -- 2 pts with transient ischemic attack -- 1 pt with stroke -- 3 pts with PV stenosis >50% - No deaths reported
Haissaguerre, 2004 (42)	CPVI + CTI	35	- No complications associated with ablation procedure
	CPVI + LA	35	- No complications associated with ablation procedure
Katritsis, 2004 (43)	Superior PVI	27	- No pts had detectable PV stenosis
	4 PVI	25	- 2 pts with asymptomatic PV stenosis
Wazni, 2003 (44)	PV-LAJ + CTI ablation	49	- Did not report data on complications
	PV-LAJ	59	

* CPVI indicates circumferential pulmonary vein isolation; CT, cavotricuspid isthmus; LA, left atrium; NS, not significant; PV-LAJ, pulmonary vein-left atrial junction; pt, patient; SPVI, segmental pulmonary vein isolation.

Because complications are such an important concern when investigating the effectiveness of RFA, the complication results of a large non-randomized comparison (N = 1,171) will be described. Pappone et al. (47) compared patients undergoing circumferential pulmonary vein isolation (n = 589) to patients receiving drug therapy (n = 582). Table 14 lists the complications reported by patients in these groups. Mean follow-up was 29.6 months. There were 38 (6.5%) deaths in the ablation group during follow-up and 83 (14.3%) deaths in the medical therapy group. Two patients in the ablation group died due to strokes, and 6 other patients in this group had (but did not die from) strokes during the follow-up period.

In the medical therapy group, 14 patients died due to strokes, and 22 others had (but did not die from)

strokes. It is important to note that the patients were not randomized; however, at baseline, the 2 groups were not significantly different in terms of age, gender, or medical history (hypertension, diabetes, smoking, cholesterol, valvular disease, or prior stroke). The groups were different at baseline in terms of duration of AF (patients in the ablation group had had it longer than had patients in the medical therapy group [5.5 years (SD, 2.8) versus 3.6 years (SD, 1.9), respectively; $P < .001$]). Patients in the ablation group had also tried more AADs than had patients in the medical therapy group (3.1 dugs (SD, 2.1) versus 2.3 drugs (SD, 1.5); $P < .001$).

Table 14: Causes of Mortality and Morbidity in the Comparison Study by Pappone et al.*†

	Cause	Circumferential PVI Group	Medical Therapy Group
Deaths, no. (%) of patients	Congestive heart failure	8 (1.3)	23 (4.0)
	Myocardial infarction	8 (1.3)	10 1.7)
	Sudden cardiac death	0	12 (2.1)
	Ischemic stroke	2 (0.3)	14 (2.4)
	Noncardiovascular causes	20 (3.4)	24 (4.1)
	Total	**38 (6.5)**	**83 (14.3)**
Adverse events, no. (%) of events	Congestive heart failure	32 (5.4)	57 (9.8)
	Myocardial infarction	7 (1.2)	8 (1.4)
	Peripheral embolism	1 (0.2)	3 (0.5)
	Transient ischemic attack	8 (1.3)	27 (4.6)
	Ischemic stroke	4 (0.7)	15 (2.6)
	Hemorrhagic stroke	2 (0.3)	7 (1.2)
	Total	**54 (9.2)**	**117 (20.1)**

* Pappone et al. (47)
† PVI indicates pulmonary vein isolation.

Treatment of Drug-Refractory Atrial Fibrillation in Patients with Other Heart Conditions Requiring Surgical Intervention

It is important to note that the proportion of patients with AF requiring additional heart surgery represents a very small proportion of the AF population. One clinical expert estimated that less than 1% of the patients with AF would require additional heart surgery (Personal communication, November 2005).

Seven RCTs were identified that met the inclusion criteria. They compared various ablative techniques for patients with AF undergoing concomitant heart surgery. In most cases, patients were having mitral valve repair or replacement surgery in addition to the ablation. Table 15 outlines the quality of the individual studies. GRADE scores are applied to the studies in Appendix 2. The GRADE quality assessment ranged from high to moderate. In terms of the individual study quality assessment, they were assessed as moderate. Only one (48) of these studies reported quality of life as an outcome measure.

There is substantial evidence of effectiveness supporting the use of ablation in addition to other surgery. Four of the RCTs compared an ablative technique to no ablation, and all 4 (regardless of the ablative technique) reported that ablation was significantly better at increasing freedom from AF compared with no ablation at all.

Table 15: Quality of RCTs Investigating Ablative Techniques for Patients With Drug-Refractory AF That Do Not Require Additional Surgery for Other Heart Conditions*

Study, Year	Adequate Sample Size?	Randomization Process	Clearly Defined Endpoints?	Treatment Arms Similar at Baseline?	Lost to Follow-up	Other Strengths/ Limitations	MAS Overall Assessment
Doukas, 2005 (49)	Yes N = 101	Computer-generated numbers, sealed envelopes	Presence of sinus rhythm at 12 months	Yes	No patients were lost	A lot of detail reported study	**High quality**
Gaita, 2005 (50)	Unknown; no power calculation provided N = 105	List of randomization	No	Yes	None reported	3 treatment groups No statistical comparison between the 3 groups	**Moderate quality**
Vasconcelos, 2004 (51)	Unknown; no power calculation provided N = 27	Sealed envelopes	Freedom from AF	Yes	None reported	Small sample size (N=27)	**Moderate quality**
Schuetz, 2003 (32)	Unknown; no power calculation provided N = 43	Not described	No	Pts in control group had a significantly longer duration of AF prior to surgery	None reported	Poor description of methodology	**Moderate-quality**
Akpinar, 2003 (52)	Unknown; no power calculation provided N = 77	Not described	No	Pts in surgery only arm had significantly worse NYHA class ratings at baseline	None reported	Poor description of methods	**Moderate quality**
Jessurun, 2003 (48)	Unknown; no power calculation provided N = 35	Not described	Sinus rhythm without AF following surgery	Yes	None reported	Clearly defined endpoints Small sample (N = 35)	**Moderate quality**
Deneke, 2002 (34)	Unknown; no power calculation provided N = 30	Not described	Sinus rhythm at follow-up	Yes	None reported	Clearly defined endpoints Small sample (N = 30)	**Moderate quality**

* AF indicates atrial fibrillation; MAS, Medical Advisory Secretariat; QoL, quality of life; RCT, randomized controlled trial.

The RCT by Gaita et al. (50) reported results for the entire group of patients (N = 105), but they also reported results for a subgroup of patients (n = 51) who underwent electroanatomic mapping after the ablation to observe changes in the heart. Given that less than one-half of the patients in the study were included in the subgroup analysis, the review will focus on the results presented for the entire group.

In July 2004, NICE (31) published an overview of microwave ablation for AF in addition to other cardiac surgery. They identified 6 studies that met their inclusion criteria: 1 RCT, 2 prospective comparison studies, and 3 case series. The RCT is included in the Medical Advisory Secretariat analysis (Tables 16–18). The other 5 studies did not meet the inclusion criteria for this report. Since the publication of this NICE overview, no additional RCTs investigating microwave ablation were identified that met the

inclusion criteria for this report.

Table 16: Description of Follow-up in Studies Investigating Ablative Techniques in Patients With Drug-Refractory AF With Other Heart Conditions Requiring Surgery*

Study, Year	How Arrhythmia Was Measured During Follow-up
Doukas, 2005 (49)	- At 3, 6, 12 months patients had clinical examination and a 12-lead ECG - At 6 and 12 months a transthoracic ECG and SWT were also carried out - If patients had symptoms suggestive of dysrhythmia at a visit or between visits, they were monitored with 24 hour Holter monitoring
Gaita, 2005 (50)	- At 3, 6, 9, 12, 18, 24 months patients were followed up with clinical examination, ECG and Holter monitoring.
Vasconcelos, 2004 (51)	- Patients followed monthly with clinical examination and ECG.
Schuetz, 2003 (32)	- At 3, 6, and 12 months, patients had clinical exam, ECG monitoring. - At 12 months they also received Holter monitoring
Akpinar, 2003 (52)	Data was collected for 16 months—do not report the frequency of data collection, or how they measured arrhythmia
Jessurun, 2003 (48)	- 3 and 12 months after surgery, clinical examination, Holter monitoring, bicycle stress testing, ECG
Deneke, 2002 (34)	- Follow-up at day 1, day 12, 3, 6, 9, 12 months, medical and clinical history, and ECG. - Holter monitoring at 6 and 12 months

* AF indicates atrial fibrillation; ECG, electrocardiogram; SWT, shuttle walk test.

