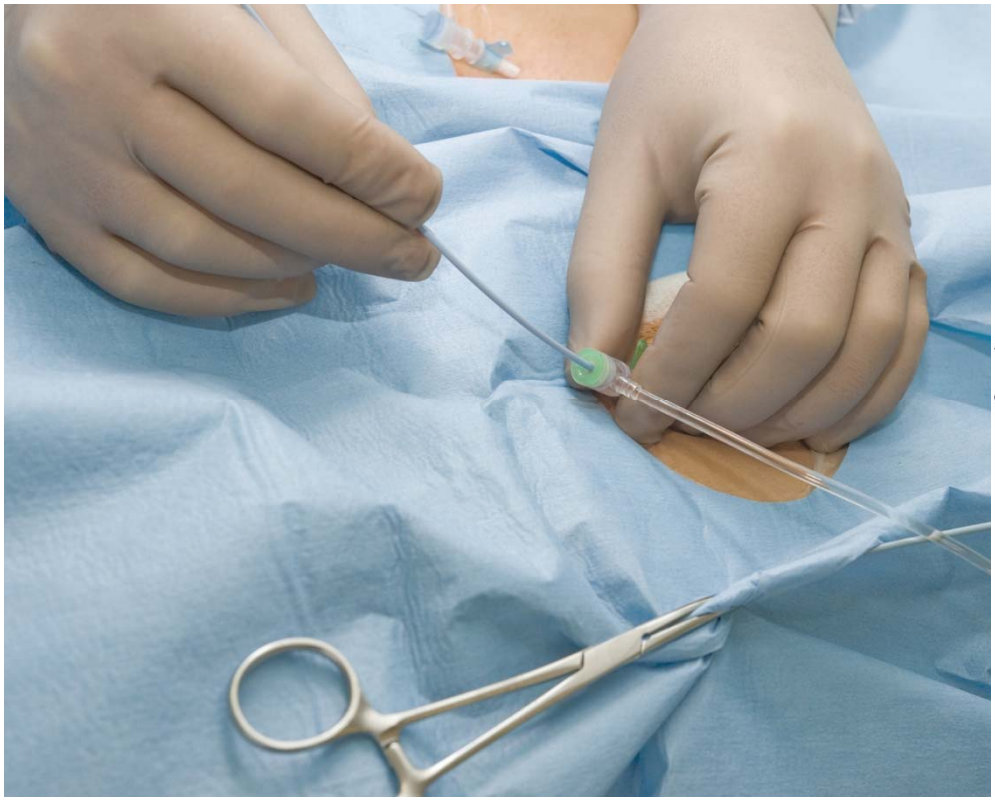
KCE REPORT 184C

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

CATHETER ABLATION OF ATRIAL FIBRILLATION



Belgian Health Care Knowledge Centre

The Belgian Health Care Knowledge Centre (KCE) is an organization of public interest, created on the 24th of December 2002 under the supervision of the Minister of Public Health and Social Affairs. KCE is in charge of conducting studies that support the political decision making on health care and health insurance.

Executive Board

	Actual Members	*Substitute Members*
President	Pierre Gillet	
CEO - National Institute for Health and Disability Insurance (vice president)	Jo De Cock	Benoît Collin
President of the Federal Public Service Health, Food Chain Safety and Environment (vice president)	Dirk Cuypers	Chris Decoster
President of the Federal Public Service Social Security (vice president)	Frank Van Massenhove	Jan Bertels
General Administrator of the Federal Agency for Medicines and Health Products	Xavier De Cuyper	Greet Musch
Representatives of the Minister of Public Health	Bernard Lange	François Perl
	Marco Schetgen	Annick Poncé
Representatives of the Minister of Social Affairs	Olivier de Stexhe	Karel Vermeyen
	Ri De Ridder	Lambert Stamatakis
Representatives of the Council of Ministers	Jean-Noël Godin	Frédéric Lernoux
	Daniel Devos	Bart Ooghe
Intermutualistic Agency	Michiel Callens	Frank De Smet
	Patrick Verertbruggen	Yolande Husden
	Xavier Brenez	Geert Messiaen
Professional Organisations - representatives of physicians	Marc Moens	Roland Lemye
	Jean-Pierre Baeyens	Rita Cuypers
Professional Organisations - representatives of nurses	Michel Foulon	Ludo Meyers
	Myriam Hubinon	Olivier Thonon
Hospital Federations	Johan Pauwels	Katrien Kesteloot
	Jean-Claude Praet	Pierre Smiets
Social Partners	Rita Thys	Leo Neels
	Paul Palsterman	Celien Van Moerkerke
House of Representatives	Lieve Wierinck	

Control

Government commissioner — Yves Roger

Management

Chief Executive Officer — Raf Mertens
Assistant Chief Executive Officer — Jean-Pierre Closon

Managers Program Management — Christian Léonard
Kristel De Gauquier

Contact

Belgian Health Care Knowledge Centre (KCE)
Doorbuilding (10th Floor)
Boulevard du Jardin Botanique, 55
B-1000 Brussels
Belgium

T +32 [0]2 287 33 88
F +32 [0]2 287 33 85
info@kce.fgov.be
http://www.kce.fgov.be

KCE REPORT 184C
HEALTH TECHNOLOGY ASSESSMENT

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

CATHETER ABLATION OF ATRIAL FIBRILLATION

HANS VAN BRABANDT, MATTIAS NEYT, CARL DEVOS

COLOPHON

Title:	Catheter ablation of atrial fibrillation
Authors:	Hans Van Brabandt, Mattias Neyt, Carl Devos
External experts:	Alessandro Cirrincione (Johnson & Johnson AGI Zwitzerland), Mattias Duytschaever (AZ Sint Jan Brugge),Patrick Galloo (Socialistische Mutualiteit), Sébastien Knecht (CHU Brugmann, Bruxelles), Georges Mairesse (Cliniques du Sud Luxembourg, Arlon), Karen Moeremans (IMS Health), Stelios Tsintzos (Medtronic), Stijn Van de Velde (CEBAMvzw), Thierry Verbeet (CHU Brugmann), Antonine Wyffels (INAMI – RIZIV)
External validators:	Johan De Sutter (UGent), Luc Jordaens (Erasmus MC Rotterdam), Stefan Sauerland and Stefan Lhachimi (Institute for Quality and Efficiency in Healthcare (IQWiG) Germany)
Conflict of interest:	Owner of subscribed capital, options, share or other financial instruments: Alessandro Cirrincione, Stelios Tsintzos Fees or other compensation for writing a publication or participating in its development: Georges Mairesse, Luc Jordaens A grant, fees or funds for a member of staff or another form of compensation for the execution of research: Luc Jordaens Consultancy or employment for an organisation that may gain or lose financially due to the results of this report: Alessandro Cirrincione, Antonine Wyffels, Luc Jordaens Payments to speak, training remuneration, subsidised travel or payment for participation at a conference: Georges Mairesse Any other direct or indirect relationship with a producer, distributor or healthcare institution that could be interpreted as a conflict of interests: Stelios Tsintzos
Layout:	Ine Verhulst
Disclaimer:	**The external experts were consulted about a (preliminary) version of the scientific report. Their comments were discussed during meetings. They did not co-author the scientific report and did not necessarily agree with its content.** **Subsequently, a (final) version was submitted to the validators. The validation of the report results from a consensus or a voting process between the validators. The validators did not co-author the scientific report and did not necessarily all three agree with its content.** **Finally, this report has been approved by common assent by the Executive Board.** **Only the KCE is responsible for errors or omissions that could persist. The policy recommendations are also under the full responsibility of the KCE.**

Publication date:	04 January 2013
Domain:	Health Technology Assessment (HTA)
MeSH:	Atrial fibrillation; Catheter ablation; Technology assessment, biomedical
NLM Classification:	WG 330
Language:	English
Format:	Adobe® PDF™ (A4)
Legal depot:	D/2012/10.273/57

How to refer to this document? Van Brabandt H, Neyt M, Devos C. Catheter ablation of atrial fibrillation. Health Technology Assessment (HTA). Brussels: Belgian Health Care Knowledge Centre (KCE). 2012. KCE Report 184C. D/2012/10.273/57.

This document is available on the website of the Belgian Health Care Knowledge Centre.

PREFACE

In the preface of our report on pacemaker therapy for bradycardia in Belgium, we discussed the instant and at times miraculous clinical results, where complaints promptly disappeared. A successful catheter ablation in patients who repeatedly or continuously suffer from palpitations as a result of atrial fibrillation tells a similar story. In fact, it is one of these procedures that will always fill both doctors and patients with enthusiasm as it is not dissimilar to taking a jerking, sputtering car to the garage and picking it up a day or two later, driving like a dream again. No psychosomatic issues, no hassle with sticking to therapies, but medicine in all its mechanistic glory, with full control.

There is no doubt that, when the procedure is a success, it is a fantastic, ingenious and clever feat of high technology. All the more so when it produces lasting results and patients no longer have to continuously take antiarrhythmic drugs. If a one-off, albeit expensive, procedure can help patients remain complaint-free for life, the expense would indeed seem warranted.

That having been said, no procedure is 100% effective. At that, the initially high expectations tend not to be fully met. Indeed, as this has been seen on more than a few occasions, it no longer comes as a surprise of course. The question is therefore not *whether* there is a risk of failure or complications but *what the incidence rate of these failures or complications is.* And here also, all too often a similar pattern emerges. The studies published originally are far more positive than their subsequent and unpublished counterparts; studies that fall short on methodology are more positive than the high-quality ones; figures from actual, daily practice are not as glowing as the clinical trials would lead us to believe. Another classic feature is that the technology has become widely used without the long-term effects being known, let alone having been proven.

The KCE was approached with the request to objectify matters a little, on the basis of (the rather scarce) literature and the (fairly inaccurate and limited) Belgian data. All we can do for our part is hope that all these research efforts will contribute to a serene and responsible debate, one that looks beyond the poorly documented clinical impressions and the slogan-filled language in the media. A 100% success rate will probably be a lot to ask for. Yet, that won't be for the lack of effort the many people who contributed to this study put in: the clinical experts, the people validating the information, our colleagues from the IMA, for it is to them we are indebted.

Jean-Pierre CLOSON
Deputy General Manager

Raf MERTENS
General Manager

SUMMARY

ATRIAL FIBRILLATION

Atrial fibrillation (AF) is a common form of cardiac arrhythmia marked by an irregular and mostly too fast heartbeat. Its prevalence increases with age. 5 to 15% of over-eighty-year-olds have been diagnosed with AF. AF may occur periodically and can last minutes, hours or a number of days and spontaneously disappear before reappearing again at a later stage. This is known as *paroxysmal* AF. If the bouts of AF last longer than seven days, the condition is referred to as *persistent* AF. In some people, the condition may persist for ever, in which case we talk about *permanent* AF.

Some people have no complaints whatsoever when they develop AF, others complain of palpitations or shortness of breath. AF is treated by means of antiarrhythmic agents (referred to as “rhythm-control strategy”) or by means of a drug that ensures that the heart rate does not become excessively high (known as “rate-control therapy”). Rhythm-control aims to prevent the occurrence of AF, yet in that respect, antiarrhythmic therapy does not seem all that effective. Luckily enough, in most patients, rate-control therapy keeps the symptoms under control.

The greatest risk associated with AF is that patients might suffer a stroke. This is most prevalent in older patients and patients suffering from additional heart conditions such as heart failure. With the help of antithrombotic medication, this risk can be significantly reduced.

CATHETER ABLATION FOR ATRIAL FIBRILLATION

Treating atrial fibrillation by means of catheter ablation entails inserting a catheter via the groin, to “burn” certain zones in the left atrium to ensure that the abnormal electrical impulses from the pulmonary veins, which cause AF, are no longer transmitted. Catheter ablation for AF is a complex procedure that requires a high level of expertise from the medical team. Life-threatening complications may arise in 1 to 3% of cases. Less serious complications, requiring admission to hospital or surgical intervention, have been reported in 5% of cases.

There are various types of ablation catheters on the European market, using different forms of energy. The most commonly used physical principles are radio frequency waves and freezing, known as cryoablation.

OBJECTIVES

The object of the present report is to assess the efficacy and effectiveness of treating atrial fibrillation by means of catheter ablation, based on international scientific literature. The report also contains a literature review and an assessment of the health economic evaluations published on this topic to date. It furthermore features an analysis of Belgian AF catheter ablation practice and the cost involved.

The aim of the present report is to arrive at recommendations that can help optimise the use of catheter ablation for AF in Belgium.

CLINICAL EFFECTIVENESS

Randomised controlled trials (RCTs) have demonstrated that, in the short term, catheter ablation in selected AF patients can be more effective than antiarrhythmic therapy. Here we are talking about patients aged between 50 and 60 years, with few or no associated structural heart problems who, in spite of being on medication, remain highly symptomatic. In these RCTs, AF following catheter ablation reoccurred in 11 to 34% of patients diagnosed with paroxysmal AF and in 20 to 44% of patients suffering from non-paroxysmal AF. The chances of AF reoccurring in patients on antiarrhythmic therapy range between 63 and 84%, and 42 and 91% respectively. Based on observational studies, it is presumed that, one year after the index procedure, 6 to 9% of patients suffer a relapse every year. There are no data available as regards the effectiveness of the procedure after more than 5 years.

Up and until now, RCTs have only demonstrated that catheter ablation is more effective in terms of reducing the chances of AF reoccurring than antiarrhythmic therapy. There is no conclusive evidence to suggest that ablation has an impact on any other hard relevant endpoints such as mortality or the risk of patients suffering a stroke.

In as yet unpublished RCTs on patients at higher risk of thromboembolic complications than in the RCTs run earlier, or in patients who underwent an ablation as first-line treatment, catheter ablation seems to be less effective than earlier trials indicated.

As yet unpublished RCTs furthermore bring to light that a number of newly developed AF ablation catheters give rise to serious safety concerns, in spite of the fact that they have been awarded the CE mark.

BELGIAN PRACTICE

Between 2008 and 2010, the number of catheter ablations for AF performed in Belgium more than doubled, rising from 993 to 2,064 a year. The procedure is performed in 30 Belgian hospitals. During 2011, 18 hospitals each performed at least 50 AF ablations, while another 6 centres carried out more than 100 procedures during that same year.

In 2008, the average cost of catheter ablation for AF was €9 600 for the initial procedure.

77.3% of these patients were treated for paroxysmal AF and 22.7% for non-paroxysmal AF. We calculated that up to 15.8% of these patients underwent ablation as first-line treatment, i.e. without having been put on antiarrhythmic or rate-control therapy first.

We used 3 parameters from our administrative database to assess whether AF reoccurred following ablation: the fact whether the procedure was repeated, whether electrical cardioversion was required or whether antiarrhythmic agents were prescribed afterwards. On the basis of these parameters, we noticed that, following a single ablation, AF reoccurred in 37.3 to 59.8% of patients after one year and in 49.9 to 65.9% of patients after two years. These figures are higher than those observed in the RCTs, but they are in line with the (broad) estimates of the reoccurrence of AF in the observational studies.

COST EFFECTIVENESS

The initial cost of catheter ablation for AF is high (€9 600). Published economic evaluations mainly assume that ablation has an impact on the risk of heart failure and/or on quality of life one year after the procedure. However, there is no hard evidence to corroborate these assumptions. There is a lack of soundly underpinned information about relevant endpoints such as quality of life (measured by means of a generic utility questionnaire), mortality, heart failure, side effects, etc. On account of these imponderables it is difficult, not to say impossible, to assess the cost effectiveness of this procedure.

CONCLUSION

AF patients may continue to suffer unpleasant symptoms in spite of the fact that they have been prescribed a suitable drug therapy. For some of these patients, catheter ablation as an alternative treatment is currently recommended. RCTs have brought to light that the chance of a successful outcome in the short term is greatest when the procedure is performed by experienced teams on rigorously selected paroxysmal AF patients with no or minimal underlying heart disease. Although it would be fair to expect that the procedure would benefit patients for a number of decades, there are no data about the procedure's lasting effects five years down the line. The present Belgian study has shown that more than half of patients suffer an AF relapse after 1 to 2 years.

Catheter ablation for AF is a complex procedure that entails a risk of patients suffering life-threatening complications running into a couple of percentage points.

Patients for whom catheter ablation is considered to be an option should be clearly informed about the uncertainties surrounding the potential benefits and about the risks inherent to the procedure.

So far, there is no hard evidence as to the cost effectiveness of catheter ablation for AF.

RECOMMENDATIONS[a]

To the Minister, on the advice of the Insurance Committee

- **The KCE recommends that catheter ablation for atrial fibrillation (AF) reimbursement should henceforth be limited to patients suffering from paroxysmal AF with no or minimal structural heart disease and who feel that their symptoms could not be sufficiently controlled by means of prior therapy with antiarrhythmic and rate-control drugs.**
- **It would be wise to restrict the performance of the procedure itself to doctors and centres with sufficient experience. As a guideline we would recommend that only centres where catheter ablations on at least 50 different patients a year were performed over the past 3 years should be retained.**
- **For other forms of AF, or as first-line treatment for any type of AF, catheter ablations should only be performed within the framework of a randomised trial.**
- **This amended reimbursement should be reviewed on the basis of the results of a new study that should be carried out by the "College of Physicians" in collaboration with the sickness funds. The latter can request clinical patient data via their advisory physicians. The protocol of this particular study should be validated by the KCE. The objective of this study would be to gain an up-to-date insight into the effectiveness of catheter ablation in function of patients' profiles, the type of AF, the technology used, the medication taken prior to and after the procedure, the clinical indications for the use of this medication and the immediate and delayed complications of the procedure.**

To the National Body for Quality Promotion

- **The KCE recommends that, in collaboration with the College of Physicians, the Belgian Heart Rhythm Association (BeHRA), and independent patients' representatives, an information brochure should be compiled which tells patients about the advantages and the disadvantages of the procedure. It must be made compulsory to furnish patients with this brochure and to discuss its content with them before a decision to opt for catheter ablation is taken.**

[a] The policy recommendations are under the full responsibility of the KCE

To the European Health Authorities

- **In respect of catheters and accompanying equipment – such as innovative high-risk devices – the European bodies should not only demand that safety and performance data on devices are furnished but also that their clinical effectiveness is demonstrated before these devices become widely used in daily practice.**
- **An improved registration of RCTs should be pursued and the results of these RCTs should be published timely and in a transparent fashion.**

Recommendations for further investigation

- **RCTs are needed to compare catheter ablation with rate control drugs. Crossovers to catheter ablation in the course of the study should be avoided. Information about patient-relevant endpoints (mortality, quality of life measured with a utility instrument, stroke and other side effects) should be compiled in the course of these.**

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

Abbreviation	Definition
AAD	antiarrhythmic drug
ACC	American College of Cardiology
AF	atrial fibrillation
AHA	American Heart Association
AIM	Agence Intermutualiste
AR	Absolute Risk
ARR	Absolute Risk Reduction
AV node	atrioventricular node
BeHRA	Belgian Heart Rhythm Association
CA	catheter ablation
CADTH	Canadian Agency for Drugs and Technologies in Health
CA-AF	catheter ablation of atrial fibrillation
CCP	Cardiac Care Program
CDSR	Cochrane Database of Systematic Reviews
CEA	Cost-Effectiveness Analysis
$CHADS_2$ acronym	Cardiac failure, Hypertension, Age ≥75 years, Diabetes, prior Stroke
CHD	Coronary Heart Disease
CRD	Centre for Reviews and Dissemination
CT	Computed tomography
CUA	Cost-Utility Analysis
CVD	Cardiovascular Disease
DM	Diabetes mellitus
ECG	Electrocardiogram
EF	Ejection Fraction
EP	Electrophysiological
EPS	Electrophysiologic Study
EPT	Electrophysiological testing

ESC	European Society of Cardiology
FDA	US Food and Drug Administration
GP	General Practitioner
HF	Heart Failure
HIFU	High-intensity focused ultrasound
HR	Hazard Rate
HR-QoI	Health-Related Quality of Life
HT	Hypertension
HTA	Health Technology Assessment
ICE	Intracardiac echography
ICER	Incremental cost-effectiveness ratio
ICER	Institute for Clinical and Economic Review
ICH	Intracranial haemorrhage
IMA – AIM	Intermutualistisch Agentschap – Agence intermutualiste
INAHTA	International Network of Agencies for Health Technology Assessment
INR	International normalized ratio
ITT	Intention to treat
LACA	Left atrial catheter ablation
LVEF	Left Ventricular Ejection Fraction
LYG	Life-Years Gained
MI	Myocardial Infarction
NHS	National Health System
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Clinical Excellence
NIHDI	National Institute for Health and Disability Insurance (= RIZIV – INAMI)
NNT	Number Needed to Treat
NSR	Normal sinus rhythm
NYHA	New York Heart Association

OAC	Oral anti-coagulation
PV	Pulmonary vein
QALY	Quality-Adjusted Life Year
QoL	Quality of Life
RCT	Randomized Controlled Trial
RF(C)A	Radiofrequency (catheter) ablation
RIZIV – INAMI	National Institute of Health and Disability Insurance (Rijksinstituut voor Ziekte en Invaliditeits Verzekering - Institut national d'assurance maladie - invalidité) (= NIHDI)
RR	Relative Risk
RRR	Relative Risk Reduction
SCD	Sudden Cardiac Death
SR	Systematic Review
TIA	Transient ischemic attack
VASc acronym	Vascular disease, Age from 64-74, Sex category

SYNTHESIS

1. OBJECTIVES

The objective of the present report is:

- to assess the safety and efficacy/effectiveness of treating atrial fibrillation by means of catheter ablation, based on international scientific data and evaluations;
- to assess Belgian catheter ablation practice and the costs involved;
- and to review the cost-effectiveness literature.

The goal is to formulate recommendations that could optimise the use of catheter ablation for atrial fibrillation in Belgium.

2. INTRODUCTION

2.1. Atrial fibrillation

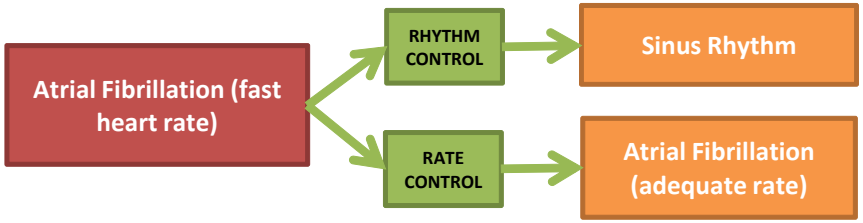
Atrial fibrillation (AF) is a common heart rhythm disorder (arrhythmia) characterised by a heartbeat that is irregular and too fast. In normal conditions, the heartbeat is determined by an electrical impulse that originates from the sinus node, a group of cells located in the right atrium of the heart. This normal heart rhythm is known as the sinus rhythm. In patients suffering from AF, the heartbeat is no longer driven by the sinus node but by abnormal impulses originating in the wall of the pulmonary veins, close to their entry into the left atrium of the heart. AF may occur in people with no other heart problems, but it is also commonly seen in patients suffering from other conditions such as high blood pressure, ischemic heart disease, heart valve disease and heart failure. The prevalence of AF increases with age. Less than 0.5% of people under the age of 50 suffer from AF, while 5 to 15% of over-eighty-year-olds have been diagnosed with AF.

AF may occur periodically and can last minutes, hours or a number of days and spontaneously stop before reappearing later on. This is known as *paroxysmal* AF. If the bouts of AF last longer than seven days, the condition is referred to as *persistent* AF. If the AF is lasting more than 1 year, and it is decided to still adopt a rhythm control strategy, the AF is called *long-standing persistent*. In some cases, the condition persists forever and treatment is no longer aimed at rhythm control, in which case it is referred to as *permanent* AF.

Some patients have no direct complaints when they develop AF, others complain of palpitations, being short of breath or of tiring easily. In some cases AF may lead to heart failure. The most dreaded complications of AF are thrombo-embolic events, particularly stroke. In AF, stroke is caused by blood clots that have formed in the left atrium coming loose and being carried along by the blood supplying the brain where they block an artery. This is most commonly seen in people over the age of 65 or in people suffering from an underlying heart condition. Therefore, these high-risk patients are treated with anticoagulants ("blood thinners").

Aside from being prescribed anticoagulants to prevent thrombo-embolic complications, AF patients are also treated with medication that targets the arrhythmia itself. There are two distinct management strategies: "rhythm control" and "rate control" (Figure I). *Rhythm control* aims to reverse AF back to normal sinus rhythm, traditionally by means of antiarrhythmic agents such as flecainide, propafenone, cibenzoline or amiodarone. *Rate control*, on the other hand, ensures that the heart rate does not become excessively fast even though the AF continues to exist. These patients are commonly prescribed beta-blockers, digitalis or specific calcium antagonists. Several randomised clinical trials have shown that rate control is sufficient to prevent the symptoms in most patients with AF. Furthermore, rate-control medication is easier to manage and has fewer side effects than the drugs prescribed for rhythm control. The latter medication is therefore essentially indicated for patients who continue to experience symptoms even when they are following an adequate rate control therapy.

Figure I – Management of atrial fibrillation



Usually the heart rate is inappropriately fast in patients with AF. With a rate control management, the heart rate becomes adequately controlled while the AF as such remains.

2.2. Atrial fibrillation ablation

AF ablation is a management strategy for AF aimed at rhythm control. It has been first implemented by cardiac surgeons in patients with AF undergoing surgery for other cardiac conditions. The original procedure consisted of making incisions in certain areas of the atria, thus blocking electrical circuits needed to initiate or sustain AF. The better understanding of the pathophysiology of AF led to the improvement and simplification of the surgical technique. Nowadays, the surgical procedure is still in use and can be accomplished through a thoracoscopic approach on a beating heart. In parallel with the advances of surgical ablation, electrophysiologists introduced less invasive catheter based approaches with the same aim of interrupting electrical currents involved in AF. Surgical ablation is beyond the scope of the present report that will focus on catheter ablation.

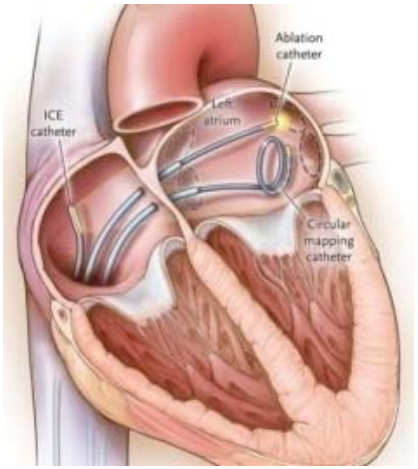
3. CATHETER ABLATION OF ATRIAL FIBRILLATION: TECHNOLOGY DESCRIPTION

Catheter ablation (CA) of AF involves the introduction of one or more catheters into the left atrium of the heart. This can be reached via the venous system and requires a puncture through the inter-atrial septum, guided by radioscopic control (Figure II). It may take several hours to complete the procedure. The aim is to “burn” the inner surface of the left atrium surrounding the mouth of the pulmonary veins to ensure that the electrical impulses from the pulmonary veins, which cause AF, are no longer transmitted. This electrical conduction may however reappear after a first ablation necessitating a repeat procedure after a number of weeks or months. Sometimes, (during a second or subsequent procedure) other zones in the left atrium may have to be ablated to cure AF.

Catheter ablation of AF is a complex procedure that is performed under radioscopic control, usually under general anaesthesia. On account of the fact that one or more catheters are inserted into the heart via the veins and that the interatrial septum must be penetrated to reach the left atrium, the procedure is not devoid of risk and requires outstanding expertise by the person who performs it.

There are various types of ablation catheters on the European market, with different forms of energy to perform the ablation. The most commonly used physical principles are radiofrequency waves and freezing (cryoablation) but certain techniques use laser beams or ultrasound as energy source.

Figure II – Positioning of catheters in the heart during catheter ablation



ICE: intracardiac echography. Source: Wazni, New England Journal of Medicine, 2011, 365 (24):2296-304.

4. THE EFFECTIVENESS OF CATHETER ABLATION OF ATRIAL FIBRILLATION

4.1. Literature search procedure

We conducted a systematic literature review to try and answer the question: “In patients suffering from atrial fibrillation, what is the effect of catheter ablation in comparison to medical therapy, on heart rhythm, symptoms and quality of life, the occurrence of complications and on survival?” We found 9 randomised controlled trials (RCTs), published from 2003 to 2011.

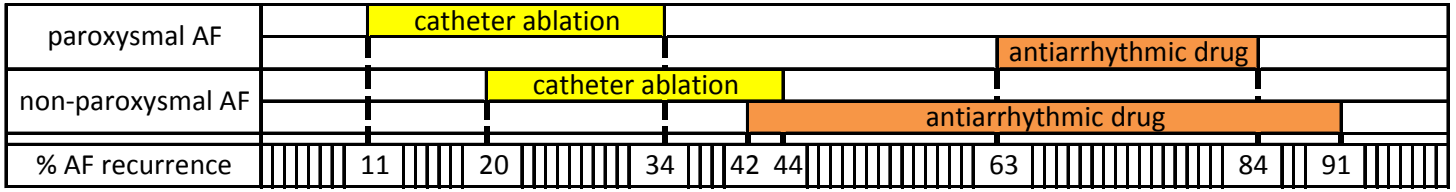
We also identified two recent systematic reviews and three recent HTA reports (Canada, US, Sweden). All of them included the same major RCTs from our search.

4.2. Clinical effectiveness of catheter ablation of AF

In the published RCTs, 971 patients presenting with AF and with a mean age between 51 and 62 years, were randomised between catheter ablation and medical therapy. In all but one study, medical therapy in the control group consisted of an antiarrhythmic drug, whereas in one, drug therapy was directed to rate control. All the trials were open label and relatively small (n=30 to 198) and they all used radiofrequency waves as energy source. A comparison between the trials is difficult because of differences in patient profiles, ablation techniques and definitions of endpoints. Furthermore, in some of the trials cross-over of patients between study arms or a second ablation attempt were accepted. In general, the primary endpoint of the RCTs was to check for the reoccurrence of (symptomatic or electrocardiographic) AF. The follow-up period typically was 1 year, which is too short a period of time to estimate the effect of hard and relevant endpoints such as stroke or death. Because of the heterogeneity between trials, we considered pooling of the results of the separate RCTs in a meta-analysis inappropriate.

These RCTs showed that AF recurred within one year in 11 to 44% of patients who had undergone ablation, versus in 42 to 91% of patients who had been treated with an antiarrhythmic agent (Figure III). Recurrence rates after CA were lower in patients with paroxysmal AF (11 to 34%) than in those with non-paroxysmal AF (20 to 44%).

Figure III – Recurrence rates of AF after catheter ablation and antiarrhythmic drug treatment from published RCTs.



Scale from 0 to 100%; AF recurrence expressed in % within 1 year after ablation, taking into account a blanking period of 1 to 3 months. In some of the trials (see text for details), cross-over from one study group to the other was allowed.

As far as the long-term effects of catheter ablation are concerned, we have to base ourselves on observational studies which, on account of their methodological limitations, are less reliable. These studies also show a marked variability in the reported success of catheter ablation. When looking at the larger studies of patients with paroxysmal AF, recurrence rates vary from 22 to 53% within five years after a single ablation without taking any further antiarrhythmic medication. In patients treated for non-paroxysmal AF, this figure ranges between 33 and 71%. Data from observational studies suggest that hospital experience in performing catheter ablation of AF is independently related to outcome in terms of success rates, procedural complications and re-hospitalisations.

When looking at the effects of a successful catheter ablation on patients' quality of life, there are indications that patients with clear symptoms of AF experience an improvement in their condition, at least in the short term. In the long run, the evidence is weaker because of the small number of patients included in the trials and the high cross-over rate.

4.3. Results of as yet unpublished clinical studies

In the course of our literature review, we discovered unpublished trials that compare catheter ablation with medical therapy and from which preliminary data are available through congress proceedings (see text box). In the full text version of the present report, we discuss these studies in detail. The effect of catheter ablation on AF recurrence in these trials is much less prominent than in the earlier trials, both in patients at high risk for future events as in patients with paroxysmal AF in whom catheter ablation is used as a first line treatment (i.e. before a tryout with drugs).

1. In the STOP-AF trial (Sustained Treatment of Paroxysmal Atrial Fibrillation), cryoablation (freezing) is compared to ablation that makes use of radiofrequency energy.
2. The Medical Anti-Arrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation (MANTRA-PAF) trial investigates catheter ablation as a first line treatment for paroxysmal AF.
3. The RAAFT-2 trial (Radiofrequency Ablation versus Antiarrhythmic drugs as First-line Treatment of symptomatic atrial fibrillation) also studies radiofrequency ablation as a first-line treatment for paroxysmal AF.
4. The CABANA pilot trial (Catheter Ablation versus Anti-arrhythmic Drug Therapy for Atrial Fibrillation) studies radiofrequency ablation in patients with AF who are at a higher risk for future events than in earlier RCTs.

5. THE SAFETY OF CATHETER ABLATION OF ATRIAL FIBRILLATION

Catheter ablation of AF is a complex procedure requiring high technical skills from the interventional cardiologist. Severe complications have been reported in up to 3% of cases and include death (0 to 0.24%), heart tamponade (0.78 to 2.79%) and transient ischemic attack or stroke (0.22 to 0.94%). There is also an additional risk of up to 5% less severe complications, some of which however requiring hospitalisation or surgical correction.

Patients undergoing a catheter ablation are exposed to X-rays for a protracted period of time. Effective radiation doses between 1.10 and 27.25 milliSievert per ablation procedure are reported, which corresponds to the doses a person would be subjected to when undergoing 50 to 1350 chest X-rays. From these numbers, a fatal malignancy risk attributable to X-ray exposure has been estimated to be between 0.2 to 2.1 pro mille per procedure.

An unexpectedly high complication rate of catheter ablation of AF has been documented in some as yet unpublished randomised trials in which new ablation devices were tested (see text box). Notably, these devices had already been granted the European CE label years before randomised trial evidence brought to light their safety problems.

1. The TTOP-AF study (Tailored Treatment of Permanent Atrial Fibrillation) studied a specially designed radiofrequency catheter (Medtronic Ablation Frontiers Cardiac Ablation System®) which facilitates the ablation of a relatively large area in one single application. This catheter received the European CE mark in December 2006. However, the TTOP-AF study showed that this type of catheter was flawed with a safety problem. 17 in 138 patients (12.3%) suffered serious complications among which 1 death, 4 strokes and 2 cases of cardiac tamponade.
2. The MACPAF trial (Mesh Ablator versus Cryoballoon Pulmonary Vein Ablation of Symptomatic Paroxysmal Atrial Fibrillation) compared cryoablation to a specific type of radiofrequency catheter, the Bard Mesh Ablator®, which has been carrying the CE mark since 2006. The trial was concluded early because of the 15 patients who had been treated with the Mesh ablator, not one had been treated successfully.
3. In 2010, the results of a German trial were published, in which ablation was performed by means of ultrasound (high intensity focused ultrasound or HIFU (ProRhythm Inc.), with an instrument that had been awarded the CE mark in 2005. The trial itself was discontinued early because 8 of the 28 patients (28.6%) had suffered serious complications among which 2 deaths and 1 stroke.

A cautionary note is needed on the very high rate in RCTs of cross-over of patients initially allocated to drug treatment, towards catheter ablation. In one trial, 77% of patients crossed over to ablation by one year. In the 4 year follow-up results of another trial, every patient who initially was allocated to drug treatment and subsequently developed AF recurrence, crossed over to catheter ablation. Although cross-over of patients from one study arm to another may dilute the presence or absence of an effect of an interventional procedure, it may also mask a difference in the occurrence of adverse events in an intention to treat analysis. This is no trivial matter when comparing an invasive procedure that is accompanied with up to 3% life threatening complications, with drug treatment in which severe adverse events very rarely occur.

6. CATHETER ABLATION OF ATRIAL FIBRILLATION IN BELGIUM

6.1. Introduction

On 1 November 2007, a reformed electrophysiology nomenclature came into effect which, in greater detail than before, assigned a nomenclature code to every type of CA intervention. For the first time, it also provided a fixed reimbursement amount to cover the cost of the devices used. The number of catheter ablations of AF in Belgium doubled from 993 in 2008, to 2 064 in 2010. In 2008, 5.2 million euro was spent on AF ablations (only taking into account the electrophysiologists' fees + catheter material). This figure rose to 8.5 million euro in 2009 and to 12.5 million euro in 2010.

Over the years 2009-2011, 30 Belgian hospitals performed at least one catheter ablation of AF. In the year 2011, 18 hospitals performed at least 50 AF ablations, and 6 did more than 100 such procedures.

In order to assess Belgian practice of catheter ablation of AF, we obtained information from the InterMutualistic Agency (Intermutualistisch Agentschap/Agence Intermutualiste – IMA - AIM) database about patients who underwent a catheter ablation for AF between 1 November 2007 and 31 December 2008. Two year follow up data were available for all patients, with an average observation period of about 30 months.

6.2. Belgian data

We identified 830 patients (median age 59 years; 71.9% men) who underwent a first AF ablation from November 2007 to December 2008. Prior to the ablation, 148 (17.8%) patients had been following a maintenance therapy with anticoagulants; after the ablation this figure dropped to 88 (10.6%). Following ablation, 62% of patients still used, at least temporarily, an antiarrhythmic agent (amiodarone, flecainide, propafenone or cibenzoline).

84.2% of patients were treated with amiodarone or sotalol or a combination of an antiarrhythmic drug and a rate control drug before they underwent their first ablation, indicating that up to 15.8% of patients underwent catheter ablation as a first line therapy of AF.

134 patients (16.0%) underwent a second ablation during the first year following the index procedure. Over an average observation period of 30 months, 220 patients (26.5%) underwent more than 1 ablation, which boils down to an average of 1.3 ablations per patient.

The cost for a catheter ablation for AF from the perspective of the health care payer (government and patient) on average amounted to about €9 550 for the initial intervention. The yearly cost of a treatment of atrial fibrillation with rate and rhythm control drugs is about 300 euro per year.

Data from the voluntary BeHRA register (with most of the Belgian centres included) related to 5 546 patients treated from 2008 to 2011 reveal that 77% of them were treated for paroxysmal AF and 23% for non-paroxysmal AF.

Complications suffered following an ablation cannot be reliably checked on the basis of the administrative IMA data. The BeHRA register mentions a complication rate of 2.3% on a total of 5 932 cases. This figure compares to the rate of 2.8% life-threatening complications reported in a recent European survey.

6.3. Assessment of the clinical effectiveness of AF ablation in Belgium

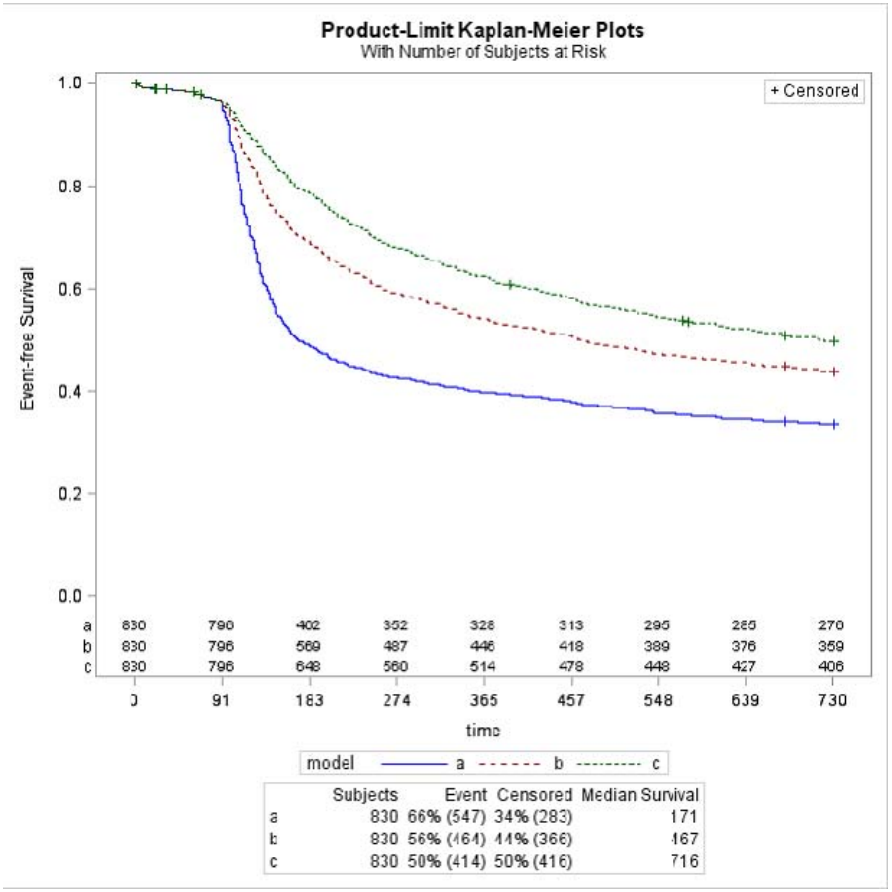
We do not have clinical data at our disposal which would allow us to precisely calculate in how many patients an ablation was successful, i.e. the number of patients that became free from AF. We do however have some administrative data that allow us to broadly estimate this.

First, we considered a redo ablation as a failure of the index procedure, assuming that an electrophysiologist would not decide to go for a second procedure if he were not convinced that the first intervention was unsuccessful. Next we took into consideration a blanking period of 3 months, a time window traditionally accepted as a period during which the ablation scar has to heal and where recurrent AF is not considered a failure of the procedure. If a patient underwent an electric cardioversion, or continued to use an antiarrhythmic drug beyond the blanking period, we also considered the index procedure having failed. When taking these considerations into account we ended up with an estimate of the recurrence of AF after a single catheter ablation one year after the index procedure in 59.8% of patients. After two years, this figure was 65.9%.

Some physicians and/or patients might prefer “to play it safe” and choose to continue prescribing/taking an antiarrhythmic agent even though the patient no longer has any complaints. It has also been argued that patients may respond better to an antiarrhythmic drug following ablation, even though the drug proved to be ineffective before. Therefore, we considered two additional models, more optimistically favouring ablation, to estimate recurrence rates. In one, ablation was considered having failed only if we could demonstrate that antiarrhythmic drug use occurred after a drug-free period of at least 1 month beyond the blanking period. Another model was constructed where this additional drug-free month was not considered for amiodarone. These two less conservative models led us to estimate AF recurrence in 37.3 and 45.5% of patients. After two years, these figures were 49.9, 55.9%.

The Kaplan-Meier time-to-event analyses of the abovementioned models are displayed in Figure IV.

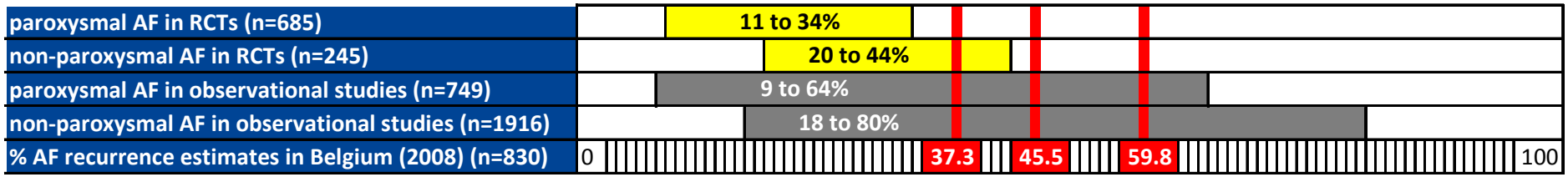
Figure IV - Kaplan-Meier curves of time to AF recurrence according to 3 different models



In model a (blue bottom line), AF recurrence is considered in case of a redo ablation (anytime), or cardioversion or the use of an antiarrhythmic drug beyond a blanking period of 3 months. In model c (green top line), recurrence is considered in case of a redo ablation (anytime), a cardioversion beyond the blanking period of 3 months, or the use of an antiarrhythmic drug after a drug-free window of at least one month beyond the blanking period. In model b (red intermediate line) this additional drug-free month was not considered for amiodarone.