Table 17: Results of Studies Investigating Ablative Techniques in Patients With Drug-Refractory Atrial Fibrillation With Other Heart Conditions Requiring Surgery*

Study, Year	Procedure		No. of Patients	Mean (SD) Follow-up, Months	Mean (SD) Fluoroscopy Time, Minutes	Mean (SD) Ablation Time, Minutes	Long-term Success‡ Without Drug Therapy, %	Long-term Success‡ With Drug Therapy. %
Doukas, 2005 (49)	Surgical ablation + mitral valve surgery		48	> 12	NR	12 months 44.4%	—	—
	Mitral valve surgery		48		NR	12 months 4.5%	—	—
Gaita, 2005 (50)	Linear cryoablation of LA ± concomitant surgery	U	35	41 (17)	Ablation 18 (3)	24 months 57%	24 months 90%	—
		7	35		Ablation 15 (4)	24 months 57%	24 months 90%	—
	PV cryoisolation ± concomitant surgery		35		Ablation 14 (4)	24 months 20%	24 months 59%	—
Vasconcelos, 2004 (51)	Cox maze III ± mitral valve surgery		14	11.5	NR	79%	—	—
	Mitral valve surgery alone		13	10.3	NR	46%	—	—
Schuetz, 2003 (32)	Microwave ablation ± open heart surgery		24	> 12	244 (63)	—	—	12 months 80%
	Open heart surgery alone		19		229 (62)	—	—	12 months 33.3%
Akpinar, 2003 (52)	RF maze procedure ± mitral valve surgery		33	Median, 10	NR	—	—	6 mos 87.2% 12 mos 93.6%
	Mitral valve surgery alone		34		NR	—	—	6 & 12 mos 9.4%
Jessurun, 2003 (48)	Cox maze III ± mitral valve surgery		25	> 12	NR	—	—	At 12 mos 92% (52% of whole group were using AADs)
	Mitral valve surgery alone		10		NR	—	—	At 12 mos 20% (90% of whole group using AADs)
Deneke, 2002 (34)	RF maze procedure ± mitral valve surgery		15	22 (7)	NR	—	—	12 mos 82%
	Mitral valve surgery alone		15	21 (6)	NR	—	—	12 mos 21%

* AF indicates atrial fibrillation; N/A, not applicable; NR, not reported.

Complications

There were more serious complications and deaths in patients that underwent concomitant surgery than there were in patients that underwent catheter ablation and no additional surgery. Because these patients were more likely to be in poorer health than patients with AF alone, the complications (listed in Table 18) are more likely related to the nature of the surgery, rather than the ablation (Personal communication, November 2005).

There were 403 patients in the 7 studies that investigated ablation for AF for patients requiring additional surgery. There were 25 deaths reported among these patients. About 6% of the patients undergoing ablation died, and 7% of the patients undergoing surgery without ablation died. Twelve of the deaths occurred in hospital (during or after surgery). One death was attributed to stroke; this patient was randomized to the surgery without ablation group in the study by Vasconcelos et al. (51) Two other patients suffered from strokes after surgery: one patient who had received ablation and another who did not undergo ablation.

Table 18: Complications Reported in Studies Investigating Ablative Techniques in Patients With Drug-Refractory AF With Other Heart Conditions Requiring Surgery

Study, Year	Treatment		No. of Patients	Complications
Doukas, 2005 (49)	Surgical ablation + mitral valve surgery		48	- 3 in-hospital deaths - 2 pts required re-operations for mitral valve repair complications
	Mitral valve surgery		48	- 4 in-hospital deaths - 2 pts had transient ischemic attacks (4 and 9 months after surgery)
Gaita, 2005 (50)	Linear cryoablation of LA ± concomitant surgery	U	35	- 1 perioperative death - No deaths or complications were attributed to the procedure - 2 pts died in follow-up period: 1 with heart failure, 1 with valvular endocarditis
		7	35	- 1 perioperative death - No deaths or complications were attributed to the procedure
	PV cryoisolation ± concomitant surgery		35	- 1 perioperative death - No deaths or complications were attributed to the procedure
Vasconcelos, 2004 (51)	Cox maze III ± mitral valve surgery		14	- 1 pt had a stroke - Authors of the study noted that there was not a significant difference in the number of complications in each group
	Mitral valve surgery alone		13	- 1 death due to hemorrhagic stroke
Schuetz, 2003 (32)	Microwave ablation ± open heart surgery		24	- 1 in-hospital death due to cerebral air embolism of unknown origin
	Open heart surgery alone		19	- 1 in-hospital death due to refractory heart failure
Akpinar, 2003 (52)	RF maze procedure ± mitral valve surgery		33	- 1 death 27 after surgery due to multi-organ failure after long-lasting pulmonary infection - 1 follow-up death (traffic accident) - 1 pt reoperation for bleeding - 1 pt late pericardial tamponade
	Mitral valve surgery alone		34	- 1 death 5 days after surgery to a gastrointestinal complication - 2 follow-up deaths: 1 sudden cardiac death, 1 stroke - 1 pt reoperation for bleeding - 2 pts late pericardial tamponade
Jessurun, 2003 (48)	Cox maze III ± mitral valve surgery		25	- 1 pt required inotropic drugs due to an intra-operative MI
	Mitral valve surgery alone		10	- 1 pt with stroke
Deneke, 2002 (34)	RF maze procedure ± mitral valve surgery		15	- 1 pt postop pacemaker - 1 death due to renal bleeding - 1 death due to mediastinitis - 1 sudden cardiac death - 1 death due to severe lung fibrosis
	Mitral valve surgery alone		15	- 1 pt postop pacemaker - 1 death due to server chronic obstructive bronchial disease

* AF indicates atrial fibrillation; pt, patient.

Emerging Evidence

This health technology policy assessment was limited to reviewing evidence from published RCTs. However, there is a tremendous amount of research being conducted on improving and developing new ablation techniques. For instance, there is preliminary research on the safety and effectiveness of minimally invasive surgical ablation for patients with drug-refractory AF who do not require additional heart surgery. A limitation of surgical ablation is that patients need to be able to have their lungs deflated. Thus, to undergo surgery, patients cannot have any conditions that would not allow this.

It is important to clarify the definition for minimally invasive as it can refer to any of the following:

a. Heart surgery through very small incisions in general
b. Heart surgery through small incisions *without* the utilization of the heart-lung machine and *without* stopping the heart
c. Heart surgery through small incisions *with* the utilization of the heart-lung machine and *without* stopping the heart
d. Heart surgery through small incisions *with* the utilization of the heart-lung machine and *with* stoppage of the heart

In general, (b) is associated with less morbidity than (d), because the heart-lung machine increases the risks of bleeding, stroke, and renal impairment. The aim of the emerging technology is to optimize the effectiveness while minimizing the overall risk to the patients; in this sense, (b) constitutes the best option to treat drug-refractory lone AF surgically right now (Personal communication, November 2005).

Most of the studies on minimally invasive surgical ablation for lone AF are case reports. (53-57) There were, however, a few cohort studies investigating a minimally invasive approach that were identified. (58-60) Unfortunately, no RCTs were identified that comparing minimally invasive surgical RFA to catheter ablation in patients with drug-refractory AF who do not require additional heart surgery.

The most recent study was published by Wolf et al. (58) in 2005. Wolf et al. used a minimally invasive procedure defined as (b) above (heart surgery through small incisions without the utilization of the heart-lung machine and without stopping the heart). They used a bipolar radiofrequency probe, instead of a unipolar probe to reduce the risk of perforation adjacent tissues (i.e., esophagus). (21) They reported the results of 27 with drug-refractory, lone AF undergoing minimally invasive surgical ablation with radiofrequency energy. Three of the patients suffered from minor complications that had resolved within 48 hours. One patient had right pneumothorax; 1 patient, right forearm phlebitis; and 1 patient, suspected pericarditis which resolved after steroid administration. Another patient suffered from more significant complications. This patient was morbidly obese (410 lbs), and was re-admitted to hospital 3 weeks after discharge with dyspnea and anemia. He was admitted again at 3.5 months after surgery for congestive heart failure and AFL. At the last follow-up this patient had a regular sinus rhythm. Wolf et al. reported 3-month follow-up on 23 of the patients. At that time, 21 (91%) were free from arrhythmia.