The 1-year estimates from Belgian practice are schematically depicted in Figure V, where they are compared with recurrence rates observed in RCTs (extracted from Figure III) and reported in observational studies.

Figure V – Short term recurrence rates of AF after catheter ablation from literature and estimates of recurrence in Belgian patients (2008).



Scale is from 0 to 100%. In some of those RCTs, cross-over to AAD in the ablation group was allowed per study protocol. Observational data are extracted from a systematic review by Viles-Gonzales et al. and contain studies with a follow-up from 6 to 18 months reporting recurrence rates "off-AADs". Pooling of the results of the separate studies in a meta-analysis was considered inappropriate because of substantial clinical heterogeneity between them. Red vertical bars indicate the estimate of recurrence of AF from different models, one year after a single AF ablation executed in Belgium in the year 2008.

7. ECONOMIC EVALUATION OF CATHETER ABLATION

During our literature search for economic evaluations we identified several analyses. The models by and large assume that catheter ablation leads to a reduction in the number of strokes (and consequently indirectly to a drop in mortality) and/or a long-term improvement in patients' quality of life. However, there is currently no hard evidence to support these assumptions.

Assumptions in the economic models related to the use of drugs (and the related side effects, impact on quality of life and costs) seem to be optimistic in comparison to what has been observed in more recent literature and in Belgian practice where we have shown that the use of antiarrhythmic agents following ablation is particularly high. Aside from the possibility that this might be an indicator of the success or failure of the ablation, it does have an impact on the health economic evaluation. The published models do in fact take into account the lack of need for antiarrhythmic agents following ablation and the disappearance of side effects and their ensuing costs.

The impact on the quality of life has not been measured in any randomised trial by means of a generic utility instrument. As a result, the models had to resort to extra assumptions to translate the improvement in the quality of life into utilities, which are required when performing economic evaluations. This creates even more uncertainty in the analyses. Moreover, the impact on the quality of life has been modelled via the (undemonstrated) effect on strokes and via the (overly optimistic) disappearance of side effects that accompany the use of certain medication.

The lack of sound information on the relevant endpoints such as quality of life (measured by means of a utility instrument), mortality, stroke, side effects, etc. means that calculating the cost-effectiveness is associated with major uncertainties. The assumptions being modelled qualify the result. Hard evidence on these patient-relevant endpoints is needed to estimate the intervention's cost-effectiveness.

Considering these elements, we decided not to model the cost-effectiveness of catheter ablation of AF, due to a lack of hard evidence on these outcomes.

8. ORGANISATIONAL ISSUES

Catheter ablation is a complex procedure that requires a combination of dexterity and mastery of complex tools and technologies, and teamwork. Observational data suggest that hospital experience is independently related to outcome in terms of therapeutic success and procedural complications. The most recently published international consensus statement assigns a class IA recommendation only to catheter ablation for paroxysmal AF and only conditional to the fact that the procedure is "performed by an electrophysiologist who has received appropriate training and is performing the procedure in an experienced centre". Of the 30 centres where catheter ablation for AF is performed in Belgium in 2011, 12 performed less than 50 such procedures a year.

It is not clear how many procedures would be required per year for a centre to qualify as being "experienced" or "high volume". As an example, the European Society of Cardiology's Observational Research Programme defines hospitals "with a medium to high expertise" as those performing ≥50 AF ablations per year.

9. CONCLUSION

Catheter ablation for atrial fibrillation is a complex and expensive procedure, and its use in Belgium is rapidly increasing over the last years, with more than 2 100 such procedures performed in 2011 in 30 different centres.

Randomised clinical trials have revealed that the probability that strictly selected patients remain free from AF one year after a single radiofrequency ablation ranges between 55 and 90%. In experienced hands, the success rate is highest in patients suffering from drug-refractory symptomatic paroxysmal AF who have no structural heart disease.

A conservative estimate of the outcome of the procedure as it is currently practised in Belgian hospitals, shows that within two years after the ablation, half of the patients suffer a relapse. These performance estimates are inferior to those observed in RCTs, but they are contained within the wide estimates of AF recurrences from other observational studies. In the Belgian AF ablation population, almost a quarter of patients had non-paroxysmal AF, an estimated 15% of them did not go through a tryout with drugs before proceeding to ablation, and 12 out of the 30 centres applying this technique, performed less than 50 AF ablations in 2011.

From observational data, experts estimate that beyond one year after the index procedure, AF relapses in 6 to 9% of patients each year. Yet, there are almost no data on the effectiveness beyond 5 years. Neither are hard data available on the impact of catheter ablation on relevant endpoints such as quality of life, mortality, and stroke. Hence, it was not possible to make a reliable estimate of the cost-effectiveness of the procedure.

The procedure itself is not devoid of risks. It has a mortality rate of 1.5 per thousand, and serious, life-threatening complications such as cardiac tamponade or stroke occur in 1 to 3% of the cases. Added to this is the substantial exposure to radiation, estimated to be equivalent to 50 to 1350 chest X-rays, with a risk of cancer death of 0.2 to 2.1 per thousand ablations.

The performance of cryoablation is similar to that of radiofrequency ablation, according to a number of (as yet unpublished) randomised trials. Of note, there have been serious problems with some other newly developed ablation devices which, notwithstanding their CE labelling, ultimately turned out to perform poorly, both in terms of safety as in terms of efficacy.

The cost of the procedure is close to €10 000, and in 2010, over 12 million euro were spent for AF ablations.

In August 2012, an update of the guidelines for the management of AF has been issued by the European Society of Cardiology (ESC). It attributes a “class I - level A”, i.e. a strong recommendation for catheter ablation for symptomatic paroxysmal AF in drug refractory patients, which implies that the evidence for this recommendation is derived from “multiple RCTs or meta-analyses”. In the same document, the ESC attributes a “class IIA – level B” recommendation for catheter ablation as a first line therapy in selected patients, which implies that, based on “data derived from a single RCT or from large non-randomised studies”, the procedure “should be considered”.

On the basis of our study, we conclude that the efficacy of catheter ablation as observed in the RCTs has not been reproduced in observational studies, including the present study on Belgian practice. Moreover, terminated but as yet unpublished RCTs have shown that ablation as a first-line treatment for AF is not holding the promises of the earlier trials either. Therefore, we consider that these two ESC recommendations are not supported by conclusive evidence. This, in addition to the not negligible risk of the procedure itself, suggests that this procedure should be used with great caution.

SCIENTIFIC REPORT

1. SCOPE

The present report assesses the clinical effectiveness (chapter 4) and safety (chapter 5) of catheter based ablation of non-valvular atrial fibrillation (CA-AF) as compared to drug treatment to achieve rhythm control. Trans-thoracic approaches or ablation procedures during cardiac surgery are beyond the scope of the report.

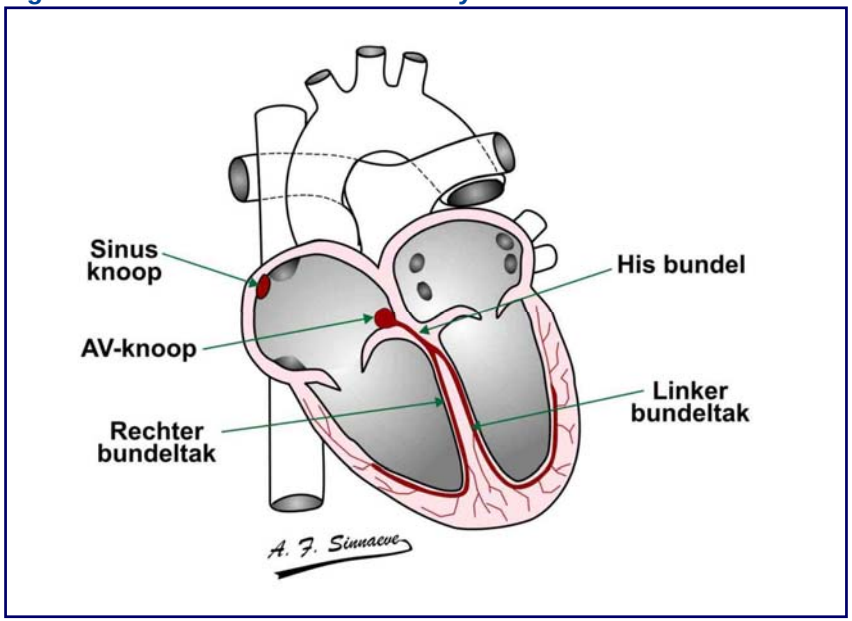
It will also describe current Belgian CA-AF practice (chapter 6), and review the literature on the intervention's cost-effectiveness (chapter 7). Finally, some patient and regulatory/organisational issues are discussed in chapter 8 and 9.

2. CLINICAL BACKGROUND

2.1. Normal heart rhythm

During "normal" heart rhythm, called "sinus rhythm", the electrical impulse that determines the heart beat originates from the sinus node, a group of cells located in the right atrium. From the sinus node, the electric impulse travels through both atria down to a tissue bridge (the atrioventricular or AV-node) to reach the ventricles of the heart, triggering them to contract (Figure 1).

Figure 1 – The cardiac conduction system.



Source: R. Stroobandt, Hartcentrum, UZ Gent. Sinusknoop: sinus node; AV-knoop: atrioventricular node; Rechter bundeltak: right bundle branch; Linker bundeltak: left bundle branch.

2.2. Atrial fibrillation

Atrial fibrillation (AF) is both a heart rhythm and a heart rate disorder. AF being a heart rhythm disorder refers to the fact that the sinus node no longer drives contraction of the heart. Instead, a myriad of foci within the atrial wall simultaneously stimulate the atria to contract. Part of these electrical signals pass through the AV-node and produce a rapid and irregular heart rate. The heart's rate is considered abnormal when the heart beats inappropriately slow or fast in a given clinical context (e.g. at rest, during exercise). Patients with untreated AF often have 120 and over heartbeats per minute at rest, in contrast to the normal rate of 70 beats per minute.

Electrophysiologically, AF requires both a trigger that initiates the arrhythmia and a substrate that can sustain it. The most common triggers are ectopic atrial beats that arise from muscle cells in the wall of the pulmonary veins. Fibrosis and inflammation of an enlarged atrium serve as a substrate for sustaining AF. With persistence of AF, further changes in the atria occur, resulting in recurrences and continuation of the arrhythmia.[1]

AF often complicates mitral valve disease in which case the arrhythmia's prognosis and management differs from AF that develops in the absence of valvular heart disease. The former type of AF is beyond the scope of the current report. Non-valvular AF can present as an isolated condition or it may be associated with other cardiac or non-cardiac disease, such as high blood pressure, heart failure, coronary heart disease, chronic obstructive lung disease and thyroid disease. AF affects 1-2% of the population. Its prevalence increases with age, from <0.5% at 40-50 years to 5-15% at 80 years.[2]

AF may last for only a few minutes or hours or days, and then stop spontaneously. It may recur from time to time later on. It often begins with infrequent and short-lasting episodes that later on may become more frequent and longer in duration, in some patients progressing to permanent AF. In patients with paroxysmal AF at initial clinical evaluation, progression to persistent forms is documented in approximately 10% at 1 year, 25% to 30% at 5 years, and >50% beyond 10 years.[3]

Various classification systems have been proposed for AF. In the 2006 guidelines for the treatment of AF, in a combined effort the American College of Cardiology (ACC), the American Heart Association (AHA) and the European Society of Cardiology (ESC) have developed a common system in which five types of AF are distinguished, based on the duration and recurrence of the arrhythmia:[4]

1. First diagnosed AF: every patient who presents the first time with AF
   After 2 or more episodes, AF is considered *recurrent*.
2. Paroxysmal AF[a]: AF that terminates spontaneously, usually within 48 hours, but may continue for up to 7 days
3. Persistent AF: when AF lasts longer than 7 days or requires termination
4. Long-standing persistent AF: AF lasting >1 year with the decision to still adopt a rhythm control strategy
5. Permanent AF[b]: when the arrhythmia is accepted as such, i.e. a decision is taken not to try to restore normal sinus rhythm

Although some patients with AF may remain unaware of the condition, in others it causes symptoms of palpitations, decreased exercise tolerance or shortness of breath. These symptoms result from the loss of synchronous atrial contractions and the rapid ventricular rates.[5] Whereas in some patients symptoms may spontaneously improve over time,[6] in others AF may lead to heart failure and death.

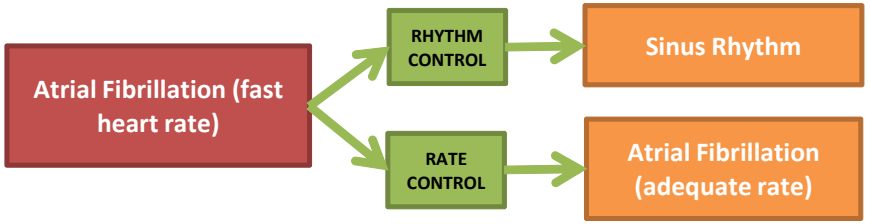
Apart from the symptomatic issue, patients presenting with AF are prone to developing blood clots (thrombi) within the atria. These may dislodge, migrate to the brain or other areas of the body, and cause acute ischemia and stroke. The risk of ischemic stroke among patients with non-valvular AF which is dependent on the presence of 1 or more other risk factors averages 5% per year.[1]

2.3. Treatment

The management of patients with AF aims at controlling symptoms and preventing thrombo-embolic events in patients at high risk for such complications.

The therapeutic modalities in AF are schematically depicted in Figure 2.

Figure 2 – Therapeutic modalities in atrial fibrillation



Usually the heart rate is inappropriately fast in patients with AF. With a rate control management, the heart rate becomes adequately controlled while the AF as such remains.

2.3.1. Rhythm control

Rhythm control can be achieved medically, through direct current cardioversion (discussed below), or through "ablation therapy" (representing the topic of the present report). Anti-arrhythmic drugs (AAD) currently most often used for pharmacologic cardioversion of AF are flecainide, propafenone, amiodarone and sotalol (a beta-blocker with particular anti-arrhythmic properties).[2, 7] The long term efficacy of AADs for maintaining sinus rhythm in patients with recurrent AF is suboptimal. The effectiveness of AAD in patients who recovered sinus rhythm after AF was studied in a Cochrane review.[8] Pooled recurrence rates of AF at 1 year was 42-67% in patients treated with AAD, as compared to 71-84% in controls not receiving AADs. In the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study, the effect of long-term AAD in AF was studied.[9] More than 4000 patients were randomised to a rhythm or a rate control strategy in order to study those two treatment options. Rhythm control could be achieved by different AADs and/or direct current cardioversion when needed. The prevalence of sinus rhythm in the rhythm-control group at follow-up was 82.4%, 73.3%, and 62.6% at 1, 3 and 5 years respectively.

Direct current cardioversion involves the application of an electric shock to the chest wall under general anaesthesia. In most patients with AF it leads to an at least temporarily restoration of sinus rhythm.

---

[a] Further in this report, "non-paroxysmal AF" is defined as persistent or long-standing or permanent AF.

[b] The term "Chronic AF" is no longer used.

2.3.2. Rate control

Restoration of sinus rhythm is not always achievable but avoiding the heart to beat inappropriately fast (i.e. rate control) most often leads to adequate symptom control in patients with AF. Rate control can be obtained medically by a number of drugs: beta-blockers, non-dihydropyridine calcium channel blockers, and digoxin. It can also be achieved by a trans-venous catheter intervention that alters the conduction properties of the AV-node (so-called His bundle ablation, a distinct type of catheter ablation that is beyond the scope of this report).

2.3.3. Prevention of thrombo-embolic complications

As mentioned earlier, patients presenting with AF are prone to developing thrombo-embolic complications irrespective whether or not the AF is symptomatic. The propensity to develop thrombo-embolic events in AF, and hence the need for anticoagulant treatment is dependent on a number of risk factors, identified via the CHA_2DS_2-VASc acronym: Cardiac failure, Hypertension, Age ≥75 years (doubled), Diabetes, prior Stroke (doubled), Vascular disease (myocardial infarction, peripheral arterial disease, ...), Age from 64-74, and Sex category. Any of these risk factors is assigned 1 point but previous stroke and age ≥75 are assigned 2 points. Patients with a CHA_2DS_2-VASc score of ≥2 have a stroke risk of ≥2.2% per year and are to be considered for anticoagulation treatment. This can be achieved by anticoagulants (vitamin K antagonists or direct thrombin inhibitors).

It has been shown that heart rhythm is not an independent risk factor for stroke in patients with AF.[10] Therefore, even after successful restoration of sinus rhythm, anticoagulation therapy is to be continued in patients in whom such treatment was indicated before.

2.3.4. The rate vs. rhythm control enigma

In a systematic review of 5 RCTs, involving 5239 patients that were followed from 1 to 3.5 years, it was found that a rate control strategy compared with rhythm control was associated with a significantly *reduced* risk of a combined endpoint of all-cause mortality, major bleeds and cerebral or systemic embolism (odds ratio 0.84; 95%CI 0.73 to 0.98).[11, 12]

Counter intuitively the superiority of rhythm control with AADs over rate control to improve quality of life could also not be documented in clinical trials. One trial revealed a similar improvement in QoL for both rate and rhythm-control groups.[9, 13] Three large RCTs demonstrated a greater improvement in QoL in patients receiving rate control.[14-16] In a more recent Japanese study that was restricted to patients with paroxysmal AF, limited data suggested that rhythm control might be superior to rate control in improving quality of life. In the rhythm control group, 46 patients (11.0%) requested a change to rate control, whereas 67 rate control patients (16.6%) requested a change to rhythm control, defined as the request of patients to cross-over.[17]

The reality that it has thus far not been proven that rhythm control is superior to rate control has been explained by some experts by the fact that AADs are not very effective in sustaining sinus rhythm and/or by their potentially serious side effects annihilating their presumed benefit on rhythm control.[11] Others argue that currently used QoL instruments lack sensitivity to demonstrate an improvement in AF-related symptoms[2] or that QoL improvement can be achieved only in selected patients, whose improvement does not emerge from trials that include broad categories of AF patients.[18]

Key points

- **Atrial fibrillation is a common arrhythmia. It causes symptoms of palpitations and dyspnoea and in some patients it may lead to stroke.**
- **Symptoms attributed to atrial fibrillation can be treated by restoring normal sinus rhythm ("rhythm control") or by preventing the heart to beat too fast ("rate control"). So far, rhythm control has not been proven to be superior over rate control.**
- **Antithrombotic treatment is indicated in patients at high risk for stroke. They can be identified by the presence of additional risk factors such as high age, hypertension, previous stroke, heart failure and diabetes.**

3. CATHETER ABLATION: TECHNOLOGY DESCRIPTION

AF ablation is a management strategy for AF aimed at rhythm control. It has been first implemented by cardiac surgeons in patients with AF that underwent surgery for other cardiac conditions such as bypass grafting or valve replacement. The procedure involved producing incisions in certain areas of the atria, thus blocking electrical circuits that were necessary to initiate or sustain AF. The better understanding of the pathophysiology of AF led to the improvement and simplification of the surgical technique. Nowadays, the surgical procedure is still in use and can be accomplished through a thoracoscopic approach on a beating heart. Instead of making incisions, lesions are created from the outside of the heart by using different possible energy sources.[19, 20] Surgical ablation of AF is beyond the scope of the present report.

In parallel with the advances of surgical ablation, electrophysiologists introduced less invasive catheter based approaches with the same aim of interrupting electrical currents involved in AF. It represents the subject of the present report.

In patients with paroxysmal AF, the cells that trigger the development of AF reside in electrical active foci that are predominantly located in the wall of the pulmonary veins.[21] Hence, eliminating these foci, or electrically isolating the pulmonary veins by means of destroying conductive tissue surrounding them, forms the cornerstone for CA-AF. In patients with persistent AF, it has been shown that besides the pulmonary veins, other foci of AF initiation may be present in the right and left atrium, whereas parts of the atrial wall may be required to sustain the AF. Therefore, in some patients, adjunctive targets for ablation within the atria are targeted in combination with pulmonary vein isolation.

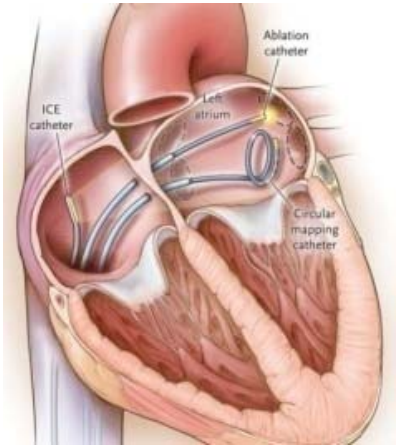
CA-AF is often performed under general anaesthesia. It involves the introduction of one or more catheters into the left atrium of the heart. This can be reached via the venous system and requires a puncture through the inter-atrial septum (Figure 3), guided by radioscopic control. It may take several hours to complete the procedure. Ablations performed during cardiac surgery or by means of thoracoscopy are beyond the scope of the present report.

Several techniques for ablating the electrical active foci and the tissue surrounding the pulmonary veins have been developed. Initially, a focal approach with the application of selective point ablations within the pulmonary veins was used, but because of the induction of pulmonary vein stenosis, electrophysiologists introduced a segmental or a circumferential approach by ablating the junction of the pulmonary veins and the left atrium, thus isolating the veins from the atrium.[22]

Reconnections between the atria and the pulmonary veins can occur, necessitating repeat procedures.[23] Early recurrence of AF after CA may be a transient phenomenon induced by the damage to the atrial wall caused by the ablation. Therefore, during the first few months after the CA, while the ablation lesion is healing, patients generally remain on AAD therapy.[1] This time window is defined as the “blanking period” and some authors do not count AF occurring during this period as a failure of the procedure.[24]

In order to achieve faster and more stable lesions, catheters that can induce single-shot circular lesions around the pulmonary veins were developed (phased radiofrequency, balloon based devices).[25, 26]

Figure 3 – Positioning of catheters in the heart during CA-AF



ICE: intracardiac echography. Source: Wazni.[1]

Different types of energy as well as variations in the catheters required for its delivery have been developed. Radiofrequency energy is the most commonly used energy source, but freezing (cryo-ablation) and laser techniques are used as well.[26, 27] Some authors have combined radiofrequency and cryoballoon approaches in one single procedure.[23]

The following manufacturers are involved in devices intended for CA-AF: Biosense Webster (J&J), Medtronic, Biotronik, St.Jude Medical, Boston Scientific, BARD, ProRhythm Inc.

Key points

- **Catheter ablation of atrial fibrillation is a complex cardiac intervention, often performed under general anaesthesia, and involving prolonged exposure to X-rays.**
- **It aims at destroying areas located at the inner surface of the left atrium that are involved in the initiation and propagation of the electrical signals that produce atrial fibrillation**

4. CLINICAL EFFECTIVENESS OF CA-AF

4.1. Literature search

4.1.1. Search strategy

In the present report, we limit ourselves to comparisons of CA-AF with medical treatment, excluding thus studies that compared different ablation modalities. A standard literature search protocol was accomplished in January 2012 and is presented in detail in appendix 1.

4.1.2. Studies selected from the systematic literature search

4.1.2.1. Health Technology Assessments

We selected two HTA reports, originating from Canada and the US respectively.[20, 28] Both reports were of very good quality according the INAHTA 2007 checklist (appendix 2). We also identified a 2010 “Alert Report”, originating from SBU, the Swedish Council on Health Technology Assessment. This is a 16-page document written in Swedish and including a 2-page English summary.[29]

4.1.2.2. Systematic reviews

The methodological quality of two systematic reviews (SRs) we selected from our literature search[30, 31] was assessed by using the Dutch Cochrane appraisal instrument (appendix 1.1). The literature search strategy, as well as the selection and quality appraisal of RCTs was considered adequate in both SRs. However, pooling of the results of the separate RCTs in our view was inappropriate because of a substantial clinical heterogeneity between trials that we will discuss further on.

At our first external expert meeting on April, 27th, an expert drew our attention to a Cochrane review on catheter ablation that was published in The Cochrane Library 2012, Issue 4. Later on, we were alerted to this study through a weekly update from PubMed on July, 28th 2012. Its literature search extended to August 2009 and as such, it did not include additional information to that provided by the SRs that were published in 2010-2011.

4.1.2.3. Primary studies

Table 1depicts the primary studies that were selected according to our literature search.[32-40] We found 9 RCTs, one of which[35] was not yet mentioned in any of the HTA reports or SRs.

In the published RCTs, 971 AF patients were randomised between catheter ablation and medical therapy. In all but one study, medical therapy in the control group consisted of an antiarrhythmic drug, whereas in MacDonald's study,[35] drug therapy was directed to rate control. We considered the latter study to be less relevant in the present report because of its very small size (n=41), the particular target population, i.e. patients with advanced heart failure and its primary endpoint being left ventricular ejection fraction.

All the trials were open label and relatively small (n=30-198) and they all used radiofrequency waves as energy source. The clinical effectiveness evaluation of CA-AF in the present report is essentially based on the SRs and HTA reports mentioned in Table 1.

Table 1 – RCTs, HTA reports and SRs on CA-AF, retrieved from the literature search

		RCT	HTA			SR	
year	Study acronym	Author/Institution	CADTH	ICER	SBU	Bonanno	Parkash
		search until →	April 2010	May 2010		<June 2009	July 2010
		published →	Sep 2010	Sep 2010	2010	June 2010	July 2011
2003		Krittayaphrong[34]	√		√	√	√
2005	RAAFT	Wazni[39]	√	√	√	√	√
2006	CACAF	Stabile[38]		√	√	√	√
2006	APAF	Pappone[37]	√	√	√	√	√
2006		Oral[36]		√	√	√	√
2008	A4	Jais[33]	√	√	√	√	√
2009		Forleo[32]	√	√	√	√	√
2010		Wilber[40]	√	√	√		√
2011		MacDonald[35]					

Name of RCT refers to first author; Year: year that corresponding RCT was published.
CADTH: Canadian Agency for Drugs and Technologies in Health.[28] HTA: Health Technology Assessment. ICER: Institute for Clinical and Economic Review.[20] SBU, the Swedish Council on Health Technology Assessment.[29] RCT: randomised controlled trial; SR: systematic review.

In December 2011 a 4-year follow-up data from the APAF study were published.[37, 41] This study came out of our literature search only as a congress abstract. The results are reported in the paragraph on long term effectiveness of CA (see 4.2.5).

4.1.3. Unpublished and ongoing RCTs

We came across several RCTs that are either ongoing or not yet published in a peer reviewed medical journal. They study a variety of energy sources for CA and target different patients groups. Some data from these RCTs are available from interim reports or presentations at cardiologic congresses or could be found in the grey literature or through contacts with the manufacturers involved. In other cases, we were aware of the fact that a given study had been undertaken but no results were found.

4.2. Clinical effectiveness of radiofrequency ablation of atrial fibrillation

Since all of the published randomised trials used radiofrequency waves as the energy source for the ablation, the evidence on this will be first described. In the chapter 4.3, catheter ablation using energy sources other radiofrequency, will be discussed.

4.2.1. Conclusions of previous systematic reviews and HTA reports

The scientific quality of most of the RCTs has been rated as moderate. Fewer than half of them were considered as “good quality studies” by the Institute for Clinical and Economic Review (ICER), based on the criteria employed by the US Preventive Services Task Force.[20] In the CADTH report, that used the Jadad score to rate quality, only two[39, 40] out of six RCTs received a Jadad score of 3 or greater, indicating “high quality”.[28] The recently published Cochrane review, using the guidance provided by the Cochrane Handbook, concludes that “overall, the RCTs were small in size and of poor quality”.[42]

In Parkash’ systematic review the primary endpoint was freedom from AF after a single procedure. The authors conclude that radiofrequency ablation is superior over AADs for the treatment of symptomatic, drug refractory AF in either paroxysmal (relative risk of recurrence of AF with AADs = 2.26; 95%CI: 1.74-2.94) or persistent (relative risk 3.20; 95%CI: 1.29-8.41) AF.[31]

Bonanno concludes that radiofrequency CA-AF in selected patients with AF is an effective intervention with the majority of patients remaining free from AF at 12 months after one or more ablation procedures (relative risk of AF recurrence after ablation = 0.29; 95%CI: 0.20-0.41). Complications and adverse events associated with the procedure are reported to occur rarely but to be not negligible.[30] The authors found evidence of quantitative heterogeneity. Meta-regression showed no statistical evidence for heterogeneity related to percentage of men or method used for arrhythmia detection, but heterogeneity was present for mean age and percentage of patients with paroxysmal AF.

In the Cochrane review, issued in April 2012, only 7 out of the 9 abovementioned RCTs are included, which is explained by the fact that its literature search ended in August 2009. From their meta-analysis, the authors conclude that catheter ablation has a better effect on inhibiting recurrence of AF than medical therapies (relative risk = 0.27; 95%CI 0.18-0.41) but that there is a significant statistical heterogeneity between studies.[42]

The 2010 CADTH HTA report concludes that CA increases the rate of maintenance of sinus rhythm compared with AADs in patients for whom the use of one or two drugs failed (relative risk: 2.82; 95%CI: 2.13-3.74).[28] The studies are reported to be of insufficient size and duration to evaluate the impact on stroke, heart failure, and mortality. Better results are obtained in patients with paroxysmal AF. The HTA report from the Institute for Clinical and Economic Review concludes that no mortality benefit has been documented in RCTs. As far as freedom from AF recurrence at 12 months is considered, patients undergoing CA were nearly three times as likely to be free from AF (range: 56-87%) relative to those receiving AADs (range: 9-58%), the advantage being more pronounced for patients with paroxysmal AF.

The Swedish “alert report” concludes that in patients who are refractory to conventional treatment, CA is more effective than continuing AADs in treating symptoms, but long term effects are uncertain. Patients with paroxysmal AF respond more favourably than those with persistent AF. CA-AF carries risks for serious complications.

In the paragraphs below we further comment the findings reported in the aforementioned HTA reports and SRs, and supplement them with data we could obtain from unpublished or ongoing trials.

4.2.2. Data obtained from published randomised trials

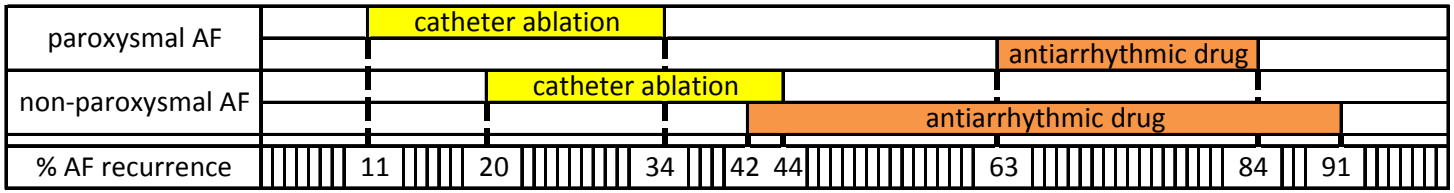
Since these trials are extensively discussed in the HTA reports and SRs mentioned above, we do not consider them in full detail in the present report.

The follow-up of patients enrolled in those studies never exceeded 1 year and the number of patients enrolled was rather low, ranging from 30 to 198.

We found a profound clinical heterogeneity between the RCTs in relation to patient characteristics, procedural modalities and definition of clinical endpoints. Four trials enrolled paroxysmal AF patients only; two studies were limited to non-paroxysmal AF whereas two other studies enrolled both paroxysmal and non-paroxysmal AF patients. In one trial drug treatment of the control group consisted of rate control, whereas in the others control treatment was an antiarrhythmic drug. One trial compared catheter ablation on top of amiodarone, versus amiodarone only. One trial only enrolled patients with diabetes mellitus, in another trial, only patients with heart failure were included. Procedural success was defined by a single ablation procedure in some studies, while in others additional ablation attempts or re-initiation of AADs were allowed in determination of success. In 4 trials, cross over from drug treatment to ablation occurred in more than 40% of patients. The blanking period during which an AF recurrence was not counted as a failure, varied between 1 and 3 months across trials. In one study, catheter ablation was studied as the first line treatment for AF, whereas in the other studies patients were only eligible if they had failed at least one trial with an antiarrhythmic drug. Because of this substantial clinical heterogeneity between trials, we considered pooling them in a meta-analysis inappropriate. This point of view has also been proclaimed by other authors.[43]

We extracted the most relevant data as depicted in Table 2, 971 patients were studied in 9 RCTs. Radiofrequency was the energy source in all of them. Drug therapy consisted of an AAD, except for one study[35] where drug therapy was directed at rate control. In all but one,[35] any recurrence of symptomatic or asymptomatic AF at 1 year was the primary endpoint. In those studies, AF recurrence was observed in 42.0-91.3% of AAD patients and in 11.0-44.1% of CA-AF treated patients, in some of them after a repeated procedure. Recurrences after CA were lower in patients with paroxysmal AF (11 to 34%) than in those with non-paroxysmal AF (20 to 44%), but the data showed a large overlap (Figure 4 and Table 2).

Figure 4 – Recurrence rates of AF after catheter ablation and antiarrhythmic drug treatment in published RCTs.



Scale from 0 to 100%. Data extracted from Table 2. % AF recurrence is within 1 year after ablation, taking into account a blanking period of 1 to 3 months. MacDonald's trial is not included since treatment in the control group consisted of rate control drugs only.[35]

Two out of nine RCTs reported recurrence of symptomatic AF separately. In one study, elimination of symptomatic AF was achieved in 70% of patients after CA and in 16% of patients with AADs. These figures were 63% and 17% respectively if one considered the elimination of any arrhythmia, irrespective of symptoms.[40] In another study, 22 (63%) of 35 patients who received AADs had at least 1 recurrence of symptomatic AF during the 1-year follow-up period compared with 4 (13%) of 32 in the CA group. Asymptomatic AF was documented in 16% of the AAD group and in 2% of the CA group.[39]

Hard endpoints such as mortality or stroke occurred rarely in these small trials: in most studies there were no deaths or strokes being reported in either study group.

The impact of catheter ablation on quality of life will be discussed in detail in a separate paragraph (4.5).

Table 2 – Outcome of radiofrequency catheter ablation of AF as reported in RCTs

Year	Reference	mean age	N interv	N control	Prim. endpoint	Redo	Blanking period	Intervention			Control			Risk ratio	FU
								AF free		Cross over	AF free		Cross-over		
								n	%	n	n	%	%		
Studies including >95% paroxysmal AF patients															
2005	Wazni	53±8	33	37	AF, QoL,	no	2 mo	29	87.0	?	14	37.0	no	0.20 (0.08-0.51)*	1 yr
2006	Pappone	55±10	99	99	AF	9%	6 we	85	86	0	22	22	42%	0.19 (0.11-031)*	1 yr
2008	Jais	49.7±10.7	53	59	AF	23%	3 mo	47	89	9%	14	23	63%	0.17 (0.08-0.34)*	1 yr
2010	Wilber	55.5	106	61	AF (QoL)	12.6%	3 mo	70	66	7.5%	10	16	yes	0.30 (0.19-0.47)	9 mo
Studies including 100% non-paroxysmal AF patients															
2006	Oral	55±9	77	69	AF	25%	3 mo	57	74.0	0	40	58.0	77%	0.24 (0.14-0.39)*	1 yr
2009	Forleo	63.2±8.6	35	35	AF	no	5 we	28	80.0	0	15	42.9	no	0.35 (0.17-0.72)*	1 yr
2011	MacDonald	64.4±8.3	22	19	LVEF	27%	3 mo	11	50.0	rate control	0	0.0	no	-	6 mo
Studies including both paroxysmal and non-paroxysmal AF patients															
2003	Krittayaphrong	?	15	15	AF	no	?	12	78.6	?	6	40.0	?	0.33 (0.11-0.99)*	1 yr
2006	Stabile§	62.2±9	68	69	AF	no	1 mo	38	55.9	100%	6	8.7	52%	0.48 (0.37-0.64)*	1 yr

*CA: catheter ablation. AADs used in the control groups include class I or class III drugs. FU: follow-up time. AF: atrial fibrillation. QoL: quality of Life. LVEF: left ventricular ejection fraction. References: see Table 1. In MacDonald's study, medical therapy in the control group was only directed at rate control.[35] § In this study, patients were randomised to CA plus AAD, or to AAD therapy alone.[38] AF. *: risk ratio calculation extracted from Cochrane Review.[42]*

4.2.3. Unpublished RCTs investigating radiofrequency catheter ablation

A number of RCTs on radiofrequency CA-AF have been finished but are not yet published in a peer reviewed journal. We identified some findings related to these trials on the internet (presentations at congresses, press releases, FDA, clinicaltrials.gov, and comments in dedicated websites such as Medscape and theheart.org). Since some of these trials have generated relevant data that have not been included in earlier HTA reports or SRs, we considered it pertinent to discuss them in detail in the present report.

4.2.3.1. CABANA pilot study

The Catheter Ablation versus Anti-arrhythmic Drug Therapy for Atrial Fibrillation (CABANA) study is a trial sponsored by the US National Heart, Lung and Blood Institute and two device manufacturers (St Jude Medical and Biosense Webster).[c] The trial is designed to test the hypothesis that CA-AF is superior to current state-of-the-art therapy with either rate control or rhythm control drugs for reducing total mortality. Secondary endpoints include mortality, stroke, hospitalisations and cost. Eligible patients have to be 65 years of age or more, or have to have more than 1 risk factor for stroke and hence, they are in general sicker than those traditionally enrolled in CA-AF studies.

In a pilot study 60 patients (31 AAD, 29 CA) were enrolled and followed for nine months following a three-month blanking period. Results were presented at the March 2010 ACC convention in Atlanta. 61% of patients had a CHADS2 score of ≤1, ±32% had paroxysmal, ±37% persistent and ±32% long standing persistent AF. In the AAD arm of the study 4/31 patients crossed over to CA. In the CA arm, 8/26 (28%) patients were prescribed an AAD and 6/29 (21%) underwent a redo ablation.

At completion of the trial, 65% of ablated patients had no recurrence of *symptomatic* AF, versus 41% of patients treated with AADs (HR 0.46; 95%CI: 0.21-0.99). When recurrence of *any* AF was taken into account, these figures decreased to 45 and 31% respectively, which were no longer statistically significant different (HR for recurrence 0.56; 95%CI: 0.28-1.11).

Following the CABANA pilot study, a pivotal trial has been initiated that is currently ongoing. 3000 patients will be enrolled and the study is estimated to be completed by September 2015.[d] A website is dedicated to this trial (cabanatrial.org).

4.2.3.2. TTOP-AF

The TTOP-AF study (Tailored Treatment of Permanent Atrial Fibrillation) enrolled 210 patients with longstanding and persistent AF and made use of a distinct "multi-electrode, phased" radiofrequency catheter (Medtronic Ablation Frontiers Cardiac Ablation System®). This device allows the simultaneous application of radiofrequency energy across multiple electrodes, obviating the need for point-by-point ablation. The results of the TTOP-AF study were presented at the Venice Arrhythmias 2011 congress and some of the outcome data presented are available from the internet.[e] 138 patients were randomised to CA and 72 to medical therapy. They were on average 60 years of age and were followed for 6 months. Ablation significantly reduced "AF burden" in 55.8% of patients vs. 26.4% of those treated medically. Apparently, these figures were largely dependent on the definition of success: when the more stringent Heart Rhythm Society (HRS) definition of chronic treatment success was used, the six-month success rate of ablation was reduced to 37%. If treatment success did not require patients to be off AADs, six-month treatment success increased to 47.8%.

Within 7 days of the ablation, there were 21 serious adverse events, occurring in 17 subjects (12.3%), including 1 death, 4 strokes, 2 cases of tamponade and 2 pseudo-aneurysms. When the 43 patients who crossed over from the medical arm were included, the rate of serious adverse events was 21.6%.[f]

c http://clinicaltrials.gov/ct2/show/study/NCT00911508?term=cabana&rank=1

d http://www.theheart.org/article/1057265/print.do

e http://www.theheart.org/article/1293651/print.do; http://www.medscape.com/viewarticle/752486

f http://www.medscape.com/viewarticle/752486

The Medtronic Ablation Frontiers Cardiac Ablation System® is approved for use in Europe since December 2006. Based on the TTOP-AF data, an FDA Advisory Panel on October 27, 2011 voted 10 to 0 that the device is effective, but 9 to 1 that available data did not provide reasonable assurance about its safety. Therefore it was concluded that market approval could not yet be granted.[g]

4.2.3.3. CAMTAF

The CAMTAF trial (Catheter ablation vs. Medical Treatment of Atrial Fibrillation) randomised 54 patients with persistent AF, symptomatic heart failure and a left ventricular ejection fraction <50% to radiofrequency ablation or medical treatment. The primary endpoint was the difference in left ventricular ejection fraction (LVEF) between groups at 6 months. Results were presented at the 2011 Heart Rhythm Congress.[h] Patients underwent 1.6±0.7 procedures. There were two (7.7%) complications: one stroke and one tamponade. Freedom from AF off AADs was achieved in 21 of 24 (88%) ablated patients. Left ventricular ejection fraction in the ablation group at 6 months was 39 ± 10% compared with 32 ± 13% in the medically treated group (p<0.05).

4.2.3.4. MANTRA-PAF

In the randomised controlled multicenter Medical Anti-arrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation (MANTRA-PAF) trial, radiofrequency ablation was compared with AADs as a first line treatment of paroxysmal AF in 294 patients, on average 55 years of age. The primary endpoints were cumulative AF burden (percentage of time spent in AF) during 35-day (every 3 months a period of 7-days) ambulatory monitoring, and AF burden during each 7-day ambulatory monitoring. Results were presented at the November 2011 AHA Scientific Sessions (Orlando, Florida).

There was no difference in AF burden between the two groups at baseline or at 3, 6, 12 and 18 months. After 2 years the difference was significant in favour of CA. There was no significant difference in cumulative AF burden. We have no numerical data on these endpoints. There were three deaths in the ablation group and four deaths in the drug group. One patient in the ablation group had a stroke during the procedure.

4.2.3.5. RAAFT-2

The RAAFT-2 trial (Radiofrequency ablation versus anti-arrhythmic drugs as first-line treatment of symptomatic atrial fibrillation) was designed to compare radiofrequency ablation with drug therapy as first-line treatment.[i] The study included 127 patients (mean age 55) with symptomatic recurrent paroxysmal AF who had not been previously treated with AADs. After the initial 3-month period, patients in both groups received trans-telephonic monitors with which to send in results every 2 weeks. Follow-up lasted for 21 months.