The case-control study by Ad and Cox (59) compared retrospective data in patients with AF who underwent minimally invasive surgery (n = 72) to patients with AF who underwent standard surgery (n = 290). The minimally invasive approach is categorized as (d) above (heart surgery through small incisions with the utilization of the heart-lung machine and with stoppage of the heart). About one-third of the patients in both the minimally invasive group and the standard surgery group underwent concomitant heart surgery in addition to ablation (32% and 35 %, respectively). They used cryoablation technology rather than radiofrequency for the ablation procedures. Ad and Cox reported that there was no significant difference in the rate of transischemic attacks or strokes during the perioperative (< 3 months) or late (> 3 months) period between the minimally invasive and standard surgery groups. Within 3 months of surgery,

78% of patients in the minimally invasive group and 58% of patients in the standard surgery group were free from arrhythmia ($P < .05$).

The prospective study by Kottkamp et al. (60) investigated 70 patients with drug-refractory AF who had minimally invasive surgical ablation. The minimally invasive approach is categorized as (d) above (heart surgery through small incisions with the utilization of the heart-lung machine and with stoppage of the heart). Six months after surgery, 93% of patients were free from arrhythmia. In terms of major complications, 1 patient suffered from esophagus perforation and another patient had coronary artery stenosis.

Thus, minimally invasive surgical ablation appears to be a promising alternative to catheter ablation in patients with drug-refractory, lone AF; however, there is limited evidence available to support or refute its widespread use.

Summary of Findings of Literature Review

First-Line Catheter Ablation for Atrial Fibrillation or Atrial Flutter

Wazni et al. and Natale et al. each concluded that catheter ablation was associated with significantly improved long-term freedom from arrhythmias and quality of life compared to medical therapy. However, these studies investigated different patient populations: Wazni et al., patients with AF; Natale et al., patients with AFL. The study by Wazni et al. was a pilot RCT. This same group of researchers is working on a full, multicentre RCT to ensure consistency of their results across centres. Catheter ablation as first-line therapy for arrhythmias is promising; however, it is important to see the results of the full RCT comparing catheter ablation to medical therapy for AF before making any conclusions about its effectiveness and safety.

Catheter Ablation Versus Medical Therapy in Patients With Drug-Refractory, Lone Atrial Fibrillation

Three RCTs compared catheter ablation to medical therapy in patients with drug-refractory, lone AF. All 3 of the trials trials indicated that freedom from arrhythmia was significantly improved in patients who received catheter ablation compared to medical therapy alone ($P \leq .05$).

A large non-RCT by Pappone et al. (47) compared catheter ablation to medical therapy in patients with drug-refractory, lone AF. This study was not included in the analysis of the results of this review because it did not meet the inclusion criteria. However, it is worth noting that this study of 1,171 patients with drug-refractory AF found an improvement in freedom from AF, survival, and quality of life compared with the patients receiving medical therapy. This study also provided an extensive complications profile of patients included in the study (Table 13). They reported a rate of death of 6.5% after 2.5 years follow-up in the catheter ablation group compared with 14.3% in the medical therapy group. Similarly, the rate of adverse events was higher for the patients in the medical therapy group compared with those the catheter ablation group (20.1% versus 9.2%).

Various Catheter Ablation Techniques

There does not appear to be a clearly superior catheter ablation technique for patients with drug-refractory, lone AF. All of the RCTs comparing various techniques isolated some or all of the pulmonary veins. The techniques are continually evolving, improving the effectiveness and safety of catheter ablation (expert opinion) (Personal communication, November 2005).

Ablation in Addition to Heart Surgery Versus Heart Surgery Alone in Patients With Atrial Fibrillation

It is clear that patients with drug-refractory AF who are undergoing concomitant heart surgery benefit significantly from surgical ablation in terms of long-term freedom from AF, without substantial additional risk compared with those who have only open heart surgery. It is important to note that the proportion of patients with AF requiring additional heart surgery represents a very small proportion of the AF population. One clinical expert estimated that less than 1% of the patients with AF would require additional heart surgery (Personal communication, November 2005).

There insufficient evidence at this time supporting the use of surgical ablation for patients with drug-refractory, lone AF.

Microwave and Cryoablation for Patients With AF Undergoing Additional Heart Surgery

Microwave and cryoablation seem to be promising sources of energy for catheter and surgical ablation, but there is limited evidence available on the effectiveness of these techniques compared with radiofrequency energy. None of the studies using microwave or cryoablation used radiofrequency energy in their control groups. The RCT on microwave ablation compared microwave ablation to no ablation, and the cryoablation RCT compared different techniques for cryoablation. More studies need to be conducted on these forms of energy comparing them to radiofrequency energy.

Economic Analysis

Notes & Disclaimer

The Medical Advisory Secretariat uses a standardized costing methodology for all of its economic analyses of technologies. The main cost categories and the associated methodology from the province's perspective are as follows:

Hospital: Ontario Case Costing Initiative (OCCI) cost data is used for all program costs when there are 10 or more hospital separations, or one-third or more of hospital separations in the ministry's data warehouse are for the designated International Classification of Diseases-10 diagnosis codes and Canadian Classification of Health Interventions procedure codes. Where appropriate, costs are adjusted for hospital-specific or peer-specific effects. In cases where the technology under review falls outside the hospitals that report to the OCCI, PAC-10 weights converted into monetary units are used. Adjustments may need to be made to ensure the relevant case mix group is reflective of the diagnosis and procedures under consideration. Due to the difficulties of estimating indirect costs in hospitals associated with a particular diagnosis or procedure, the Medical Advisory Secretariat normally defaults to considering direct treatment costs only. Historical costs have been adjusted upward by 3% per annum, representing a 5% inflation rate assumption less a 2% implicit expectation of efficiency gains by hospitals.

Non-Hospital: These include physician services costs obtained from the Provider Services Branch of the Ontario Ministry of Health and Long-Term Care, device costs from the perspective of local health care institutions, and drug costs from the Ontario Drug Benefit formulary list price.

Discounting: For all cost-effective analyses, discount rates of 5% and 3% are used as per the Canadian Coordinating Office for Health Technology Assessment and the Washington Panel of Cost-Effectiveness, respectively.

Downstream cost savings: All cost avoidance and cost savings are based on assumptions of utilization, care patterns, funding, and other factors. These may or may not be realized by the system or individual institutions.

In cases where a deviation from this standard is used, an explanation has been given as to the reasons, the assumptions and the revised approach.

The economic analysis represents an estimate only, based on assumptions and costing methods that have been explicitly stated above. These estimates will change if different assumptions and costing methods are applied for the purpose of developing implementation plans for the technology.

Ontario-Based Economic Analysis

This health technology and policy assessment was developed in conjunction with the Medical Advisory Secretariat's health technology and policy assessment on "Advanced Mapping Systems for Catheter Ablation". The economic analysis encompasses the costs of the advanced mapping systems in addition to the cost of the ablation procedure.

Budget Impact

Hospitalization Costs

The Ontario Case Costing Initiative (OCCI) cost per hospitalization for catheter ablation (including mapping and ablation) during FY 2003 was $5,608. (search criteria: most responsible ICD-10 diagnosis

code of I48.0 [atrial fibrillation] combined with a CCI principal procedure code of 1.HH.59.GP-AW) Adjusting this by 3% per annum to reflect FY 2004 expected costs produced a cost estimate of $5,776. Since there currently is no separate procedure code for advanced mapping techniques, this cost estimate should be considered as an average cost over all mapping techniques.

Based on data in the hospital discharge database for Ontario, there were 365 unique hospital separations for atrial fibrillation with a catheter procedure performed during fiscal year (FY 2004). Therefore, the total annual cost of hospitalization associated with these mapping and ablation procedures was $2.1 M during FY 2004..

Physician Costs

Estimated first year professional costs of $3,815 per treated patient are based on the numbers and calculations in the Tables 19-21 below:

Table 19. Procedure costs associated with mapping and ablation procedures

Procedure costs	Rate	50%	Value used in calculation (min.)		(max.)
+/- J021 - insertion of catheter	$110.98		$110.98		$ 110.98
+/- Z437 Cardioversion (electrical) if applicable	$65.99				$ 65.99
# G178 - catheter ablation therapy	$352.05		$352.05		$ 352.05
The following codes are paid at 50%					
# G176 - atrial Endocardial activation mapping	$334.25	$167.13	$167.13		$ 167.13
+/- G179 - repeated (up to three times)	$111.18	$55.59	$55.59		$ 166.77
# G249 Electrophysiologic measurements	$231.64	$115.82	$115.82		$ 115.82
# G261 - induction of atrial arrhythmias	$331.04	$165.52	$165.52		$ 165.52
+/- G297 Angiograms (one or two times)	$109.65	$54.83	$54.83		$ 109.65
# Z441 – transeptal	$274.38	$137.19	$137.19		$ 137.19
			$ 1,159	to	$ 1,391
				Avg.	$ 1,275

* Source: Ontario Ministry of Health and Long-term Care - Physician Schedule of Benefits 2003 (totals adjusted by 2% to reflect latest OMA agreement

Table 20. Perioperative costs associated with mapping and ablation procedures

Perioperative costs	Cost (Cdn)	Source
CT chest scan + Physician Fee (X407 = $76.60)	$ 357	Ontario Schedule of Benefits
Physician Fees for procedure	$ 1,275	Table 19
3 months post procedure follow-up	$ 1,442	1/4 of annual follow-up costs + CT scan
Total	$ 3,074	

Table 21. First year costs associated with mapping and ablation procedures

First Year Costs

Perioperative cost of ablation procedure	$ 3,074	(Using Medium Success Rate 20% w/o catheter costs)
Annual follow-up cost for successful patients	$ 112	*(Based on 1 specialist visit per year: A605)*
Annual follow up cost for unsuccessful patients	$ 3,257	*(Based on annual costs of clinical tests and visits*--1rst year is 0.75 yrs))
Weighted avg. annual follow up cost	$ 741	*(Based on 80% success rate)*
Estimated First Year Professional Costs	$ 3,815	*(Perioperative + avg. follow-up costs)*

Device Costs

The cost of the catheters for mapping and ablation range from between $1,800 - $2,500 for 2-3 catheters needed for fluoroscopy procedures and from between $5,700 - $6,900 for the 2 catheters plus patches needed for advanced mapping procedures (source: vendor estimates)

Downstream Cost Savings

Based on the prevalence of hospitalization for stroke and congestive heart failure in the population with atrial fibrillation, we estimate that there will be an average annual cost savings of $971 (Source: Ontario hospital data) per treated patient due to avoided hospitalizations with these diagnoses and approximately $700 per treated patient in annual cost savings due to reduced use of anticoagulants and antiarrhythmics (Source: expert opinion?). Since 78% (76,000/98,000) of population with AF is over the age of 65, this savings will accrue directly to the Ontario Drug Benefits program for a large majority of patients (Source: Ontario Ministry of Finance and Go et. al., 2001 (8)).

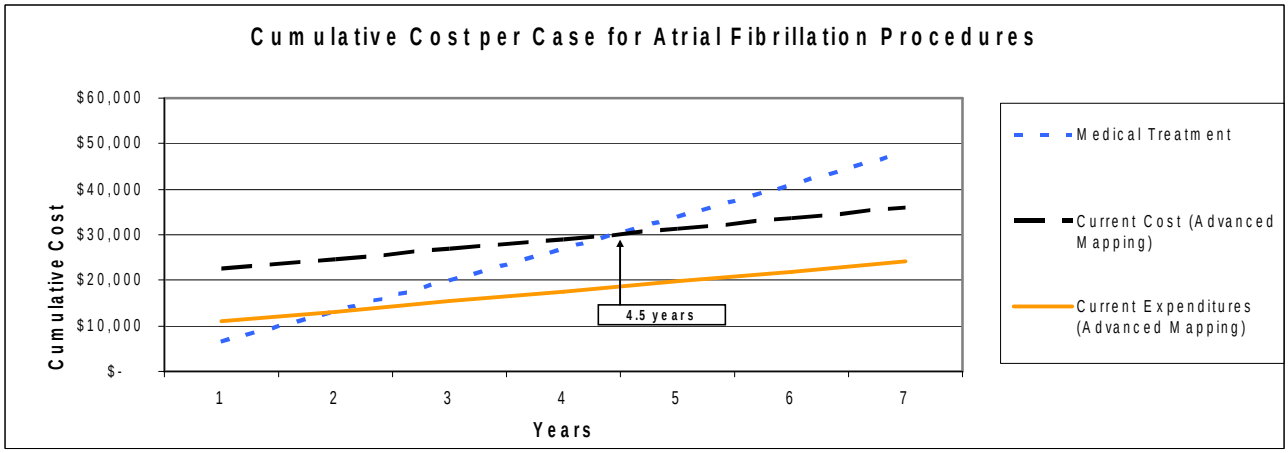
The ongoing costs per case of medical management versus advanced mapping ablation for the treatment of atrial fibrillation including the downstream cost savings attributed to the latter are presented in Table 22. Based on a model adapted from a vendor, the costing model includes up-front high-end estimates of the costs of hospitalizations, physician fees, device costs, drugs, labs, diagnostic radiology, repeat procedures for initial unsuccessful treatments, and attrition to medical management for patients who become refractory to ablation. A 2% annual inflation rate is assumed. The current MOHLTC direct funding formula provides $1,000 for an EP study and $1,600 for a catheter ablation procedure, regardless of the

Table 22. Costs of medical management versus mapping and ablation for patients with atrial fibrillation

	Annual Cost		Cumulative Cost of Treatment by procedure				
Treatment Path (high est. for Adv. Mapping)	Year 1 Cost	Annual Cost	Year 1	Year 2	Year 3	Year 4	Year 5
Medical Treatment	$ 6,475	$6,475	$ 6,475	$ 13,080	$ 19,817	$ 26,688	$ 33,697
Current Cost (Advanced Mapping)	$22,465	$2,054	$ 22,465	$ 24,560	$ 26,697	$ 28,876	$ 31,100
Current Expenditures (Advanced Mapping)	$11,068	$2,054	$ 11,068	$ 13,163	$ 15,299	$ 17,479	$ 19,702