Results of the study were presented at the 2012 Heart Rhythm Society meeting.[j] Patients who underwent CA-AF had a significantly lower risk of a first recurrence of atrial fibrillation, atrial flutter, or atrial tachyarrhythmia (55% versus 72%; HR 0.56, 95%CI: 0.35 to 0.90, p=0.02) representing the primary efficacy endpoint of the study. However, removing the events identified through trans-telephonic monitoring and focusing solely on those identified clinically eliminated the significant difference between the two groups (24% with ablation versus 31% with drug therapy; HR 0.86, 95%CI 0.42 to 1.72, p=0.66). In the ablation group, 10 (15.2%) of the patients required a redo ablation and 7 (10.6%) crossed over to the AAD group. In the AAD group, 29 (47.5%) crossed over to the ablation group.

g http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM278251.pdf

h http://europace.oxfordjournals.org/content/13/suppl_4/iv3.abstract

i Todd Neale, Senior Staff Writer, MedPage Today, May 12, 2012: http://www.medpagetoday.com/MeetingCoverage/HRS/32652

j Morillo C, et al "Radiofrequency ablation versus antiarrhythmic drugs as first-line treatment of symptomatic atrial fibrillation (RAAFT 2): A randomized trial" *HRS* 2012; Abstract LB02-1.

4.2.4. Short-term data from observational studies

Whereas a limited number of patients underwent a catheter ablation for AF within the context of an RCT, hundreds of thousands have been treated so far in electrophysiology labs around the world. In Table 3 we summarise observational data, obtained through a non-systematic literature search. In a worldwide survey, data on CA-AF were collected from 85 centres that performed 20 825 ablations on 16 309 patients between 2003 and 2006. During a follow-up of 10±8 months and after a mean of 1.3 procedures per patient, a median of 70.0% (interquartile range: 57.7-75.4%) became asymptomatic in the absence of any AAD, whereas another 10.0% (0.5-17.1%) became asymptomatic with the continued use of formerly ineffective AADs. Overall, 80.0% (74.0-83.8%) obtained resolution of symptoms.[44] This paper is not clear in its definition of "success" since it mentions that centres reported "freedom from documented AF" as the definition of success, but on the other hand the numbers reported in the survey are related to "patients who became asymptomatic". This distinction is important since patients may be asymptomatic in spite of developing AF.

In a recent narrative review, Viles-Gonzalez et al.[43] list the reported effectiveness of CA from observational studies in patients with paroxysmal (16 studies; n=53-254) and persistent (17 studies; n=43-1619) AF. In those studies, follow-up ranged between 1 and 3 years. Numerical details from this review are also shown in Table 3.

Table 3 – Short term (6-18 months) success rates of radiofrequency ablation reported in observational studies

	Author	Paroxysmal AF	Non-paroxysmal AF
off AAD - %	Viles-Gonzalez	36-91	20-82
	Cappato [median per centre, (IQR)]	74.9 (64.9-82.6)	64.8 (52.4-72.0)
on/off AAD - %	Viles-Gonzalez	45-94	36-94
	Cappato [median per centre, (IQR)]	84.0 (79.7-88.6)	74.8 (66.1-80.0)

"off AAD" refers to patients with no AF recurrence and who no longer were treated with an AAD after the procedure; "on/off AAD" refers to successful CA-AF, irrespective whether or not a patient was still treated with an AAD. References: Viles-Gonzales[43]; Cappato[44]

There is a huge variance across the results obtained by different authors or centres. This variance may be related to several factors such as patient selection, definition of success, the use of different devices or differences in experience across centres.

4.2.5. Long term effectiveness data

No RCTs reporting long term efficacy (i.e. more than 1 year) were identified during the search procedure (January 2012) for the present report. Data were available from observational studies only and these have to be interpreted cautiously given their inherent risk of bias and the fact that standardised monitoring protocols and endpoints are generally not employed.[19]

Table 4 lists recently published follow-up data during up to 6 years. From these observational studies, originating from experienced centres, it can be roughly estimated that recurrence of AF after a single intervention occurs in half of the patients within 6 years.

Table 4 – Long term effectiveness of radiofrequency catheter ablation of AF from observational studies

	N		age	AF subgroup	risk profile	FU	n (%) success after single CA	# attempts	n (%) success at end of FU
Weerasooriya	100		55.7±9.6	64% par.	43% HT, 8% CHD, 3% DM	all patients 5 yrs	28.5%	median 2	62.9±5.4%
Ouyang	161		59.8±9.7	100% par.	67% HT, 11.8% CHD, 5.0% DM	median 4.6 yrs (0.33-5.5)	75 (46.6%)	median 1	128 (79.5%)
Hussein	831		58.7±9.9	69.2% par.	35.6% HT, 14.2% CHD, 8.1% DM	median 55 mo (54-56	67.3%	1.2±0.4	660 (79.4%)
Katritsis	39		51.9±10.3	100% par.	54% HT, 15% CHD	mean 42.2±6.0 mo	21.4%	mean 1.8	17 (43.5%)
Medi	100		54±10	100% par.	27% HT, 6% CHD 2% DM	mean 39±10 mo	49 (49%) off AAD	1.2±0.5	82% (57% off AAD)
Hunter	713		58±11	56% par.	CHADS 0.7±0.9 CHADS-VaSc 1.4±1.3	3.1 (1.0-9.6) years	NA	1.7±0.8	85% (76% off AAD)
	560			44% pers.			NA	1.9±0.9	72% (60% off AAD)
Gaita	41	PVI	53.3±9.0	par.	12% structural	41.4±6.2 mo	12 (29%)	mean 1.7	24 (58.5%)
	84	PVI+	56.0±9.9		15% structural	39.7±5.5 mo	45 (53%)	mean1.3	63 (75.0%)
	26	PVI	53.3±9.0	pers.	12% structural	41.4±6.2 mo	5 (19%)	mean 1.7	9 (34.6%)
	53	PVI+	56.0±9.9		15% structural	39.7±5.5 mo	22 (41%)	mean 1.5	35 (66.0%)
Bhargava	728		54.5±11.8	par.	48.5% HT or structural	59±16 mo	565 (77.6%)	mean 1.17	673 (92.4%)
	676		57.2±10.2	non-par.	64.8% HT or structural	53±17 mo	454 (67.2%)	mean 1.25	568 (84.0%)
Sorgente	40		53.5±13,3	par.	47% HT, 8% CHD, 6% DM, 6% valvular	median 6 years (4.88-7.27)	36%	median 1	50%
	63			non-par.			15%		31%

Highlighted rows indicate studies including patients with paroxysmal AF only. par.: paroxysmal AF; pers.: persistent AF; non-par.: persistent or long-standing persistent AF; HT: hypertension; DM: diabetes mellitus; CHD: coronary heart disease; off AAD indicates that patient had to be without AAD therapy for a procedure to be considered successful; PVI: pulmonary vein isolation; PVI+: pulmonary vein isolation plus additional linear lesions; CHADS and CHADS-VaSc scores: thrombo-embolic risk scores associated with AF (see text). References: Weerasooriya[45], Ouyang[46], Hussein[24], Katritsis[47], Medi[48], Hunter[49], Gaita[50], Bhargava[51], Sorgente[52]

In December 2011, 4-year follow-up data from the APAF study were published.[37, 41] Among patients randomly assigned to CA-AF, 72 (72.7%) were free from recurrence at 4 years, compared to 56 (56.5%) in the AAD group. However, all patients that were initially enrolled in the AAD group and developed AF recurrence (87.9%) crossed over to CA during the trial. The mean time to cross-over was 10.1±7.2 months (range 4-31).

If one considers only studies that included at least 100 patients, it can be inferred from Table 4, that after a single procedure, long term success (4 to 5 years) of catheter ablation is reported in 47 to 78% of patients treated for paroxysmal AF, and in 29 to 67% of patients treated for non-paroxysmal AF. Success rates after multiple ablations are from 80 to 92% in paroxysmal AF and from 62 to 84% in non-paroxysmal AF.

In a recently published narrative review, the yearly recurrence rate of AF after the first year is estimated to be between 6 to 9% per year.[1]

4.3. Clinical effectiveness of CA-AF with energy sources other than radiofrequency

In all published RCTs, radiofrequency was used as the energy source for the ablation. However, some data related to other ablation modalities are available from other sources.

4.3.1. Cryo-ablation

In October 2011, an interim HTA report from NICE on cryo-ablation has been published. It was updated in March 2012 and the corresponding "NICE interventional procedure guidance 427" was issued in May 2012. No RCTs were included in this systematic review. NICE concludes that "current evidence on the efficacy and safety of cryo-ablation for AF is adequate to support its use".

Several RCTs that use cryo-ablation are in progress. One RCT has been completed (Sustained Treatment of Paroxysmal Atrial Fibrillation trial - STOP-AF) in 2009 with part of the results being presented at the 2010 ACC Scientific Meeting. More detailed data are available from the FDA's website since this was a US premarket approval study.[k] The STOP-AF study randomised 245 patients to cryo-ablation (n=163) or AAD (n=82). Anti-arrhythmic study drugs could be flecainide, propafenone or sotalol. Amiodarone was not considered as a study drug. After a 3-month blanking period and a 9-month follow-up, 69.9% of patients treated with cryo-ablation were free from AF, defined as no detectable AF during the non-blanking period (30 days), no use of no-study-drugs, and no AF interventions. This number was 7.3% in the AAD arm. Among the successfully ablated patients, 58% were free from AF at one year without the use of add-on AAD. The results of this study led the FDA to grant commercial distribution of the Arctic Front Cryo-catheter system in the US.

4.3.2. Laser balloon ablation

In the "Interventional procedure overview" (IP892) supporting the "Interventional procedure guidance 399", issued in June 2011 by NICE, no RCTs were included. It was concluded that "current evidence on the safety and efficacy of percutaneous endoscopic catheter laser balloon pulmonary vein isolation for AF is inadequate because of the limited number of patients reported."

At the 2011 Annual Scientific Sessions of the Heart Rhythm Society (May 2011) the experience with the worldwide first 200 cases were presented. 78% of the pulmonary veins were isolated on the first attempt. Of 107 patients with at least 6 months of follow-up, 65% was free from recurrence.[l]

4.3.3. Ultrasound balloon ablation

Catheter ablation with high-intensity focused ultrasound (HIFU) energy has been introduced as an innovative option for CA. Because the ultrasound energy is not absorbed by blood, it was presumed to have a lower risk of thrombo-embolic complications than radiofrequency ablation.[53]

In August 2005, ProRhythm Inc. received the European CE mark for its HIFU trans-catheter ablation system, allowing market access throughout the European Union.[m] In January 2008, the US Food and Drug Administration (FDA) allowed ProRhythm Inc. to proceed into the pivotal phase of an investigational device exemption (IDE) trial (known as "focusAF" - NCT00392106) to test the company's HIFU Ablation System. The clinicaltrial.gov website presently mentions that the study was voluntarily suspended by the sponsor "to investigate an anticipated serious adverse event".

k http://www.accessdata.fda.gov/cdrh_docs/pdf10/P100010b.pdf

l http://www.cardiofocus.com/pdf/Reddy,%20VY%20PV%20Isolation%20Using%20the%20Visually%20Guided%20Laser%20Balloon.pdf

m http://www.fdanews.com/newsletter/article?issueId=7932&articleId=75427

In 2010, investigators from Hamburg, Germany that were involved in most of the published HIFU studies, reported a series of HIFU ablations in which the authors focused on the safety of the procedure. Of 28 patients treated, complications occurred in 8 (28.6%): 2 patients died, 1 suffered a stroke, 2 had persistent phrenic nerve palsy, 1 had a pericardial effusion and 2 had endoscopic oesophageal thermal lesions. More than 4 years after CE marking, the authors concluded that HIFU did not meet the safety standards required for the treatment of AF.[54]

4.4. Discussion and summary of the impact of CA on rhythm control

Randomised trials published so far predominantly enrolled middle-aged men with paroxysmal AF and few co-morbidities.[19] From these trials it appears that AF reoccurred within one year in 11 to 44% of patients who had undergone ablation, versus in 42 to 91% of patients who had been treated with an antiarrhythmic agent. Recurrences after CA were lower in studies on paroxysmal AF (11 to 34%) than in those on non-paroxysmal AF (20 to 44%), but the data showed a large overlap (Table 2 and Figure 4).

Hard endpoints such as mortality or stroke occurred rarely in these small and short-term trials that were not statistically powered to estimate the impact of CA on those endpoints. To study an effect of CA on hard endpoints large trials are needed that include AF patients at higher risk than those enrolled in previous studies. The ongoing CABANA trial (NCT00911508) that will include 3000 patients is designed to this end.

The high incidence of cross overs in RCTs from drug therapy towards ablation is an important issue. As ablation therapy in selected patients performs better than antiarrhythmic drugs in (at least short-term) maintenance of sinus rhythm, these cross overs might dilute the presence or absence of an effect of ablation. On the other hand, in intention-to-treat analyses, they might conceal serious adverse effects induced by the ablation.

The interpretation of the effect of CA on rhythm control is somewhat complicated by the fact that in most trials, adequate rhythm control is defined either as the absence of symptoms, or the detection of AF by electrocardiographic monitoring during pre-specified time intervals. However, the major benefit of CA for AF is symptomatic relief.[19] It is as yet not fully clear whether the relative impact of ablation on any arrhythmia recurrence or on symptomatic recurrence differs.

A number of CA trials have been terminated and were presented at cardiology congresses but were not yet published in a peer reviewed journal. In some of them, newly developed devices were tested and performed poorly as compared to catheters used in the earlier trials.

Key points

- **RCTs indicate that catheter ablation of atrial fibrillation is more effective than antiarrhythmic drugs in the short term prevention of recurrence of AF in patients with few co-morbidities.**
- **There is a profound clinical heterogeneity between the RCTs in relation to patient characteristics, procedural modalities and definition of clinical endpoints.**
- **These RCTs are of moderate methodological quality because of their unblinded nature, the small number of inclusions and the high number of cross-over in some of them.**
- **AF recurrence at 1 year, being the primary endpoint in most trials, is observed in 11.0-50.0% of patients treated with catheter ablation and in 42.0-91.3% of those treated with an antiarrhythmic drug.**
- **The yearly recurrence rate of AF after the first year is estimated from observational studies to be between 6 to 9% per year.**
- **Results from unpublished RCTs indicate that, even though they received a European CE mark, newly developed catheters might not be as safe as older and more thoroughly tested devices.**

4.5. Impact of catheter ablation on quality of life

4.5.1. Literature search

A systematic search for quality-of-life (QoL) data was performed. In the first place, QoL data were searched in the identified HTA reports. The report of the Canadian Agency for Drugs and Technologies in Health (CADTH),[28] published in 2010, contains an overview of QoL measures with the generic SF-36 instrument (Table 5). This forms the basis for our review.

In a next step, QoL data were searched in the remaining RCTs not included in this HTA report (see Table 5).[35, 36, 38] First we checked whether QoL was included in the outcome measures mentioned on clinicaltrials.gov., with the following results:

- CACAF2 Study (NCT00227344): Quality of Life [Time Frame: 14, 26 & 38 Months] as a secondary outcome measure. No QoL data were included in the original publication. We mailed the corresponding authors for further information.[38] General results of this trial were already published in 2006.[38] One of the principal investigators was contacted for further information on QoL results, however, they remain unavailable. Study results, however, could not be retrieved.
- Curing Atrial Fibrillation in Heart Failure (NCT00292162): Quality of life is not mentioned as primary or secondary outcome measure. However, the publication includes SF-36 outcomes and is included in the overview.[35]
- The study of Oral et al.[36] is not registered in Clinicaltrials.gov, obviously because the study began already in 2002. We mailed the corresponding author for further information. A read receipt was received twice, however, no further details were provided.

Next, we performed a search in Medline and Embase. Search details are available in appendix 1. This search was a quick search since we preferred to focus on QoL results from the already identified RCTs. These studies have the advantage of having a control group and thus enabling to comment on the incremental effect of catheter ablation on QoL.

We identified 24 references in Medline and 50 in Embase. After removing duplicates, the remaining 59 references were searched by screening title, abstract and keywords. Only those studies comparing QoL in ablated patients versus a control group with another intervention were selected. Before/after comparisons without control group were not selected. As such, a study of Reynolds et al. was added to the overview.[55]

Finally, searching the grey literature, a 4-year follow-up study of Pappone et al. (APAF study) was identified.[41] Table 5 provides an overview of the selected studies that will be discussed in the following part.

Table 5 – Studies included in the QoL overview

References from the CADTH overview[28]
Wazni OM, Marrouche NF, Martin DO, Verma A, Bhargava M, Saliba W, et al. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of symptomatic atrial fibrillation: a randomized trial. JAMA 2005;293(21):2634-40.[39]
Wilber DJ, Pappone C, Neuzil P, De Paola A, Marchlinski F, Natale A, et al. Comparison of antiarrhythmic drug therapy and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: a randomized controlled trial. JAMA 2010;303(4):333-40.[40]
Forleo GB, Mantica M, De Luca L, Leo R, Santini L, Panigada S, et al. Catheter ablation of atrial fibrillation in patients with diabetes mellitus type 2: results from a randomized study comparing pulmonary vein isolation versus antiarrhythmic drug therapy. Journal of Cardiovascular Electrophysiology 2009;20(1):22-8.[32]
Jais P, Cauchemez B, Macle L, Daoud E, Khairy P, Subbiah R, et al. Catheter ablation versus antiarrhythmic drugs for atrial fibrillation: the A4 study. Circulation 2008;118(24):2498-505.[33]
Krittayaphong R, Raungrattanaamporn O, Bhuripanyo K, Sriratanasathavorn C, Pooranawattanakul S, Punlee K, et al. A randomized clinical trial of the efficacy of radiofrequency catheter ablation and amiodarone in the treatment of symptomatic atrial fibrillation. J Med Assoc Thai 2003;86 Suppl 1:S8-16.[34]
Pappone C, Rosanio S, Augello G, Gallus G, Vicedomini G, Mazzone P, et al. Mortality, morbidity, and quality of life after circumferential pulmonary vein ablation for atrial fibrillation: outcomes from a controlled nonrandomized long-term study. J Am Coll Cardiol 2003;42(2):185-97.[56]

Additional references

MacDonald MR, Connelly DT, Hawkins NM, Steedman T, Payne J, Shaw M, et al. Radiofrequency ablation for persistent atrial fibrillation in patients with advanced heart failure and severe left ventricular systolic dysfunction: a randomised controlled trial. Heart. 2011;97(9):740-7.[35]

Reynolds MR, Walczak J, White SA, Cohen DJ, Wilber DJ. Improvements in symptoms and quality of life in patients with paroxysmal atrial fibrillation treated with radiofrequency catheter ablation versus antiarrhythmic drugs. Circ Cardiovasc Qual Outcomes. 2010;3(6):615-23.[55]

Pappone C, Vicedomini G, Augello G, Manguso F, Saviano M, Baldi M, et al. Radiofrequency catheter ablation and antiarrhythmic drug therapy: a prospective, randomized, 4-year follow-up trial: the APAF study. Circ Arrhythm Electrophysiol. 2011;4(6):808-14.[41]

In our overview, the studies will be referred to by mentioning the first author of the publications.

There are different types of health-related QoL (HRQoL) instruments. The two well-known categories are the disease-specific and generic instruments. Within the latter category, a distinction can be made based on the results they present. Profile measures give a separate score for each of the health state dimensions included in the questionnaire and in some cases a summary score. An example of such a generic profile instrument is the SF-36. On the other hand, some generic instruments are utility measures and provide a single score for HRQoL on a 0 to 1 scale, where 0 is the value of death and 1 the value of perfect health. Examples of such generic utility instruments are the EQ-5D, SF-6D, and the HUI (Health Utility Index).

The identified studies used different instruments. Unfortunately, none of them used the generic utility instruments EQ-5D, SF-6D or HUI. The SF-36 was widely used. Furthermore, several disease-specific instruments were applied, such as the Kansas City Cardiomyopathy Questionnaire (KCCQ) and the Minnesota Living with Heart Failure Questionnaire (MLHFQ).[35] In general, we are more interested in the overall QoL, measured with a generic instrument. Applying disease-specific instruments might focus on e.g. the elements on which an improvement is expected while it might overlook the impact of the (un)expected side-effects. Therefore, and because all studies present results for the generic SF-36 instrument, outcomes for disease-specific instruments are not reported or discussed.

4.5.2. Overview quality-of-life measures

Table 6 provides an overview of the studies included in the Canadian HTA report,[28] reporting the impact on QoL measured with the SF-36 instrument. Table 7 present these results for the additionally identified studies.

The SF-36 (www.sf-36.org) is a health survey with 36 questions. This generic instrument yields an 8-scale profile of functional health and well-being scores as well as a physical and mental health summary measures. It works with a 4-week recall period, with the exception of the 'physical functioning' and 'general health' scales that do not have a recall period. For all SF-36 scales, higher scores represent better outcomes.

Most of the studies include paroxysmal AF patients. All but one of the studies are RCTs. The non-randomized study of Pappone et al.[56] was included in the overview of the Canadian HTA report, and therefore also presented in this overview.

The reported results of all these studies are in favor of the ablation group. There are no studies with significant worse QoL outcomes for the ablation group, whereas several of the eight subscales and/or physical and mental summary measures are often better than in the control group (see Table 6 and Table 7).

Table 6 – Quality-of-life measures (SF-36) in studies comparing catheter ablation with medical treatment.