Note: Assume a 2% per annum inflation rate

Figure 1. Cumulative Cost per Case for Atrial Fibrillation Procedures

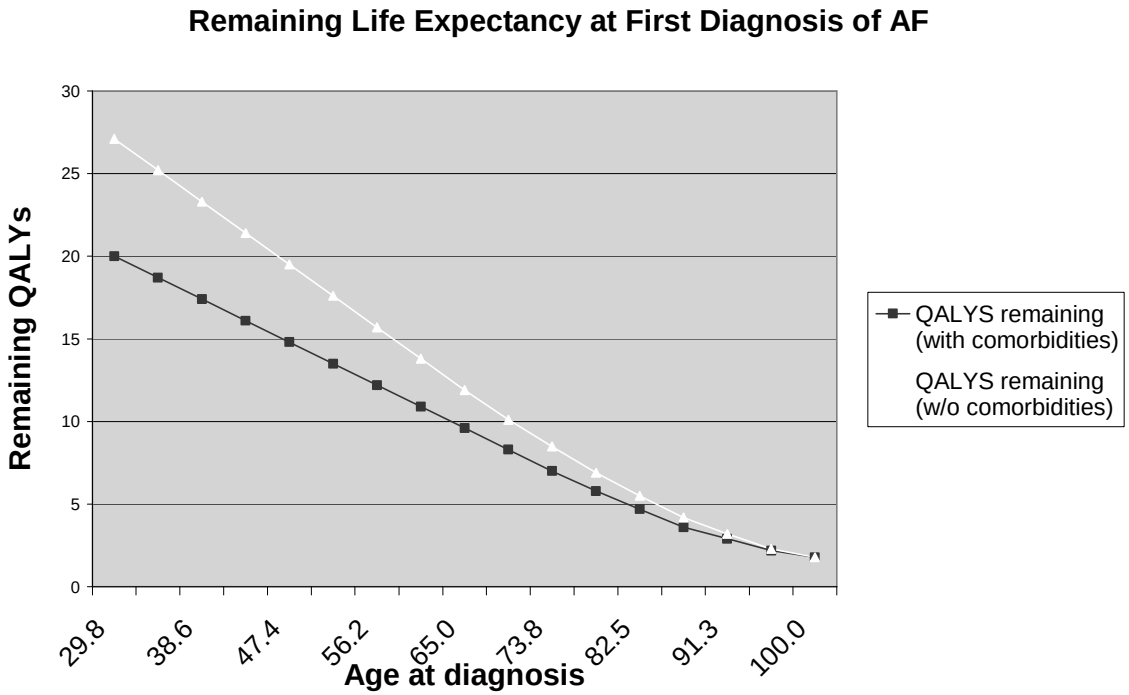


The three scenarios presented in Table 22 and Figure 1 include medical management with drugs, a high estimate for the current costs associated with advanced mapping (including $6,900 for catheters and patches), and the current expenditures for all mapping and ablation ($2,600 per case for all costs associated with the procedure: catheters, patches, cath lab, etc.). Comparing medical management and advanced mapping ablation in the graph above, the added up-front cost of the latter are recouped--through reduced use of antiarrhythmics and anticoagulants as well as fewer hospitalizations for stroke and CHF--at 4.5 years after the procedure under the proposed funding formula. Using a more conservative estimate of the cost of the advanced mapping catheters and patches (e.g., $5,700), this point of "break even" will occur at approximately 4 years. The current funding ($2,600) is well-below the costs associated with an ablation guided by advanced mapping as reported by a vendor and an academic health science centre (compare solid and hatched parallel lines in the graph).

With an expected 563 cases of atrial fibrillation per year for which advanced mapping techniques might be appropriate, the total cost of such a program could be as high as $12.6 M (563 annual cases in Ontario x $22,465 per case) in the initial year with the budget increasing by $1.2 M per year to account for each succeeding cohort requiring an expected $2,054 per patient per year in follow-up treatment.

To ensure the validity of the costing model, information about remaining life expectancy of those diagnosed with AF is needed. Evidence regarding base-line (i.e., without treatment) remaining life expectancy—in terms of Quality Adjusted Life Years (QALYs)--is given in Figure 2 below.

Figure 2.



Source: Adapted from Desbiens, Deciding on Anticoagulating the Oldest Old with Atrial Fibrillation…., 2002

Since remaining life expectancy is always greater than or equal to the number of QALYs, the graph above presents a lower bound on remaining life expectancy. Since base-line life expectancy remains in excess of five years until age-of-diagnosis of 85, it is evident that most individuals with AF treated with advanced mapping ablations will survive beyond the point at which the added up-front costs are recouped.

Review of the Cost-Effectiveness Literature

Medical treatment (anticoagulants) compared to no treatment

Desbiens (2002) found that Warfarin treatment is cost-saving (i.e., more effectiveness and less costly) than no treatment in younger non-comorbid populations and less than $30,000/QALY in older populations with comorbidities.

Catheter Ablation techniques (fluoroscopy and advanced mapping procedures and ablation) compared to medical treatment regimen (anticoagulants and antiarrhythmics)

In general, studies report either that catheter ablations are cost-saving or highly cost-effective in comparison to medical management. Cheng et al., (2000) found that catheter-ablations were cost-saving in comparison to drug therapy in patient with Severe Ventricular Tachycardia (SVT). Hogenhuis (1993) also found that catheter ablations were cost-saving in comparison to drugs and open surgical ablations for survivors of cardiac arrest with symptomatic Wolf-Parkinson-White (WPW) syndrome) but catheter ablations did not have a favourable cost-effectiveness profile for individuals with asymptomatic WPW. Calkins et al. (2000) observed that catheter ablations had a cost-effectiveness of < $33,000 CDN per QALY for individuals with both Ventricular Tachycardia (VT) and pre-existing ischaemic coronary disease.

Existing Guidelines for Use of Technology

AETNA

AETNA (61), a health insurance company in the United States, in a 2005 report titled *Cardiac catheter ablation procedures,* reported that catheter ablation is medically necessary for any of the following:

- Atrial tachycardia
- AVNRT
- Drug resistant/intolerant AFL or AF
- VT

They also reported that there is insufficient evidence regarding the effectiveness of catheter ablation for any of the following:

- Multifocal atrial tachycardia
- Unstable, rapid, multiple, or polymorphic VT that cannot be adequately localized by mapping techniques

CEDIT

CEDIT (Comité d'Evaluation de Diffusion des Innovations Technologiques) (62) in a 2004 report titled *Ablation of arrhythmogenic foci, France,* recommended the following:

- Surgical ablation should be performed if another heart surgery is planned.
- The trend toward using ablation techniques for arrhythmogenic foci via a nonsurgical approach, in particular for treating AF, appears to be corroborated.
- It is worthwhile to continue research into new ablation techniques.
- A registry should be established to measure length of stay and complications associated with the ablation techniques.

CIGNA

CIGNA, (63) a health insurance company in the United States, published a 2005 report titled *Radiofrequency catheter ablation for cardiac arrhythmia* in which they noted that catheter RFA was medically necessary for any of the following indications:

- Recurrent AVNRT
- Paroxysmal supraventricular tachycardia with only dual AV-nodal pathways in single echo beats during EP study, and no other identified cause of arrhythmia
- Accessory pathway mediated arrhythmia
- Focal atria tachycardia
- AFL
- Supraventricular tachycardia in adults with congenital heart disease
- Focal junctional tachycardia
- Ventricular arrhythmia

CIGNA does not insure catheter RFA for patients with any arrhythmias, except those specified, including

AF, because "it is considered experimental, investigational or unproven." (63)

CIGNA

CIGNA, (64) in the 2005 report titled *Maze procedure*, notes that it does not offer cover the surgical Cox maze procedure for patients with AF; however, it does cover the Maze procedure for patients with drug-refractory, chronic, symptomatic AF in whom rhythm control is essential.

Appraisal

Policy Implications

Incidence of Strokes

Based on Ontario administrative data, about 15% of people who had a stroke in fiscal year 2004, were diagnosed with AF in fiscal years 2002 to 2004. In fiscal year 2004/2005, 14,000 people were admitted to Ontario hospitals with stroke as their most responsible diagnosis (ICD10 codes I61, I63, I64). There were 2,493 (15%) in-hospital deaths among these patients. Their mean age was 74.9 years (median, 77 years; range, 0–105 years). The mean length of hospital stay was 12.9 days (median, 8 days; range, 1–499 days). Of the patients who were discharged alive, 4,172 went home without any support; 1,235 went home with home care support, and the remaining 6,100 were transferred to other health care facilities.

Cardioversion

When people present at hospital with AF that is not controlled by drugs, electrical cardioversion is frequently attempted. Table 23 outlines the number of inpatient and outpatient electrical cardioversions performed for patients with AF from 2002 to 2004 (fiscal years). Most of the patients had 1 hospital separation for cardioversion; however, 9.6% of outpatients and 3.9% of inpatients had more than 1 separation for electrical cardioversion.

Table 23: Number of External Cardioversions Performed on Patients With Atrial Fibrillation From Fiscal Years 2002 to 2004

Type of Patient	Total	Mean Age, Years (Median; Range)	1 Separation Per Patient for Cardioversion	2 Separations Per Patient for Cardioversion	3 Separations Per Patient for Cardioversion	> 3 Separations Per Patient for Cardioversion
Outpatient	2,204	61.5 (62; 19–95)	1,992	163	32	17
Inpatient	2,066	68.2 (71; 15–99)	1,986	71	6	3

Patient Outcomes – Medical, Clinical

Atrial fibrillation is a chronic condition that can severely affect a person's quality of life. (47) Ablation provides an opportunity to "cure" AF, as opposed to treating it with drugs or electrical cardioversion. The primary concern that several experts have expressed with ablation is that it is such a new technology that it is still unclear if it is a cure for AF (Personal communication, November 2005). One clinical expert that

provided feedback on this review commented that "despite all these ablative efforts, there is really no understanding as to how these [atrial fibrillation] triggers or abnormal neural inputs etc. develop in the first place. As such, it is possible that if the underlying process that resulted in these disruptions to initially cause AF is allowed to continue, then we are probably destined to see an eventual recurrence of AF in many patients who undergo ablation – it may just be a matter of time." (Personal communication, November 2005). Nonetheless, ablation, whether it is a true cure or not, seems to be the best option now available to patients with drug-refractory AF.

If access to catheter ablation for patients with drug-refractory AF is improved, then more patients would be able to receive it and potentially avoid lifelong drug therapy. Access could also decrease the incidence of strokes and congestive heart failure, and hospital admissions for electrical cardioversion. If access remains as it is, then some patients with AF will wait up to 1 year for their catheter ablation, dealing with the adverse effects of ineffective drug therapy during this time.

Ethics

Atrial fibrillation has a high prevalence and potentially devastating effects on a person's quality of life. In 2004, the Institute for Clinical Evaluative Sciences (7) estimated that the rate of hospitalization for AF in Canada was 582.7 per 100,000 population. They also reported that of the patients discharged alive, 2.7% were readmitted within 1 year for stroke. According to American data, (6) the incidence of AF increases with age, with a prevalence of 1 per 200 people aged between 50 and 60 years, and 1 per 10 people aged over 80 years. Thus, AF is very prevalent, and if there is a treatment that has the potential to treat it successfully, then it would seem appropriate to investigate the possibility of using that treatment.

Demographics

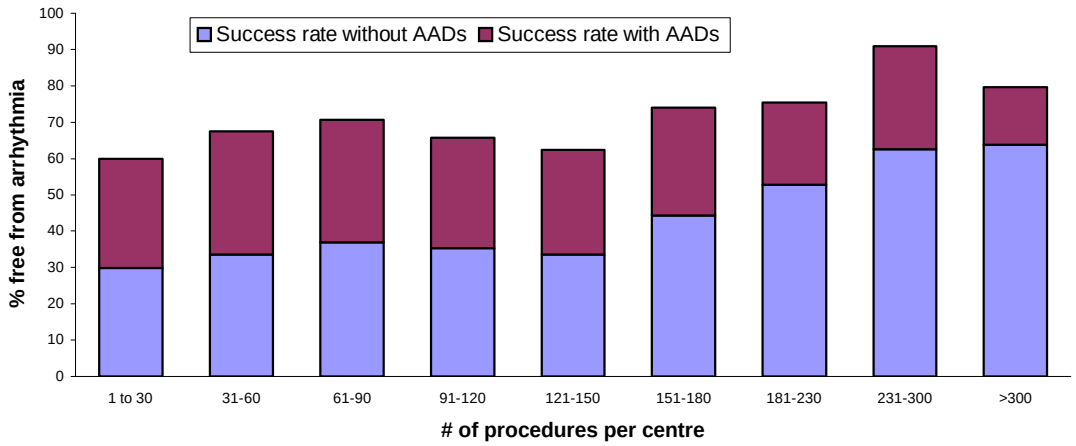
Patients with AF fall into 2 broad categories: primary AF in patients with no obvious cause of AF and who are otherwise generally healthy; and AF associated with comorbid conditions, such as heart disease or valvular disease. The prevalence of AF in Ontario has been estimated to be 98,758 based on extrapolation of the data for Go et al's study (8) of the prevalence of AF in the United States.

Diffusion – International, National, Provincial

Catheter ablation is a widely accepted procedure for various arrhythmias including AVNRT and Wolff-Parkinson White syndrome. It is becoming more and more common to use catheter ablation for patients with drug-refractory AF. In a recent publication by Cappato et al., (1) 181 centres worldwide responded to a survey of their current usage of catheter ablation. Between 1995 and 2002, the number of procedures worldwide increased from 18 to 5,050. Centres each performed between 1 and 600 catheter ablations between 1995 and 2002.

Cappato et al. also reported that the more procedures a centre had performed, the higher its success rate. For centres that performed between 1 and 30 ablations, the success rate was 60% overall and 30% for patients who were not using AADs after ablation. In centres that performed between 231 and 300 ablations, the overall success rate was 91% and 62.5% for patients who were not using AADs after ablation. In addition, the rate of success without AADs increases with more ablation procedures per centre. Thus, the success rate improves and use of medical therapy decreases in centres with more experience (Figure 3).

Figure 3: Success Rate by Number of Catheter Ablations Performed Per Centre (Cappato et al. (1))



Incidence and Prevalence of Atrial Fibrillation

Based on the data provided in the Go et al. study (8) of the prevalence of AF in the United States, the estimated number of Ontario residents aged between 20 and 79 years with AF is about 66,000. Based on the results of a large RCT (65) investigating the effectiveness of rhythm versus rate drug therapy, between 34% and 68% of patients will be effectively treated with drug therapy. Based on this, between 23,800 and 41,000 Ontario residents will not be effectively treated with drug therapy. According to clinical experts in the province, from 10% to 25% of these drug-refractory patients can be effectively treated with ablation (about 2,400–10,000 patients) (Personal communication, November 2005). One-quarter to one-half of these patients will require a second ablation procedure. (1)(Personal communication, November 2005) However, as noted, as expertise increases, so does the initial success rate, thereby decreasing the need for a second ablation procedure. Thus, the total number of ablation procedures required to manage the prevalence of AF in Ontario is estimated to range from 3,000 to 15,300. The annual incidence of AF for the population aged between 20 and 79 years is estimated to be 116 to 600 (derived from data in the Go et al. study (8)).

According to clinical experts, about 75% of patients with AF who are eligible for ablation will require ablation using advanced mapping techniques. For more detail on advanced mapping techniques, please refer to the Medical Advisory Secretariat's health technology and policy assessment titled *Advanced mapping techniques for complex cardiac arrhythmias.*

Cost

Based on available statistical and cost data, the Medical Advisory Secretariat determined the following:

- Among complex arrhythmias, AF has the greatest unmet need for catheter ablation using advanced mapping systems.
- An estimated minimum of 2,230 additional ablations using an advanced mapping system is required to meet the prevalent need of AF, costing up to $12.6 million (Cdn) per year over 5 years to manage the prevalent cases of AF.

System Pressures

If access to catheter ablation for patients with drug-refractory AF is improved, then this likely would place and increased burden on the health care system, which already has a list of patients waiting to have catheter ablation for AF.

Stakeholder Analysis

If there is a change in the policy regarding ablation, then the centres with the capacity to use catheter ablation for AF (i.e., health centres with 3-D mapping technology) will be affected, because the additional flow of patients will need to be treated in these centres. According to 2 clinical experts in Ontario, it is unlikely that patients with AF will undergo fluoroscopy-guided mapping; however, patients with some other arrhythmias (such as AVNRT, Wolff-Parkinson White syndrome, and common AFL) are effectively treated with fluoroscopy, and there is no need for mapping with advanced mapping systems (Personal communication, November 2005),.

As technology and techniques improve, more patients with AF will be candidates for ablation, which ultimately may place more pressure on the health system to manage these patients without drug therapy.

Glossary

(from Hopkins Hospital Heart and Surgery Glossary)*

Accessory pathway	An abnormal muscular connection between the upper and lower chambers of the heart. Patients with accessory pathways may develop supraventricular tachycardias.
Arrhythmia	An irregular heart rhythm, or an abnormality in the timing or pattern of the heartbeat, causing the heart to beat too rapidly, too slowly, or irregularly.
Atrial fibrillation	Rapid, uncoordinated firing of electrical impulses from multiple sites in the upper chambers, which causes ineffective contractions.
Atrial flutter	A single "short circuit" in the atria that causes the atria to beat at about 300 beats per minute while the lower chambers of the heart (the ventricles) beat at a slower rate (often 75 or 150 beats per minute).
Atrial tachycardia	A sustained, irregular heart rhythm that occurs in the upper chamber of the heart and causes it to beat too rapidly.
Atrioventricular nodal re-entrant tachycardia	An abrupt, rapid heartbeat that occurs when electrical impulses mistakenly enter an extra pathway in or near the AV node.
Atrioventricular node	The normal electrical connection between the atria and the ventricles where electrical impulses are delayed for a fraction of a second to allow the lower chambers to fill completely with blood.
Bradycardia	A slow heart rate (less than 60 beats per minute).
Cardioversion	A procedure used to shock your heart back into rhythm.
Catheter ablation	A procedure used to ablate areas of the heart that are causing arrhythmias. In a radiofrequency ablation, electrophysiologists pinpoint the area and then use radio wave energy to "cauterize" the tiny part of the heart muscle causing the heart rhythm abnormality.
Event monitor	A wearable monitor that records the heart rhythm only when activated. Typically used for one month, during which patients are instructed to trigger the device if symptoms occur.
Holter monitor	A wearable monitor used to obtain a continuous ECG recording, usually for 24–48 hours, useful for detecting abnormalities that may not occur during a resting ECG.
Paroxysmal supraventricular tachycardia	A "short circuit" arrhythmia that causes the heart to beat too rapidly.