Study	Study information	Time of Assessment (months)	Treatment (sample size)	Quality-of-Life Measure* B: Mean at Baseline, A: Mean after Intervention, C: Mean Change from Baseline [mean difference between groups, P value]							
				Physical Health				Mental Health			
				Physical Functioning	Physical Role	Pain	General Health	Vitality	Social Functioning	Emotional Role	Mental Health
Wazni et al. (2005)	RCT, first line, 96% par	6	Ablation (32/33)	B 71 ± 3 A 97 ± 3	B 73 ± 5 A 71 ± 2	B 71 ± 3 A 97 ± 1	B 57 ± 2 A 79 ± 1	B 52 ± 4 A 65 ± 1	B 78 ± 3 A 93 ± 3	B 70 ± 1 A 76 ± 1	B 65 ± 4 A 65 ± 2
			AADs (35/37)	B 69 ± 2 A75 ± 7.5 [20 (13.2 to 24.2); P = 0.001]	B 51 ± 5 A 53 ± 3 [14.9 ** (9.9 to 19.9); P = 0.047]	B 70 ± 3 A 90 ± 3 [6 (1.5 to 9.5); P = 0.004]	B 57 ± 2 A 68 ± 2 [11 (8 to 14); P < 0.001]	B 51 ± 1 A 60 ± 2 [4 (1.7 to 5.7); P = 0.21]	B 76 ± 3 A 82 ± 2 [9 (7.5 to 11.5); P = 0.004]	B 70 ± 1 A 75 ±1 [1 (−4.0 to 4.3); P = 0.90]	B 64 ± 2 A 68 ± 3 [−4 (−7.5 to −3.5); P = 0.62]
Wilber et al. (2010)	RCT, 100% par	3	Ablation (90/106)	C 6.9 (5.2 to 8.6)				C 8.5 (5.9 to 11.1)			
			AADs (39/61)	C 0.4 (-1.7 to 2.6) [6.6 (3.6 to 9.4); P < 0.001]				C 1.6 (−1.1 to 4.3) [6.9 (2.6 to 11.2); P < 0.001]			
Forleo et al. (2009)	RCT, 41% par	6	Ablation (35)	NR	NR	NR	NR	NR	NR	NR	NR
			AADs (35)	NR [8.4; P < 0.05]	NR	NR [5.9; P < 0.05]	NR [8.9; P < 0.05]	NR	NR [7.7; P < 0.05]	NR [6.8; P < 0.05]	NR
Jaïs et al. (2008)	RCT, 100% par	12	Ablation (53)	B 44.8 ± NR, A 52 ± 7.6				B 46.1 ± NR, A 56.6 ± 7.8			
			AADs (59)	B 43.0 ± NR, A 48.9 ± 7.2 [P = 0.015]				B 44.0 ± NR, A 51.9 ± 9.7, [P = 0.09]			
Krittaya-phong et al. (2003)	RCT, 66% par	12	Ablation (14/15)	B 62.7† ± NR A 85.4† ± NR	NR	NR	B 46 ± NR A 66 ± NR	NR	NR	NR	NR
			AADs (15/15)	B 70.8† ± NR A 68.1† ± NR [P = 0.69]	NR	NR	B 42 ± NR A 44 ± NR [P = 0.048]	NR	NR	NR	NR
Pappone et al. (2003)	non-randomized study	12	Ablation (109)	B 38.7† ± NR, A 50† ± NR				B 41.3† ± NR, A 49.5† ± NR			
			AADs (102)	B 39.5† ± NR, A 40.5† ± NR [P = 0.007]				B 42.6† ± NR, A 43.9† ± NR [P = 0.004]			

AAD = antiarrhythmic drug; AF = atrial fibrillation; NR = not reported.
** Data presented as mean ± standard deviation or mean (95% confidence interval).*
*** The mean difference in the study of Wazni et al. for the 'physical role' item is implausible. The published numbers show a small decrease in the score of the ablation group and vice versa for the AAD group, while the corrected difference in mean change would be in the advantage of the ablation group.*
† Numbers estimated from graphs.
Source: Assasi et al.[28]

Table 7 – Quality-of-life measures (SF-36) in studies comparing catheter ablation with medical treatment. (additional information)

Study	Study information	Time of Assessment (months)	Treatment (sample size)	Quality-of-Life Measure* B: Mean at Baseline, A: Mean after Intervention, C: Mean Change from Baseline [mean difference between groups, P value]							
				Physical Health				Mental Health			
				Physical Functioning	Physical Role	Pain	General Health	Vitality	Social Functioning	Emotional Role	Mental Health
Pappone et al. (2011)	RCT, first line, 100% par	48 (ITT)	Ablation (99)	B 44.4 ± 9, A 52.3 ± 9				B 43.7 ± 11, A 52.9 ± 9			
				B 69 ± 18	B 63 ± 19	B 68 ± 19	B 65 ± 17	B 56 ± 22	B 68 ± 22	B 70 ± 24	B 66 ± 21
				A 85 ± 12	A 82 ± 14	A 80 ± 17	A 79 ± 15	A 71 ± 23	A 87 ± 14	A 86 ± 18	A 81 ± 17
			AADs (99)	B 45.7 ± 9, A 52.6 ± 8				B 44.4 ± 10, A 51.9 ± 9			
				B 68 ± 21	B 61 ± 17	B 66 ± 24	B 67 ± 17	B 55 ± 18	B 66 ± 20	B 70 ± 22	B 67 ± 19
				A 82 ± 15	A 80 ± 15	A 77 ± 21	A 77 ± 16	A 68 ± 21	A 86 ± 14	A 84 ± 19	A 78 ± 17
		10.1 ± 7.2	AADs (87)	B 45.3 ± 9, A 44.1 ± 7 (P = 0.013)				B 43.2 ± 11, A 42.5 ± 10 (P = 0.009)			
				B 69 ± 20	B 61 ± 16	B 65 ± 23	B 65 ± 17	B 56 ± 17	B 65 ± 19	B 67 ± 22	B 63 ± 17
		(A = before crossing)		A 67 ± 16	A 61 ± 14	A 63 ± 19	A 63 ± 17	A 53 ± 16	A 64 ± 17	A 66 ± 19	A 62 ± 15
				P = 0.015	P = 0.849	P = 0.124	P = 0.020	P = 0.003	P = 0.051	P = 0.133	P = 0.183
Reynolds et al. (2010)	RCT, 100% par	9 months after blanking	Ablation (99)	C [6.1 (4.5 to 7.7); P < 0.001]				C [7.6 (5.3 to 10); P < 0.001]			
				C [13.4 (10 to 17); P < 0.001]	C [24.6 (19 to 30); P < 0.001]	C [13.7 (8 to 19); P < 0.001]	C [9.4 (5.7 to 13); P < 0.001]	C [16.9 (12 to 22); P < 0.001]	C [21.2 (16 to 26); P < 0.001]	C [15.2 (10 to 21); P < 0.001]	C [11.6 (7.8 to 15); P < 0.001]
			AADs (17)	C [0.2 (-4.1 to 4.5); P = 0.92]				C [1.4 (-4.2 to 7); P = 0.61]			
				C [3.4 (-8.1 to 15); P = 0.54	C [1.8 (-12 to 16); P = 0.78	C [-2.1 (-19 to 14); P = 0.79	C [1.1 (-11 to 13); P = 0.84	C [8.5 (-4.1 to 21); P = 0.17	C [-5.9 (-17 to 5.3); P = 0.28	C [5.4 (-9 to 20); P = 0.44	C [1.2 (-7.3 to 9.7); P = 0.77
MacDonald et al. (2010)	RCT, heart failure, 100% per	6	Ablation (20/22)	B 30.3 ± 9.2, C +4 ± 9.5				B 40.7 ± 10.2, C +0.4 ± 9.5			
			rate control (18/19)	B 30.3 ± 7.1, C -1 ± 4.4 P = 0.042				B 37.1 ± 14.0, C +5.9 ± 8.5 P = 0.07			

* *Data presented as mean ± standard deviation or mean (95% confidence interval).*

4.5.3. Discussion

The evidence on QoL impact of catheter ablation is rather weak for several reasons.

First of all, most studies include a *small number of patients*. For example, Wazni et al. included 70 patients and found a significant improvement in 5 subclasses of the SF-36 at a 6-month follow-up in the ablation versus the antiarrhythmic drug group, but concluded that larger studies are needed to confirm its safety and efficacy. The study of Forleo et al., including 70 patients, was also "*a pilot study and, therefore, inherently limited by the small number of patients enrolled*".[32] Krittayaphong et al.[34] and MacDonald et al.[35] also included only 30, and 41 patients, respectively. Results in the short-term (first three months) are positive. Nevertheless, there are much more major shortcomings that are discussed in the following parts.

The study of Wilber et al. only reported QoL outcomes in 85% (90/106) of the ablation group and only 64% (39/61) in the AAD group. It is not clear how this *loss to follow-up* has an impact on results.

Of the larger studies, QoL improvements were difficult to interpret due to the *large number of cross-overs*. In the study of Jaïs et al.,[33] patients in the AAD group were allowed to cross-over and undergo an ablation procedure after 90 days, and vice versa. In this study there were 63% cross-overs in AAD group and 9% cross-over in the ablation group. In Reynolds et al.[55] during 9 months of follow-up after the blanking period, 64% (36/56) of the patients assigned to AAD therapy underwent an ablation procedure because of recurrent AF and/or treatment-related adverse events. In the study of Pappone et al. (2011),[41] at 4 years, 87.9% (87/99) in the AAD group with recurrent paroxysmal AF (68 patients) or persistent AF (19 patients) crossed over to undergo ablation with a mean time to cross-over of 10.1 ± 7.2 months (min-max, 4–31).[41]

There is only one study in this overview with a follow-up of more than one year.[41] However, due to the large cross-over (87.9%), *long-term QoL improvements remain unknown* in comparison with the control arm. This can be important if one takes into account the 6-9% yearly recurrence of AF after the first year in the ablation arm.

In the same study,[41] the researchers also looked at *QoL just before crossover*. However, comparing the ablation arm with QoL in the control arm just before crossing over gives a distorted picture because QoL is measured in this group probably at the moment they are in the worst condition. Fichtner et al.[57] also performed QoL-research on AF patients treated with ablation. Patients had to fill in questionnaires the evening before ablation. The authors mentioned that it might be speculated that the lower QoL before ablation was biased by anxiety in the light of an upcoming invasive procedure.

The study of Pappone et al. (2003)[56] is the only *non-randomized study* in this QoL overview. 589 ablated patients were compared with 582 patients who received antiarrhythmic medications for sinus rhythm control. The QoL of 109 ablated and 102 medically treated patients was measured with SF-36. In this study, however, Kaplan-Meier analysis showed a statistically ($p<0.001$) improved observed survival for ablated patients. No RCT has ever been able to prove this, which may indicate that the populations in this study are not comparable and thus comparisons are probably not reliable.

Studies were *unblinded*, and thus QoL outcomes could have been affected by expectation or placebo effects.[55] In a before/after study of Fichtner et al.[57], ablation of AF patients significantly improved QoL irrespective of ablation success. It is not clear whether this is related to the placebo effect or to the previously reported problem related to before/after comparisons.

Finally, there is potential for *publication bias*. At clinicaltrials.gov, the CACAF2 study (NCT00227344) mentions to measure QoL at 14, 26 and 38 months as a secondary outcome measure. General results of this trial were already published in 2006.[38] One of the principal investigators was contacted for further information on QoL results, however, they remain unavailable. Vice versa, some studies do not mention QoL as a primary or secondary outcome on clinicaltrials.gov, although they publish such results later on. The Curing Atrial Fibrillation in Heart Failure (NCT00292162) trial of MacDonald et al.[35] is such an example. The study of Pappone and colleagues included its last patient on May 11, 2005. In contrast, the study was registered on June 19, 2006, i.e. when all patients already had one year of follow-up. Furthermore, clinicaltrials.gov (NCT00340314) and the first publication in 2006[37] did not mention anything on measuring QoL. In 2011, such outcomes after 4 years of follow-up are published.[41]

4.5.4. Conclusion

When looking at the effects on patients' quality of life, there are indications that patients with clear symptoms of AF experience an improvement in their condition after successful catheter ablation, at least in the short term. In the long term, the evidence is weaker because of the small number of patients included in the trials and the high crossover percentage. Trying to compensate for the latter, measurements in the control group are performed immediately prior to the crossover. However, this does reinforce the possible bias because, in that case, measurements are performed at a time when patients feel at their worst. There is also some evidence of reporting bias. For instance, we came across a study (CACAF2) where quality of life was a previously defined study endpoint, yet was never reported on in the final publication. In another study (APAF) quality of life was not an endpoint, not reported in the publication with 1-year follow-up, though it was reported on 4 years later.

Key points

- **There is evidence that catheter ablation improves the short-term quality of life (QoL), measured with the generic SF-36 instrument.**
- **The evidence is rather weak due to: small studies, large cross-over, possible placebo effect, timing of QoL measurement, and indications for publication bias.**
- **There is no evidence available on the impact on QoL, measured with a generic utility instrument.**
- **Trials are not always registered in due time and do not always mention all of the primary and secondary endpoints. Furthermore, results are not always published or available for all registered endpoints, including QoL.**

5. SAFETY OF CA-AF

5.1. Procedural risks

Catheter ablation of AF is a complex interventional procedure with relatively rare but potentially life-threatening complications. This is all the more important since the procedure is currently studied and advocated in patients with AF at low risk for complications of this arrhythmia.[19, 58] Major complications of radiofrequency CA-AF include death, cardiac tamponade, atrio-esophageal fistula, stroke, pulmonary oedema, and pulmonary vein stenosis. Less severe complications include vascular access problems and phrenic nerve paralysis. The latter results from ablation damage to the phrenic nerve that is located at the outer side of the heart, close to the right superior pulmonary vein.[59]

The systematic reviews we retrieved from our literature search for assessing clinical effectiveness of CA were of little use to assess the procedure's safety. Bonanno et al.[30] in their meta-analysis inappropriately pooled minor secondary effects of drugs such as "corneal deposits" with major events such as stroke or death. In Parkash' SR, safety was not an endpoint. A brief and poorly documented paragraph was spent on this issue, concluding that "overall, the risk of serious complications was low".[31]

A systematic review of RCTs that compared CA-AF with AADs or with a different CA approach reported an incidence of major complications occurring in 97/1964 patients (4.90%).[60] In a worldwide survey, conducted twice by the same author covering different time windows, major complications as voluntarily reported by electrophysiologists occurred in 5.90[61] and 4.54%[44] of patients (Table 8). From the most recent survey, death occurred in 0.15% of patients, stroke in 0.23% and transient ischemic attack in 0.71% (Table 8).[44] Recently, data were published from the California State Inpatient database, derived from administrative data from non-federal hospitals in California in 2005 through 2008.[62] Complications during the index hospitalisation occurred in 211/4156 (5.1%) of patients. All-cause 30-day rehospitalisation rate was 390/4156 (9.4%).

In a prospective single-centre study related to 784 patients that underwent CA-AF in 2009 and 2010, the overall rate of complications was 5.2%.[63] In a series of 1295 patients, consecutively treated in a single centre between 2007 and 2010, there were no procedure related deaths with a lower incidence of stroke (0.07%) or TIA (0.15%) compared to the other studies.[64]

In a study reporting complications in 1190 patients treated between 2002 and 2010, there were also no procedural deaths. Over the years, the overall complication rate in this series decreased from 11.1% in 2002 to 1.6% in 2010. The authors attribute this improvement to their increased institutional experience.[65]

In June 2012, a European survey (Arbelo et al.) was published ahead of print.[58] It collected data on 1410 patients treated between October 2010 and May 2011 in 72 European centres, among which five were Belgian. In-hospital complications occurred in 7.7% of patients. Major complications as depicted in Table 8 were reported in 2.82% of patients.

Table 8 – Major complications of radiofrequency CA-AF

Author Time window	Cappato 1995-2002	Cappato 2003-2006	Shah 2005-2008	Baman 2007-2010	Arbelo 2010-2011
Number of patients in study	8745	16309	4156	1295	1410
Death - %	0.05	0.15	0.24	0	0.07
Tamponade - %	1.22	1.31	2.79	1.2	0.78
TIA - %	0.66	0.71	0.77	0.15	0.28
Stroke - %	0.28	0.23		0.07	0.28
PV stenosis - %	1.63	0.29	NR	<0.01	NR
Vascular - %	0.95	1.47	5.97	1.9	1.27
Permanent phrenic nerve palsy	0.11	0.17	NR	0	0.14
Overall complications - %	5.9	4.54	5.1*	3.5	7.7

**during index admission only; NR: not reported.*

The occurrence of stroke as a complication of CA-AF has been related to thrombus formation at the tip of the catheter or on the surface of the ablated area. This may lead to clinical stroke (Table 8) as well as to silent stroke documented by MRI scanning. In a prospective analysis of 53 patients at low risk for clinical stroke, new micro-embolism was demonstrated in six of them (11%).[27, 66] The occurrence of silent micro-embolism has been found to occur especially often in patients treated with a multi-electrode radiofrequency ablation catheter. MRI documented lesions have been found in two recent studies in 37.5% and 38.9% of patients treated with the multi-electrode device, versus 7.4% and 8.3% respectively in those treated with the conventional device.[67, 68]

The results from unpublished studies mentioned above provide additional important information on the risks a patient may be running when submitted to catheter ablation.

- The different position taken by European and US regulatory authorities towards the market access of the phased radiofrequency catheter that was tested in the TTOP-AF study is remarkable, and raises questions as to whether European patients are exposed to unwarranted risks. The catheter system involved (Medtronic Ablation Frontiers Cardiac Ablation System®) already gained market approval in Europe in 2006, whereas the FDA in 2011 concluded that, although the device was believed to be effective, available data did not provide reasonable assurance about its safety.
- The debacle of high-intensity focused ultrasound (HIFU) balloon catheter ablation discussed earlier dramatically illustrates that the un-safety of certain devices may become publicly known only several years after its approval for use on the European market.[54]
- Experience with the HD Mesh Ablator®, marketed by C.R. Bard Inc. and granted CE Mark clearance in Europe in 2006, represents another example showing that CE labelling not only is no guarantee for safety, but does not indicate a given device is clinically effective. In the early months of 2012, our search through grey literature brought us to the MACPAF study, the “Mesh Ablator Versus Cryoballoon Pulmonary Vein Ablation of Symptomatic Paroxysmal Atrial Fibrillation” study. The primary objective of the RCT was to assess the efficacy of achieving pulmonary vein isolation in patients with paroxysmal AF by using a cryo-ablation device (Arctic Front®) versus the radiofrequency device (HD Mesh Ablator®). Secondary objectives were the detection of silent thrombo-embolism to the brain at 2 days and 6 months, and the determination of AF recurrence rates.[27] The study was sponsored by a German university and German federal authorities (Charite University, Berlin; German Federal Ministry of Education and Research).

The clinicaltrials.gov website mentions that the MACPAF trial (NCT01061931) has been terminated, but without providing a reason for this. In March 2012 we sent two separate e-mails to the principal investigator and to a co-author asking for the reason of the termination of the MACPAF study. Both mails remained unanswered. In April 2012, a request was forwarded to representatives of manufacturers in Belgium, specifically asking further information on unpublished and ongoing trials, among them the MACPAF trial. In answer to a first e-mail, we were informed by C.R. Bard that "the company had no trials to mention". In a second inquiry in May 2012, the company answered that "at the moment we have no official trials".

A repeat search in June 2012 learned that the results of the MACPAF study were published ahead of print.[69] The paper had been submitted for publication on January 2nd, 2012. Although the investigators mention that they had a considerable amount of experience with both devices, an interim analysis indicated that complete pulmonary vein isolation could be obtained in none of the 15 patients treated with the Mesh ablator. Early recurrence of AF in-hospital was detected in 7 of them (46.7%). One of those patients needed a pericardial drainage for heart tamponade, one other had a pericardial effusion and one developed an inguinal aneurysm. Because of these poor results, the safety board of the study decided to stop the trial prematurely.

The Mesh Ablator® account not only illustrates that CE marking of a device does neither indicate its clinical effectiveness nor its safety. It also exemplifies the information and publication bias HTA experts are confronting in doing their job.

A cautionary note is needed on the very high rate in RCTs of cross-over of patients initially allocated to drug treatment, towards catheter ablation. In one trial, 77% of patients crossed over to ablation by one year.[36] In the 4 year follow-up results of another trial, every patient who initially was allocated to drug treatment and subsequently developed AF recurrence, crossed over to catheter ablation.[41] Although cross-over of patients from one study arm to another may dilute the presence or absence of an effect of an interventional procedure, it may also mask a difference in the occurrence of adverse events in an intention to treat analysis. This is no trivial matter when comparing an invasive procedure that is accompanied with up to 3% life threatening complications, with drug treatment in which severe adverse events very rarely occur. For example, in the as yet unpublished MANTRA-PAF study mentioned before (§ 4.2.3.4), there were three deaths in the ablation group and four deaths in the drug group (total study group: n=294). It is not clear from the limited available data what the reasons for dying were and whether or not they were related to catheter ablation as a cross-over treatment in patients initially allocated to the AAD group.

5.2. X-ray burden

CA-AF is often a long procedure requiring extended periods of fluoroscopy time. In 50% of patients redo-procedures are needed and moreover, CA-AF usually is preceded and sometimes followed by radiologic investigations, further adding to the X-ray burden.[45] In a series of 1007 ablation procedures, performed between 2004 and 2007, fluoroscopy time was about 55 minutes for a single CA-AF.[70] Older studies reported mean fluoroscopy durations of 129±36,[71] 57±30,[72] and 79±29[73] minutes. Much shorter fluoroscopy times are reported in the Belgian BeHRA database: average 29.21±17 min (median 25, range 0-150) for paroxysmal AF ablation and an average 38±25 min (median 32, range 2-158) for persistent AF. These are in accordance with recent European data on 1410 patients in whom fluoroscopy time was 26 minutes (IQR: 15-45 min).[58]

Depending on the laboratory infrastructure, the operator's skills, patient characteristics and the methods used to quantify radiation exposure, this fluoroscopy time may give rise to a variable radiation exposure. Consequently, mean effective radiation doses between 1.10 and 27.25 mSv have been reported,[70] which is equivalent to a dose incurred by between 50 and 1350 chest radiographs.[74] From these numbers, a fatal malignancy risk for a typical CA-AF case attributable to X-ray exposure has been estimated to lay between 155[71] and 2099[70] per million, i.e. approximately 0.2 to 2.1 pro mille.[74]

Key points

- **Life threatening risks associated with catheter ablation of AF occur in up to 3% of patients and include cardiac tamponade (in 1 to 3% of cases), stroke (1 and 3 per 1000) and death (0 to 2 per 1000).**
- **Less severe complications that may require re-hospitalisation and surgery occur in 3 to 5% of patients.**
- **There is also a 0.2 to 2.1 in 1000 delayed risk of patients developing a fatal cancer induced by prolonged exposure to X-rays during the procedure.**
- **The fact that a device has been granted a CE mark does neither guarantee its safety nor its clinically effectiveness.**
- **Cross over of patients between study arms may in an intention to treat analysis mask differences in the occurrence of adverse events between intervention and control groups.**
- **Publication bias in its broadest sense (updating of on-line trial registers, publication in peer reviewed journals, disclosure of data by manufacturers), represents a serious threat in the full assessment of the safety of ablation devices.**

6. BELGIAN PRACTICE

6.1. Introduction

Electrophysiological (EP) testing refers to a spectrum of invasive procedures intended to diagnose cardiac arrhythmias by means of catheters that are positioned within the cardiac cavities through the vascular system. Although the technique initially was developed for diagnostic purposes, its use has been extended towards therapy through its potential to deliver energy via the catheters to distinct parts of the inner surface of the heart.

By the end of 2007, a major reform of the reimbursement of EP procedures was negotiated. Until then, there were only 3 nomenclature[n] numbers for EP testing (EPT), applicable to both diagnostic and interventional procedures and there was no reimbursement of catheters that were used during these procedures. Table 9 shows the number of procedures and INAMI-RIZIV expenses for 2007.

[n] The nomenclature is the official list of reimbursed health provisions.

Table 9 – Electrophysiology nomenclature codes (cases and RIZIV-INAMI expenditures) claimed in 2007

Nomenclature codes		Outpatients		Inpatients		Total	
		n	EUR	n	EUR	n	EUR
476291-476302	limited EPT	46	6 274	445	63 645	491	69 919
476276-476280	extensive EPT	518	459 380	7 130	6 372 613	7648	6 831 993
Total		564	465 654	7 575	6 436 258	8139	6 901 912
589315-589326*	Any ablation	50	33 461	3 384	2 269 292	3434	2 302 753
Total							9 204 665

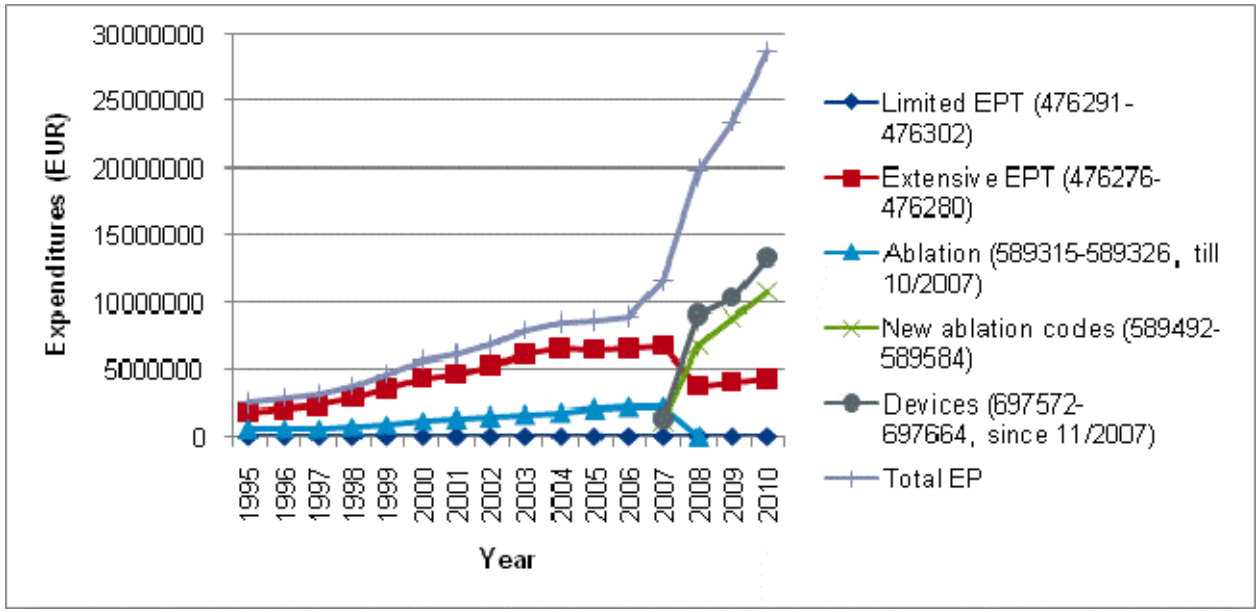
*EPT: Electrophysiological testing. *nomenclature numbers suppressed from 1 November 2007 on.*

The renewed nomenclature that became effective on 1 November 2007 provided nomenclature numbers to specific diagnostic and therapeutic interventions. Moreover, a reimbursement for the catheters was introduced. Catheter ablation of atrial fibrillation was reimbursed at €4 970 (€5 737 with 3D navigation material) per case in November 2007, including physician's fee and catheters as follows:

- €2 152 (€2 320.55 in 2012) for the procedure (589551-589562)
- €2 817.86 (€2 844.06 in 2012) for the catheters (697631-697642)
- Optionally, €766.78 for the additional material for 3D navigation (697653-697664)

The nomenclature codes are listed in Appendix.

Figure 5 – RIZIV/INAMI reimbursements for electrophysiology

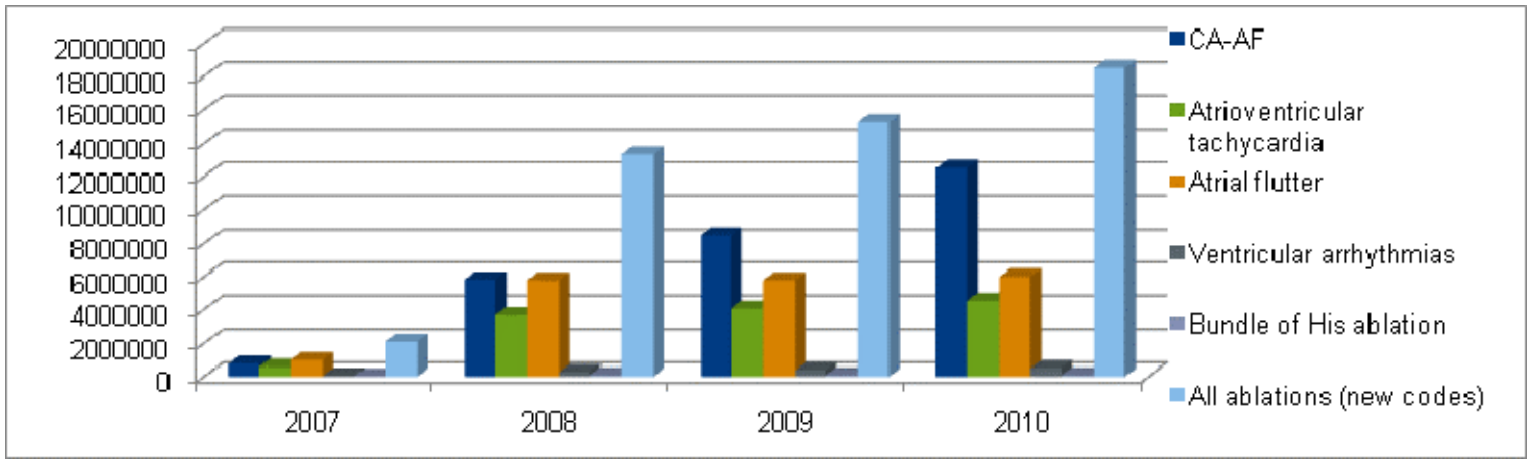


Before 2007, one single code was used for therapeutic interventions (i.e. catheter ablation), whereas two different codes were in use for diagnostic procedures (i.e. EPT – electrophysiologic testing –sensu stricto). In November 2007, the single code used for ablation procedures was replaced by several other specific codes. In the graph above, "new ablation codes" refer to all new codes for ablations, including those for AF. The increase of the expenditure for ablations after 2007 is mainly due to the increase of CA-AF.

From Nov 2007 on, the renewed nomenclature allowed to identify the cardiac arrhythmia for which the EP procedure was performed. Figure 5 indicates that the increase in total EP expenditure after 2007 is mainly related to an increase of CA-AF procedures.

The number of catheter ablations for AF doubled from 993 in 2008 to 2064 in 2010. In 2009, the amount of money reimbursed for CA-AF (fees and devices, €8.5 million) was 46% higher than the corresponding amount in 2008 (€5.2 million). In 2010 (€12.5 million), it was 47% higher than in 2009 (Figure 6).

Figure 6 – Costs of ablations: fees and devices (11/2007-12/2010)



Nomenclature codes (see Appendix): CA-AF (589551-589562, 697631-697642, 697653-697664), Atrioventricular tachycardia (589492-589503, 697572-697583), Atrial flutter (589514-589525, 697594-697605), Ventricular arrhythmias (589536-589540), Bundle of His ablation (589573-589584), all ablations (589492, 589503, 589514, 589525, 589536, 589540, 589573, 589584, 697631, 697642, 697653, 697664, 697572, 697583, 697594, 697605).

6.2. Data sources and methodology

6.2.1. IMA-AIM data

This section describes the characteristics of the patients that underwent a first catheter ablation of atrial fibrillation. Data were extracted from the Intermutualistic Agency (IMA-AIM) databases which contains health data (reimbursed health care use attestations and reimbursed drugs per patient) and population data over the members of the 7 Belgian sickness funds.

For the purpose of this study, IMA-AIM provided health consumption, drugs delivery and population data from 2006 to 2010 over patients that underwent a CA-AF (nomenclature codes 589551-589562) between 1 November 2007 and 31 December 2008. Patients included in the analysis (n=830) are those who had no previous catheter ablation procedure (nomenclature codes 589315-589326) between 1 January 2006 and 31 October 2007, suggesting that the CA-AF of interest was the first such procedure in a given patient ; patients with a planned major cardiac surgery[o] the same day as the CA-AF (n=10) were excluded. The follow-up period is thus between 24 and 38 months, depending on the date of the index CA-AF (mean=919 days or 30.2 months, n=830).

[o] Nomenclature code 229600, Dutch: "Operatie op het hart of op de grote intrathoracale bloedvaten die de plastiek of het plaatsen van een kunstklep omvat, met extracorporele circulatie", French : « Opération sur le coeur ou les gros vaisseaux intrathoraciques qui comporte la plastie ou la mise en place d'une valve artificielle, avec circulation extracorporelle »

6.2.2. Other data

The Belgian Heart Rhythm Association (BeHRA) kindly provided us aggregated data from its ablation register which contains data from most Belgian centres and about 85% of all the ablations – not only CA-AF). The overall distribution of paroxysmal/persistent AF is 77.3% for paroxysmal AF and 22.7% for persistent AF. This, along with other data available from BeHRA, is summed up in Table 10.

Table 10 – BeHRA 2008-2011 clinical data

	Paroxysmal AF		Persistent AF	
	Mean	Median	Mean	Median
procedure time (min)	185	180	204	200
fluoroscopy time (min)	29	25	38	32
age of the patient (years)	59	60	58	60
gender of the patient (% female)	29.4%		25.9%	
use of 3D (%)	89.4%		87.7%	

"use of 3D" refers to whether a 3-dimensional navigation device has been used during the procedure, for which an additional nomenclature code can be claimed (697653-697664)

The 3 main Belgian sickness funds (MC/CM, UNMS/NVSM and MLOZ), covering 90% of the insured Belgian population, also kindly shared some of their data coming from their data warehouses.

Table 11 shows an overview of the three data sources. BeHRA numbers are somewhat lower than those from IMA - AIM since not every Belgian centre participates in the BeHRA database. Based on a comparison with INAMI-RIZIV, IMA - AIM data should be complete for 2009 and almost complete (lacking at most 2% of procedures) for 2010.

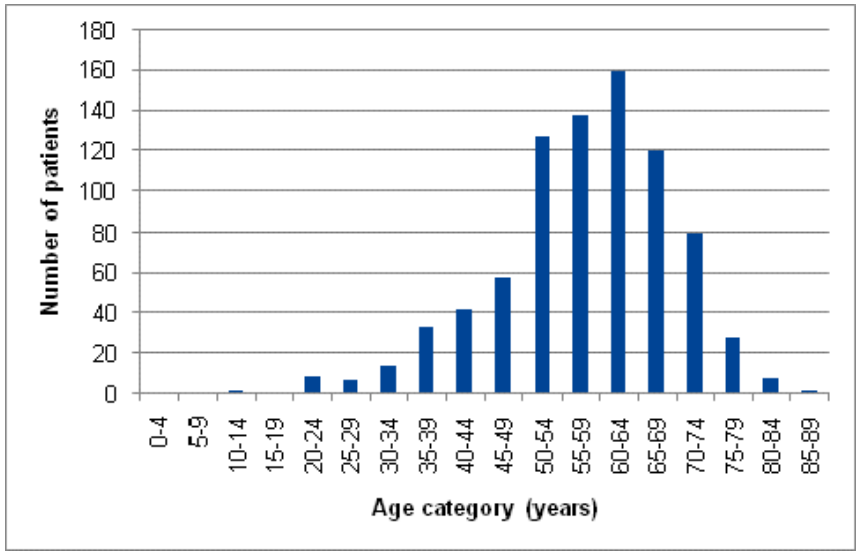
Table 11 – CA-AF procedures in Belgium: available data sources

Year	Number of procedures (589551-589562)			Number of centres (589551-589562)	
	BeHRA	IMA/AIM	3 main sickness funds	BeHRA	3 main sickness funds
2007		137			
2008	766	993		21	
2009	1475	1492	1381	23	27
2010	1947	2064	1855	25	27
2011	2183		2121	26	27

6.3. Population description

The mean (median) age is 58 (59) years old. Figure 7 shows the age distribution of the population (n=830). There were 597 men (71.9%) and 233 women (28.1%).

Figure 7 – Age distribution of the study population (n=830)



As we only have administrative data, only the month and year of decease were available, so we calculated the decease at maximum 60 days after the CA-AF (the same month or the month after). Out of the 830 patients, 6 patients (0.7%) died within maximum 60 days after the first CA-AF. The reason of death could not be determined from the available administrative data. None of the patients involved had a thoracic surgical procedure the same day as the CA-AF. In total, 20 patients died during the period studied.

6.4. Results

6.4.1. Number of CA-AF per patient

We looked at the number of CA-AF (nomenclature codes 589551-589562) per patient. There were 9 patients with 2 CA-AFs the same day, which should normally not happen and is probably due to an administrative error. Table 12 shows the number of CA-AF per patient. For the purpose of this study, repeat CA-AFs the same day as the first one weren't considered as a redo.

Table 12 – Number of CA-AF per patient

Number of CA-AF per patients	Number of patients (n=830)	Number of patients (not counting multiple CA-AF the same day)
1	610	616
2	187	183
3	31	29
4	1	2
5	1	0
Total number of patients	830	830
Total number of CA-AF	1 086	1 077
Mean CA-AF per patient	1.31	1.30

6.4.2.

6.4.3. Patients' risk profile

Patients who were chronically prescribed anticoagulants were considered as those at high risk for future events. This assumption is based on the recommendation from international guidelines that patients at high risk for thrombo-embolic complications should be treated with anticoagulants.

As a proxy to the prescription of anticoagulants drugs, we used the international normalized ratio (INR) tests (codes 554573, 554654 and 554595, see appendix) since the daily dose of a given anticoagulant may be largely different between patients. Patients with a test at least every 6 weeks for minimum 18 weeks were considered as patients on maintenance anticoagulation therapy. All of them were indeed delivered anticoagulants according to Pharmanet database. This was calculated for the period 6 months before the index CA-AF until the end of the follow-up in the present study. From a total of 830 patients, 146 (17.6%) were on maintenance anticoagulation therapy before the catheter ablation, versus 58 (7.0%) afterwards (Table 13 – Patients on maintenance anticoagulation treatment. These data confirm that most patients were not at high risk for stroke (CHA_2DS_2-VASc score of 0 or 1; cf. §2.3.3).

We did not collect data on the use of anticoagulants on the day of the intervention.

Table 13 – Patients on maintenance anticoagulation treatment

	Patients on maintenance anticoagulation drugs
Before CA-AF	146
After CA-AF (with a 3 months blanking period)	76
Treatment till December 2010 (=end of database)	58
Total patients	181

Patients treated before and after are not necessarily the same individuals.

6.4.4. Antiarrhythmic drugs

We analysed the use of antiarrhythmic drugs (AADs, ATC3 = C01B, antiarrhythmics, class I and III) before and after the first CA-AF. A patient was considered to follow an AAD treatment when receiving at least one delivery of an AAD according to the Pharmanet database[p]. We separated the treatments before the first CA-AF from those following the procedure, taking into account a blanking period of 3 months. The latter indicates that a patient is considered to be treated with a given AAD only if delivery of that drug took place more than 3 months after the index ablation.

In the present report, antiarrhythmic drugs (AAD) are those mentioned in the ATC database[q] under de heading C01B ("Antiarrhythmics, class I and III). This list does not contain sotalol, a beta-blocking agent (ATC code C07A) that also possesses antiarrhythmic class III effects.[75, 76] Therefore, data related to the use of sotalol are in some instances mentioned separately when deemed appropriate.

[p] The ambulatory (public pharmacy) delivery of medication, available from the IMA-AIM database

[q] http://www.whocc.no/atc_ddd_index/?code=C01BC04

Table 14 – Antiarrhythmic drug treatments

Molecule	ATC	number of patients	number of packages	DDD	number of patients before CA-AF	% of patients before CA-AF (n=830)	number of patients after CA-AF (with 3 m blanking period)	% of patients after CA-AF (n=830)
Amiodarone	C01BD01	378	3 362	192 640	317	38%	175	21%
Cibenzoline	C01BG07	66	595	27 890	56	7%	26	3%
Disopyramide	C01BA03	11	147	3 745	9	1%	2	0%
Flecainide	C01BC04	592	7 020	335 535	464	56%	359	43%
Propafenone	C01BC03	113	926	51 700	93	11%	34	4%
Quinidine	C01BA01	1	1	21	1	0%	0	0%
Total AAD class I and III	**C01B**	**756**	**12 051**	**611 531**	**667**	**80%**	**516**	**62%**
Sotalol	C07AA07	412	4 558	252 700	336	40%	233	28%
Beta-blockers (including sotalol)	C07A	759	14 947	564 947	683	82%	597	72%

There were 756 patients with a least one AAD prescription. After the blanking period of 3 months following the CA-AF, 62.2% of the patients (516 out of 830 patients studied) received at least one prescription of an AAD.

Half of the patients have taken more than one AAD before the index ablation (Table 15).

Table 15 – Number of class I and III AADs prescribed before the CA-AF

Number of AADs before CA-AF	Number of patients (n=830)	Time span between first prescription and index CA-AF (days)				% of patients treated with amiodarone
		Mean	Q1	Median	Q3	
0	19.6% (163)	-	-	-	-	0% (0)
1	51.4% (427)	467	138	350	801	30.9% (132)
2	25.2% (209)	643	447	707	865	77.0% (161)
3	3.5% (29)	662	492	765	881	75.9% (22)
4	0.2% (2)	812	632	812	993	100% (2)

6.4.5. Rate control drugs

We looked at prescriptions of rate control drugs, which belong to the following ATC classes:

- ATC2 = C07 (beta blocking agents)
- ATC5 = C08DA01 (verapamil) or C08DB01 (diltiazem), which are selective calcium channel blockers
- ATC4 = C01AA (digitalis glycosides)
- We analysed sotalol (ATC5=C07AA07) separately, as it has both rate and rhythm controlling properties.

Based on administrative data, it cannot be concluded that the delivery of a rate control drug was prescribed to treat AF. These drugs are also very often used for other common cardiovascular conditions such as hypertension and angina pectoris. This is in contrast with AADs that are only used to treat (supraventricular) arrhythmias, especially atrial fibrillation.

Among the patients, 95% were taking a rate control drug before the intervention (789 patients out of 830). After the intervention, 639 (75.8%) of them were prescribed a rate control drug of which 233 (28.1%) took sotalol.

6.4.6. Drug use before the index CA-AF

As current practice guidelines do not recommend CA-AF as a first line treatment, we checked the use of rate control drugs and AADs before the index intervention. We considered a patient being treated with a rate or rhythm control drug if he had been delivered at least one package of it.

Amiodarone and sotalol have both rate and rhythm control properties although amiodarone would usually not be prescribed for rate control, given its potential toxicity and the availability of safer alternatives. On the other hand, when a patient with AF is prescribed a class I AAD, rate control medication should be continued throughout follow-up, unless continuous sinus rhythm is present. The reason for this is to control the ventricular rate adequately whenever recurrent AF occurs or in case of conversion of AF to atrial flutter, which then may be conducted rapidly to the ventricles.[2]

Henceforth, one would thus expect one of the following treatments of a patient with AF before proceeding to a catheter ablation: amiodarone, or sotalol, or a combination of an AAD and a rate control drug. From Table 16 it can be inferred that 84.2% are treated in this way. In other words, these data suggest that up to 15.8% of patients may have undergone catheter ablation as first line therapy.

Table 16 – Drugs treatments before the index CA-AF

Treatment	Number of patients before CA-AF	Proportion of patients
AAD	667	80.4%
rate control	722	87.0%
AAD or rate control	789	95.1%
AAD and rate control	600	72.3%
sotalol (S)	336	40.5%
amiodarone (A)	317	38.2%
rate control (except sotalol) and AAD (except amiodarone) (C)	426	51.3%
SUM((S) or (A) or (C))	699	84.2%
Total patients	830	100.0%

6.4.7. Electric cardioversions

Electric cardioversions were also studied before and after the first CA-AF; the corresponding nomenclature codes are 475016-475020 and 212111-212122 (see appendix).