Sinus node	The sinus node, a group of specialized cells in the right atrium, is the place where the electrical impulse in the heart normally begins. It functions as the heart's pacemaker, setting the pace for the heartbeat.
Supraventricular tachycardia	A series of rapid heartbeats arising from the upper chambers of the heart that can cause the heart to beat very rapidly or erratically and may lead to inadequate blood supplies to the body.
Ventricular tachycardia	A series of rapid heartbeats that originate in the lower chamber of the heart (the ventricles) which may cause the heart to beat inefficiently.
Wolff-Parkinson-White syndrome	A specific type of heart rhythm abnormality. Patients with the WPW syndrome have an accessory pathway connecting the upper and lower chamber of the heart. These patients may develop a rapid heartbeat caused by a "short circuit" heart arrhythmia. WPW syndrome also may cause dangerous heart arrhythmias.

* Hopkins Hospital Heart and Circulatory System Glossary (http://www.hopkinshospital.org/health_info/Heart/Reading/glossary.html)

Appendices

Appendix 1: Search Strategy for Studies on Ablation for Atrial Fibrillation

Search date: March 1, 2006
Databases searched: OVID Medline, OVID In-Process and Other Non-Indexed Citations, EMBASE, Cochrane CENTRAL and DSR, and INAHTA

* The original search included studies with patients with any type of arrhythmia
Database: Ovid MEDLINE(R) <1999 to February week 3, 2006>
Search Strategy:

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1 exp tachycardia/ or exp tachycardia, paroxysmal/ or exp tachycardia, supraventricular/ or exp tachycardia, ventricular/ or exp ventricular fibrillation/ (7969)
2 exp Arrhythmia/ (23462)
3 exp Atrial Fibrillation/ (6602)
4 ((atrial or ventric$ or cardiac or supraventricular) adj2 (arrhythmia$ or fibrillation or tachycardia$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (18313)
5 or/1-4 (27534)
6 exp Catheter Ablation/ (4855)
7 (radiofrequency ablation or rfa).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (1900)
8 5 and (6 or 7) (2832)
9 limit 8 to (humans and english language and yr="2001 - 2006") (1694)
10 ((systematic$ adj2 review$) or (systematic$ adj2 overview$) or meta-analysis or metaanalysis).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (14788)
11 9 and 10 (3)
12 9 (1694)
13 limit 12 to (case reports or comment or editorial or letter or "review" or "review literature" or review, multicase or "review of reported cases") (804)
14 12 not 13 (890)
15 11 or 14 (893)
16 carto.mp. (89)
17 ensite.mp. (18)
18 noga.mp. (43)
19 ((electroanatomic$ or electro-anatomic$ or electrophysiologic$) adj2 map$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (295)
20 or/16-19 (378)
21 5 and 20 (262)
22 limit 21 to (humans and english language and yr="2001 - 2005") (193)
23 ((systematic$ adj2 review$) or (systematic$ adj2 overview$) or meta-analysis or metaanalysis).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (14788)
24 22 and 23 (0)
25 22 (193)
26 limit 25 to (case reports or comment or editorial or letter or "review" or "review literature" or review, multicase or "review of reported cases") (54)
27 25 not 26 (139)
28 15 or 27 (927)

Database: EMBASE <1996 to 2006 Week 9>
Search Strategy:
---
1 exp heart arrhythmia/ or exp heart fibrillation/ or exp tachycardia/ or exp heart ventricle tachycardia/ or exp supraventricular tachycardia/ or exp heart ventricle arrhythmia/ (60915)
2 ((atrial or ventric$ or cardiac or supraventricular) adj2 (arrhythmia$ or fibrillation or tachycardia$)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (27601)
3 1 or 2 (63044)
4 exp Catheter Ablation/ or exp Radiofrequency Ablation/ (6147)
5 3 and 4 (3992)
6 limit 5 to (human and english language and yr="2001 - 2005") (1910)
7 (systematic$ review$ or systematic$ overview$ or metaanalysis or meta-analysis).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (28634)
8 6 and 7 (17)
9 6 (1910)
10 limit 9 to (editorial or letter or note or "review") (462)
11 Case Report/ (362930)
12 9 not (10 or 11) (1013)
13 8 or 12 (1026)
14 ((electroanatomic$ or electro-anatomic$ or electrophysiologic$) adj2 map$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (364)
15 (noga or carto or ensite).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (162)
16 3 and (14 or 15) (313)
17 13 or 16 (1219)
18 limit 17 to (english language and yr="2001 - 2006") (1131)

Appendix 2: GRADE Quality Assessment Results

First-Line Therapy for Atrial Fibrillation

Quality Assessment: Comparing First-Line Catheter Ablation With Medical Therapy for Patient With Atrial Fibrillation

No. of Studies	Design	Limitations	Consistency	Directness	Other Considerations
Freedom from arrhythmia (Recurrence of atrial fibrillation during 1-year follow-up)					
1 (Wazni et al, 2005)	Randomized	None	Important inconsistency (-1)	No uncertainty	Designed as a pilot study

Summary of Findings

Outcome	No. of Patients		Effect	Quality	Importance
	Catheter Ablation	Medical Therapy	Relative Risk (95% CI)		
Freedom from arrhythmia	33/70 (47.1%)	37/70 (52.9%)	RR, 0.24 (0.09–0.59)	Moderate	1

* There was only 1 randomized controlled trial comparing first-line catheter ablation to medical therapy for atrial fibrillation; therefore, consistency is not possible to measure.

First-Line Therapy for Atrial Flutter

Quality Assessment: Comparing First-Line Catheter Ablation With Medical Therapy for Patient With Atrial Flutter

No. of Studies	Design	Limitations	Consistency	Directness	Other Considerations
Freedom from arrhythmia (Recurrence of atrial flutter at mean follow-up [21 +/- 11 months])					
1 (Natale et al., 2000)	Randomized	No limitations	Important inconsistency (-1)*	No uncertainty	None

Summary of Findings

Outcome	No. of Patients		Effect	Quality	Importance
	Catheter Ablation	Medical Therapy	Relative Risk (95% CI)		
Freedom from arrhythmia	31/61 (50.8%)	30/61 (49.2%)	RR, 0.35 (0.17–0.72)	Moderate	1

* There was only 1 randomized controlled trial comparing first-line catheter ablation to medical therapy for atrial flutter; therefore, consistency is not possible to measure.

Catheter Ablation Versus Medical Therapy for Atrial Fibrillation

Quality assessment comparing catheter radiofreqeuncy ablation to medical therapy in patients with drug-refractory AF

No of studies	Design	Limitations	Consistency	Directness	Other considerations
Freedom from arrhythmia (Recurrence of AF at 1 year)					
3 (Oral, 2006, Stabile, 2005; Krittayaphong, 2003)	Randomised trials	Serious limitations (-1)	No important inconsistency[1]	No uncertainty	None

Summary of findings

Summary of findings			
No of patients		**Effect**	**Quality**
Catheter radiofrequency ablation	**Medical therapy**	**Relative Risk (95% CI)**	
106/159 (66%)	52/153 (34%)	RR 0.32 (0.21 to 0.43)	Moderate

Footnotes:

1. Patients included had either paroxysmal, persistent or chronic AF.

Circumferential Pulmonary Vein Isolation Versus Segmental Pulmonary Vein Isolation for Atrial Fibrillation

Quality Assessment: Comparing Circumferential Pulmonary Vein Isolation With Segmental Pulmonary Vein Isolation in Patients With Drug-Refractory Atrial Fibrillation (Not Requiring Additional Heart Surgery)

No. of Studies	Design	Limitations	Consistency	Directness	Other Considerations
Freedom from arrhythmia (Recurrence of atrial fibrillation at 6-month follow-up)					
1 (Karch et al, 2005)	Randomized	No limitations	Important inconsistency (-1)*	No uncertainty	None

Summary of Findings

Outcome	No. of Patients		Effect	Quality	Importance
	Circumferential Pulmonary Vein Isolation	**Segmental Pulmonary Vein Isolation**	**Relative Risk (95% CI)**		
Freedom from arrhythmia	50/100 (50%)	50/100 (50%)	RR, 1.8 (1.3–2.6)	Moderate	1

* There is only 1 randomized controlled trial comparing circumferential pulmonary vein isolation to SPVI in drug-refractory patients not requiring additional heart surgery, which makes it difficult to assess consistency.

Circumferential Pulmonary Vein Isolation Plus Linear Ablation of Mitral Isthmus Versus Circumferential Pulmonary Vein Isolation Alone for Atrial Fibrillation

Quality Assessment: Comparing CPVI With CPVI Plus Linear Ablation of the Mitral Isthmus in Patients With Drug-Refractory Atrial Fibrillation Who Do Not Require Additional Heart Surgery*

No. of Studies	Design	Limitations	Consistency	Directness	Other Considerations
Freedom from arrhythmia (Recurrence of atrial fibrillation at mean follow-up [7 +/- 3 months)]) **[**					
1 (Haissaguerre et al, 2004)	Randomized	Serious limitations (-1)†	Important inconsistency (-1)‡	No uncertainty	None

Summary of Findings

Outcome	No. of Patients		Effect	Quality	Importance
	Circumferential Pulmonary Vein Isolation	Circumferential Pulmonary Vein Isolation With Linear Ablation of Mitral Isthmus	Relative Risk (95% CI)		
Freedom from arrhythmia	35/70 (50%)	35/70 (50%)	RR, 1.3 (0.78–2.1)	Low	1

*CPVI indicates circumferential pulmonary vein isolation.
† Unclear if study is powered to detect a significant difference between treatment groups.
‡ There is only 1 randomized controlled trial comparing circumferential pulmonary vein isolation to circumferential pulmonary vein isolation with linear ablation of mitral isthmus; thus, it is difficult to assess consistency.

Superior Pulmonary Vein Isolation Versus Isolation of All 4 Pulmonary Vein Isolation for Atrial Fibrillation

Quality Assessment: Comparing Catheter Ablation in the Superior Pulmonary Veins With Catheter Ablation in All 4 Pulmonary Veins in Patients With Drug-Refractory Atrial Fibrillation Who Do Not Require Additional Heart Surgery

No. of Studies	Design	Limitations	Consistency	Directness	Other Considerations
Freedom from arrhythmia (Recurrence of atrial fibrillation at 12-month follow-up)					
1 (Katritsis et al, 2004)	Randomized	No limitation	Important inconsistency (-1)*	No uncertainty	None

Summary of Findings

Outcome	No. of Patients		Effect	Quality	Importance
	Superior Pulmonary Vein Isolation	All 4 Pulmonary Vein Isolation	Relative Risk (95% CI)		
Freedom from arrhythmia	27/52 (51.9%)	25/52 (48.1%)	RR, 1.2 (0.71–2.0)	Moderate	1

* Only 1 randomized controlled trial was identified comparing ablation of superior pulmonary veins to ablation of all 4 pulmonary veins; thus, consistency is difficult to assess.

Pulmonary Vein Isolation With Left Atrial Junction and Cavotricuspid Isthmus Ablation Versus Pulmonary Vein Isolation With Left Atrial Junction Alone for Atrial Fibrillation

Quality Assessment: Comparing PV-LAJ and CTI With PV-LAJ Alone in Patients With Drug-Refractory Atrial Fibrillation Who Do Not Require Additional Heart Surgery*

No. of Studies	Design	Limitations	Consistency	Directness	Other Considerations
Freedom from arrhythmia (Recurrence from AF at 12-month follow-up)					
1	Randomized	Serious limitations (-1)†	Important inconsistency (-1)‡	No uncertainty	None

Summary of Findings

Outcome	No. of Patients		Effect	Quality	Importance
	PV-LAJ + CTI Ablation	PV-LAJ Alone	Relative Risk (95% CI)		
Freedom from arrhythmia	49/108 (45.4%)	59/108 (54.6%)	RR, 1.21 (0.7–2.1)	Low	1

* CTI indicates cavotricuspid isthmus; PV-LAJ, pulmonary vein isolation with left atrial junction.
† Unclear if study was powered to detect a significant difference between groups.
‡ Only 1 randomized controlled trial was identified that compared PV-LAJ + CTI to PV-LAJ alone; thus, it is difficult to assess consistency.

Radiofrequency Ablation Maze Plus Mitral Valve Surgery Versus Mitral Valve Surgery Alone for Atrial Fibrillation

Quality Assessment: Comparing Surgical Ablation Plus Mitral Valve Surgery With Mitral Valve Surgery Alone in Patients With Drug-Refractory Atrial Fibrillation Who Require Additional Heart Surgery

No. of Studies	Design	Limitations	Consistency	Directness	Other Considerations
Freedom from arrhythmia (Recurrence of atrial fibrillation follow-up: 12 months)					
2 (Akpinar et al, 2003 and Deneke et al, 2002)	Randomized	No limitations	No important inconsistency	No uncertainty	None

Summary of Findings

Outcome	No. of Patients		Effect	Quality	Importance
	Surgical Ablation With Mitral Valve Surgery	Mitral Valve Surgery Alone	Relative Risk (95% CI)		
Freedom from arrhythmia	48/97 (49.5%)	49/97 (50.5%)	RR, 0.13 (0.05–0.30)	High	1

Surgical Ablation Maze Plus Mitral Valve Surgery Versus Mitral Valve Surgery Alone for Atrial Fibrillation

Quality Assessment: Comparing Surgical Maze Plus Mitral Valve Surgery With Mitral Valve Surgery Alone

No. of Studies	Design	Limitations	Consistency	Directness	Other Considerations
Freedom from arrhythmia (Recurrence of AF at 12-month follow-up)					
2 (Vasconcelos et al, 2004 and Jessurun et al., 2003)	Randomized	No limitations	No important inconsistency*	No uncertainty	None

Summary of Findings

Outcome	No. of Patients		Effect	Quality	Importance
	Maze Surgery + Mitral Valve Surgery	Mitral Valve Surgery Alone	Relative Risk (95% CI)		
Freedom from arrhythmia	39/62 (62.9%)	23/62 (37.1%)	RR, 0.30 (0.11–0.79)	High	1

* Only 1 randomized controlled trial identified comparing surgical maze procedure with mitral valve surgery to mitral valve surgery alone; thus, it is not possible to assess consistency.

Microwave Ablation With Heart Surgery Versus Heart Surgery Alone for Atrial Fibrillation

Quality Assessment: Comparing Microwave Ablation Plus Heart Surgery With Heart Surgery Without Ablation in Patients With Drug-Refractory Atrial Fibrillation

No. of Studies	Design	Limitations	Consistency	Directness	Other Considerations
Freedom from arrhythmia (Recurrence of AF at 12-month follow-up)					
1 (Schuetz et al., 2003)	Randomized	No limitations	Important inconsistency (-1)*	No uncertainty	None

Summary of Findings

Outcome	No. of Patients		Effect	Quality	Importance
	Microwave Ablation and Heart Surgery	Heart Surgery but no Ablation Procedure	Relative Risk (95% CI)		
Freedom from arrhythmia	24/43 (55.8%)	19/43 (44.2%)	RR, 0.30 (0.13–0.70)	Moderate	1

* Only 1 randomized controlled trial was identified comparing microwave ablation to no ablation; therefore, consistency is difficult to assess.

Quality Assessment: Comparing Linear Atrial Cryoablation With Pulmonary Vein Cryoisolation in Patients with Drug-Refractory AF Requiring Additional Heart Surgery

No. of Studies	Design	Limitations	Consistency	Directness	Other Considerations
Freedom from arrhythmia (Recurrence of atrial fibrillation at a mean of 41 +/- 17 months follow-up)					
1 (Gaita et al., 2005)	Randomized	No limitations	Important inconsistency (-1)*	No uncertainty	None

Summary of Findings

Outcome	No. of Patients		Effect	Quality	Importance
	Linear Cryoablation of Left Atrium	Pulmonary Vein Cryoisolation	Relative Risk (95% CI)		
Freedom from arrhythmia	70/105 (66.7%)	35/105 (33.3%)	RR, 0.53 (0.39–0.73)	Moderate	1

* Only 1 randomized controlled trial was identified comparing LA cryoablation to PV cryoisolation; therefore, consistency is difficult to assess.

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