Of the 501 patients that underwent an electric cardioversion, 218 of them (or 26.3% of the patients studied) got it after the first CA-AF. If we don't consider the cardioversions occurring the first three months after the CA-AF (i.e. blanking period), the number of patients receiving a cardioversion drops to 159, and the mean time between CA-AF and the first cardioversion rises from 220 days to 357 days (Table 17).

Table 17 – Number of patients with at least one electric cardioversion

Electric cardioversions	Patients	Number of days between CA-AF and first cardioversion	
		Mean	Median
Before CA-AF	271		
After CA-AF	218	220	118
After CA-AF with a 3 months blanking period	159	357	288
Total	501		

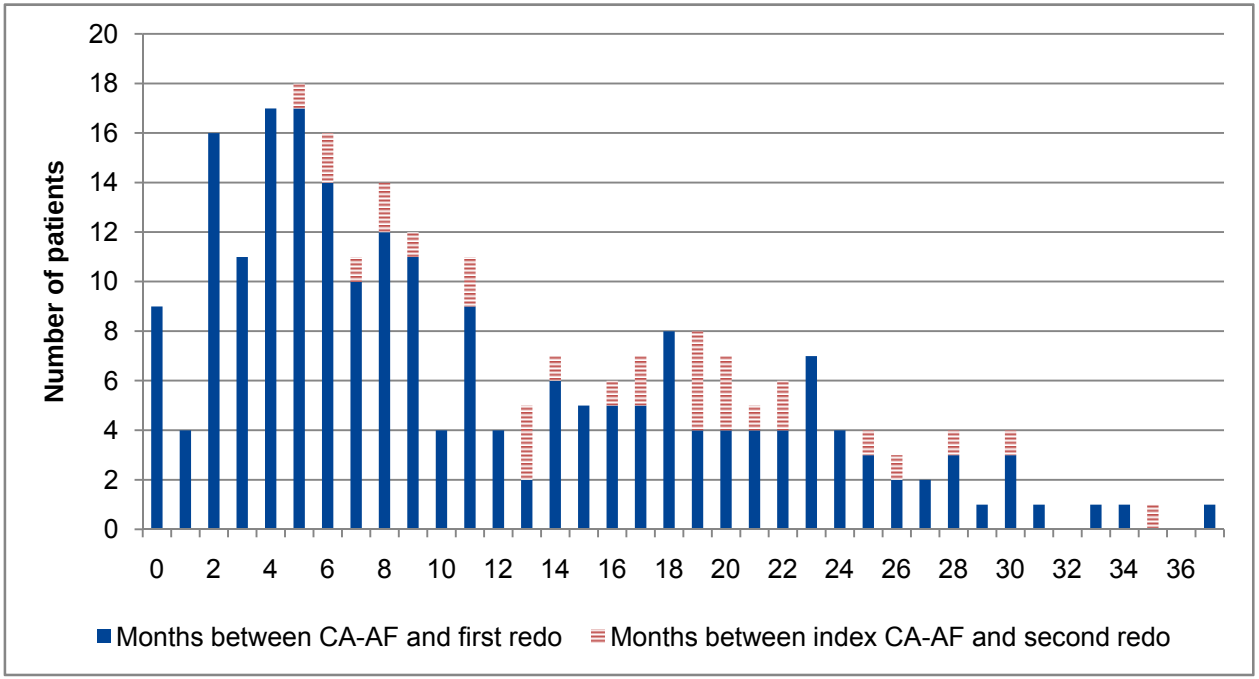
6.4.8. Redo catheter ablation of atrial fibrillation

214 patients (25.8%) underwent one or more repeat CA-AFs after their first one ("redos"). Of these, there were:

- 182 patients with one redo
- 30 patients with two redos (one patient had them the same day)
- 1 patient with 3 redos
- 1 patient with 4 redos (two of them the same day)

In Figure 8 repeat ablations are depicted graphically over time. Of the 214 patients with a repeat CA after the index procedrue, 134 got their first redo within 1 year (16.0%) and 196 within 2 years (23.6%). Over the total observation period, 220 patients (26.5%) underwent more than 1 ablation indicating an average of 1.3 ablations per patient.

Figure 8 – Delay (in months) between the CA-AFs



6.4.9. Estimate of the effectiveness of the index CA-AF

Based on administrative data, we sought to estimate the effectiveness of catheter ablation in our 2008 Belgian CA-AF population. Since we do not dispose of clinical data, the concept of effectiveness in this respect is ambiguous. Given that the major indication for catheter ablation of AF is symptom control, from a patient's point of view, a CA would be considered unsuccessful if symptoms persisted or reappeared after the procedure. On the other hand, in the eyes of a physician who decided to proceed to CA in a patient, any recurrence of AF would be interpreted as a failure, even if a patient were asymptomatic. Therefore, effectiveness in this chapter may refer both to recurrence of AF or recurrence of symptoms.

Clearly, if a patient undergoes a redo procedure, it can be regarded as a failure of the index ablation. We assume that an electrophysiologist would not decide to go for a second procedure if he were not convinced that the first intervention was unsuccessful, even within the blanking period. Within the first 12 months following the index procedure, 16.1% of patients underwent a second ablation. Within two years, the overall figure was 23.1% (Table 18 - model #0).

In agreement with the "definitions for use when reporting outcomes of AF ablation" proclaimed by the 2012 Consensus Statement on Catheter Ablation for AF,[19] we took into consideration a blanking period of 3 months when assessing the impact of electric cardioversion or the use of AADs in our estimation of the effectiveness of CA. This means that an electric cardioversion performed within 3 months after the procedure, or the use of AADs in this period, were not considered a failure. Within the 9 months following this blanking period, 11.3% of patients underwent an electric cardioversion. Within two years following the index procedure, the overall figure was 17.5% (Table 18 - model #2). Between 3 and 12 months after the procedure, 54.9% of patients were delivered at least one package of an AAD. Between 3 months and 24 months, this was 60.7% (Table 18 - model #1a).

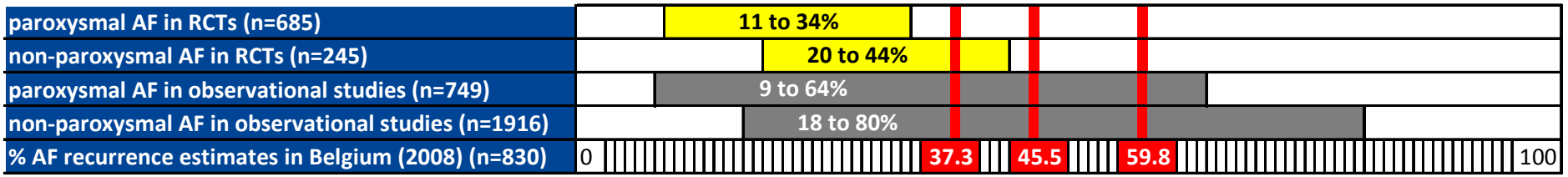
Table 18 – Alternative definitions for the estimate of AF recurrence after a single catheter ablation of AF

Parameter	Model	n=830	12 months		24 months	
			n	%	n	%
Ablation redo	0	patients with more than 1 CA (12/24 months follow-up)	134	16.1%	192	23.1%
AAD	1a	at least one delivery of one AAD over 9/21 months beyond a 3 months blanking period	456	54.9%	504	60.7%
	1b	at least one delivery of one AAD over 9/21 months beyond a 3 months blanking period, taking into account that for non-amiodarone AADs, an AAD-free window of 1 month beyond the blanking period is considered	296	35.7%	386	46.5%
	1c	at least one delivery of one AAD over 9/21 months beyond a 3 months blanking period, taking into account an AAD-free window of 1 month beyond the blanking period	211	25.4%	315	38.0%
Electric reconversion	2	electric cardioversion beyond blanking period (21 months follow-up after the 3 months blanking period)	94	11.3%	145	17.5%
Combinations	3a	SUM(0 or 1a or 2)	496	59.8%	547	65.9%
	3b	SUM(0 or 1b or 2)	378	45.5%	464	55.9%
	3c	SUM(0 or 1c or 2)	310	37.3%	414	49.9%

In the 2012 Consensus Statement on Catheter Ablation for AF,[19], success of CA-AF is defined as freedom from AF in the absence of class I and III AAD therapy following the 3 months blanking period. Combining the 3 abovementioned criteria (redo + electric conversion + AAD) results in an estimate of failure of the index ablation of 59.8% and 65.9% after 12 and 24 months respectively (Table 18 - model #3a).

These performance estimates are inferior to those observed in RCTs, but they are contained within the wide estimates of AF recurrences from other observational studies (Figure 9).

Figure 9 – One-year recurrence rates of AF after catheter ablation from literature and estimates of AF recurrence in Belgian patients (2008).



Scale is from 0 to 100%. RCT data extracted from Figure 4. In some of those RCTs, cross over to AAD in the ablation group was allowed per study protocol (see Table 2). Observational data are extracted from a systematic review and contain studies with a follow-up from 6 to 18 months that report recurrence rates "off-AADs".[43] Belgian data (red vertical bars) are 1-year results after a single ablation extracted from Table 18 (models 3a, 3b, 3c) and represent different models "off-AAD". Pooling of the results of the separate studies in a meta-analysis was considered inappropriate because of substantial clinical heterogeneity between them.

We discussed these data with the external experts to this report. For some of them, it was hard to accept that these figures realistically reflected the effectiveness of AF ablation. It was suggested that the use of AADs as such did not reflect failure of the ablation but that both physicians and patients may be reluctant to stop AADs after CA, even if it was successful. It could also be envisaged that patients continued AADs to treat extrasystoles causing palpitations, mimicking AF recurrence. Furthermore, it was contended that CA might have been "partially effective"[r], allowing a patient with previously refractive AF to become drug responsive after CA. This point is also made in the 2012 Consensus Statement on Catheter Ablation for AF.[19] However, we cannot make sure that patients who were prescribed an antiarrhythmic drug after a failed index ablation recovered sinus rhythm.

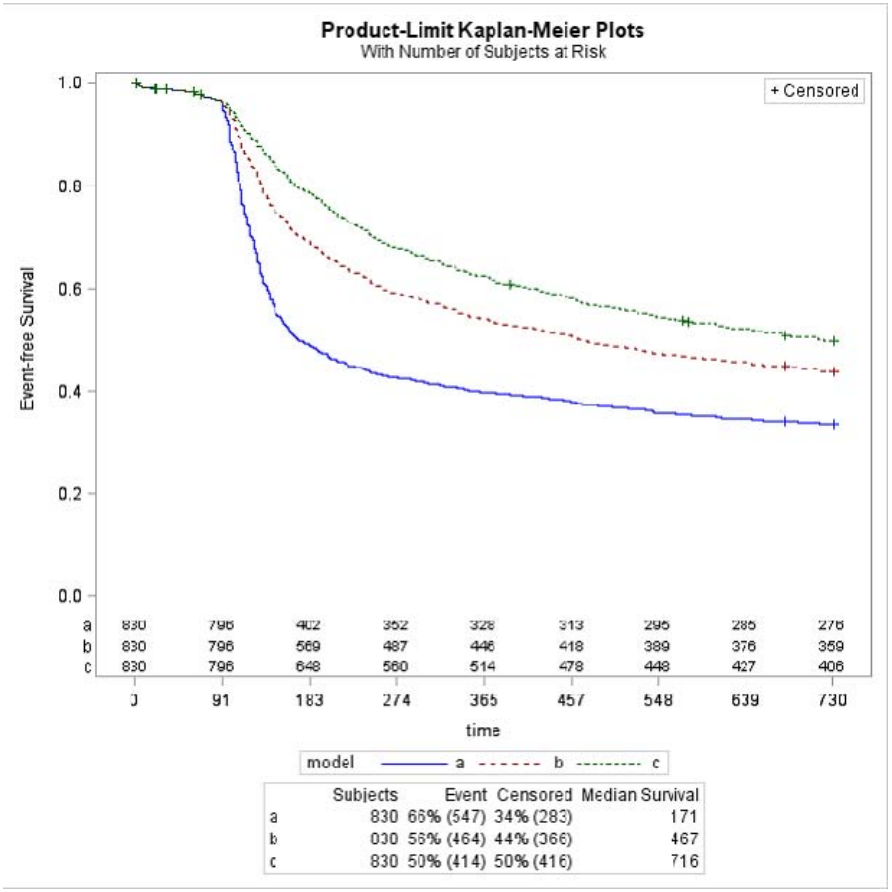
The external experts suggested that the use of AADs would be a better measure of ablation failure if it was only counted if an AAD was reinitiated after a drug-free time interval, arbitrarily put at 1 month. We thought this might not apply to the use of amiodarone, an AAD with dreaded side effects and a very long half-life.

Consequently, we took these points of view into consideration (Table 18 - models #1b and 1c), and ended up with improved results. Adding a drug-free interval of at least one month for any AAD, but not for amiodarone, results in an estimate of failure of the index ablation of 45.5% and 55.9% after 12 and 24 months respectively (Table 18 - model #3b). Adding a drug-free interval of at least one month for any AAD results in an estimate of failure of the index ablation of 37.3% and 49.9% after 12 and 24 months respectively (Table 18 - model #3c).

[r] In the 2012 international consensus document "clinical/partial success" is defined as a 75% or greater reduction in the number of AF episodes, the duration of AF episodes, or the % time a patient is in AF as assessed with a device capable of measuring AF burden in the presence of previously ineffective antiarrhythmic drug therapy.[19]

The recurrence estimate over time, according to these three approaches (model 3a, 3b and 3c), is depicted in the Kaplan-Meier plot shown in Figure 10.

Figure 10 – Estimate of AF recurrence after the index CA-AF



This graphic illustrates the three models described in

.

6.5. Costs description

Following is a description of the costs for a hospitalization due to CA-AF. Data selection was the same as explained in section 6.2.1 (n=830).The IMA-AIM database contains records of the daily fee paid by INAMI-RIZIV (pseudo-code 68025 of the nomenclature), which doesn't take into account the part subsidised by the Federal Public Service Health, Food Chain Safety and Environment. This full daily hospital fee varies with each hospital. Since we didn't have the hospital reference in the data, we matched the INAMI-RIZIV fee in a KCE reference table to get the full fee. Due to rounding, the matching was not complete. We present results for the procedures with matching full daily hospital fee (Table 19). In appendix, we also show the cost categories 'procedure', 'material' and 'others' for the non-matched procedures (Table 35). Comparison shows there are no big differences in expenses for these cost categories between matched and non-matched procedures.[s]

In Belgium, based on real-world data, catheter ablation for atrial fibrillation costs on average about €9 600 for the initial intervention. This includes the patient costs and the RIZIV-INAMI reimbursement. Extra costs ("supplements") were not taken into account. All prices are from 2007-2010 and have not been updated.

In comparison, the drug cost for rate control is much lower: e.g. bisoprolol 5mg/day costs less than €50/year. For bisoprolol 10mg/day this is less than €70/year. For a drug for rhythm control, e.g. flecaïnide 150mg/day, this is about €230/year. The combination of these two drugs costs no more than €300 per year.

s The costs for the three cost categories 'Procedure', 'material' and 'other costs' was on average €8 127.31 in the matched cases versus €8 079.26 in the non-matched cases.

Table 19 – Expenses per procedure

Total

Variable	N	Mean	25th Pctl	Median	75th Pctl	Std Dev	5th Pctl	95th Pctl
Total costs	341	9 586.68	8 086.67	8 700.43	9 499.65	4 455.52	6 835.05	11 046.30
Total costs before	160	1 880.92	998.05	1 261.84	1 468.55	2 855.76	760.39	2 158.66
Total costs after	341	8 554.43	7 444.73	8 091.23	8 649.20	3 293.36	6 276.94	9 733.17
Days	341	3.68	2	3	4	3.63	2	5

Procedure (nomenclature codes: 589551-589562)

Variable	N	Mean	25th Pctl	Median	75th Pctl	Std Dev	5th Pctl	95th Pctl
Total costs	341	2 447.57	2 152.00	2 367.20	2 367.20	933.04	2 152.00	2 492.44
Total costs before	3	4 590.93	4 304.00	4 734.40	4 734.40	248.49	4 304.00	4 734.40
Total costs after	341	2 407.18	2 152.00	2 367.20	2 367.20	712.89	2 152.00	2 492.44

Material (nomenclature codes: 697631-697642, 697653-697664)

Variable	N	Mean	25th Pctl	Median	75th Pctl	Std Dev	5th Pctl	95th Pctl
Total costs	328	3 711.50	3 584.64	3 584.64	3 584.64	1 319.86	2 817.86	3 610.84
Total costs before	3	7 169.28	7 169.28	7 169.28	7 169.28	0.00	7 169.28	7 169.28
Total costs after	327	3 657.08	3 584.64	3 584.64	3 584.64	1 075.02	2 817.86	3 610.84

100% per diem hospital prices

Variable	N	Mean	25th Pctl	Median	75th Pctl	Std Dev	5th Pctl	95th Pctl
Total costs	341	1 459.38	753.66	1 039.53	1 454.94	1 613.41	599.66	3 394.86
Total costs before	126	694.26	332.74	484.98	565.38	958.86	253.51	1 837.68
Total costs after	322	1 115.28	645.76	908.40	1 119.75	1 211.08	342.30	2 646.30

Others

Variable	N	Mean	25th Pctl	Median	75th Pctl	Std Dev	5th Pctl	95th Pctl
Total costs	341	2 109.73	1 399.53	1 806.49	2 318.22	2 121.23	454.58	4 129.53
Total costs before	160	1 113.69	801.62	872.07	981.28	1 210.38	481.41	2 155.75
Total costs after	341	1 587.18	845.84	1 421.90	1 791.89	1 763.58	208.75	3 036.60

(n=341, daily hospitalization fee matching)

We also compared the expenses for an index CA-AF compared to a redo. There is no significant difference (Table 20).

Table 20 – Comparison of expenses between index CA-AFs and redos

Index CA-AFs

Variable	N	Mean	25th Pctl	Median	75th Pctl	Std Dev	5th Pctl	95th Pctl
Total costs	263	9 555.58	8 064.27	8 727.97	9 533.51	4 302.22	6 835.05	15 426.00
Total costs before	118	1 794.71	1 164.66	1 357.79	1 586.82	1 960.66	898.56	4 838.17
Total costs after	263	8 750.35	7 561.69	8 109.71	8 697.90	3 635.47	6 399.69	12 752.60

Redos

Variable	N	Mean	25th Pctl	Median	75th Pctl	Std Dev	5th Pctl	95th Pctl
Total costs	78	9 691.55	8 108.68	8 684.07	9 418.76	4 966.21	6 276.94	16 101.83
Total costs before	42	2 123.15	789.29	869.38	1 020.01	4 536.01	729.20	14 757.96
Total costs after	78	7 893.82	6 946.11	7 973.78	8 490.87	1 532.40	5 855.13	9 933.14

Only the procedures with full daily hospitalization fee were included.

6.6. Conclusion

We analysed through administrative data all first catheter ablations of AF, executed in Belgium between 1 November 2007 and 31 December 2008. Patients included in the study (n=830) were followed until 31 December 2010. In the absence of specific nomenclature codes, the number of CA-AF per se performed before November 2007 cannot be assessed. There is a sharp increase in the use of electrophysiology procedures (in general) from 2008 on that can be attributed to an increase in catheter ablation of AF.

Whereas in 2008, €5.2 million was reimbursed for CA-AF (fees and devices), this amount rose to €8.5 million in 2009 and €12.5 million in 2010. Based on real-world data, catheter ablation for atrial fibrillation costs on average about €9 600 for the initial intervention.

Based on the use of rate and rhythm control drug in the period before the ablation, we estimate that up to 15.8% of patients may have undergone catheter ablation as first line therapy.

We used 3 factors to estimate the effectiveness of the ablation procedure: redo of the procedure, electric cardioversion, and the use antiarrhythmic drugs afterwards. Our best estimate of the recurrence rate of AF after a single CA-AF, based on administrative data, is 37.3% and 49.9% after 12 and 24 months respectively (Table 18 - row #3c). These numbers are located at the lower end of the wide estimate of recurrence from clinical trials.

Key points

- **From 2008 to 2010, the number of catheter ablations for AF in Belgium more than doubled from 993 to 2064 cases. In 2008, this procedure in Belgium costs on average about €9 600 for the initial intervention.**
- **In 2008 77.3% of patient population was treated for paroxysmal AF and 22.7% for persistent AF. We estimate that up to 15.8% of patients may have undergone catheter ablation as first line therapy.**
- **Based on 2008 administrative data, we estimate AF recurrence to occur after a single ablation in 37.3 to 59.8% of patients after one year and in 49.9 to 65.9% after two years.**

7. COST-EFFECTIVENESS OF CA-AF

7.1. Literature search

7.1.1. Search strategy

A systematic search for economic literature about the cost-effectiveness of CA-AF was performed by consulting various databases. First of all, reviews on this topic were searched by consulting the CRD HTA and CDSR Technology Assessment databases. The websites of HTA institutes mentioned on the INAHTA (International Network of Agencies for Health Technology Assessment) website (www.inahta.net) were also consulted. Websites of non-member HTA institutes such as NICE (www.nice.org.uk) were also checked for relevant analyses.

The NHS EED (CRD), Medline (OVID), and EMBASE databases were searched to retrieve both full economic evaluations and reviews of full economic evaluations of CA-AF. No restrictions on the time period and language were imposed. The search strategy was performed in February 2012, with an update in August 2012. An overview of the search strategy and results is provided in appendix 1.

7.1.2. Selection criteria

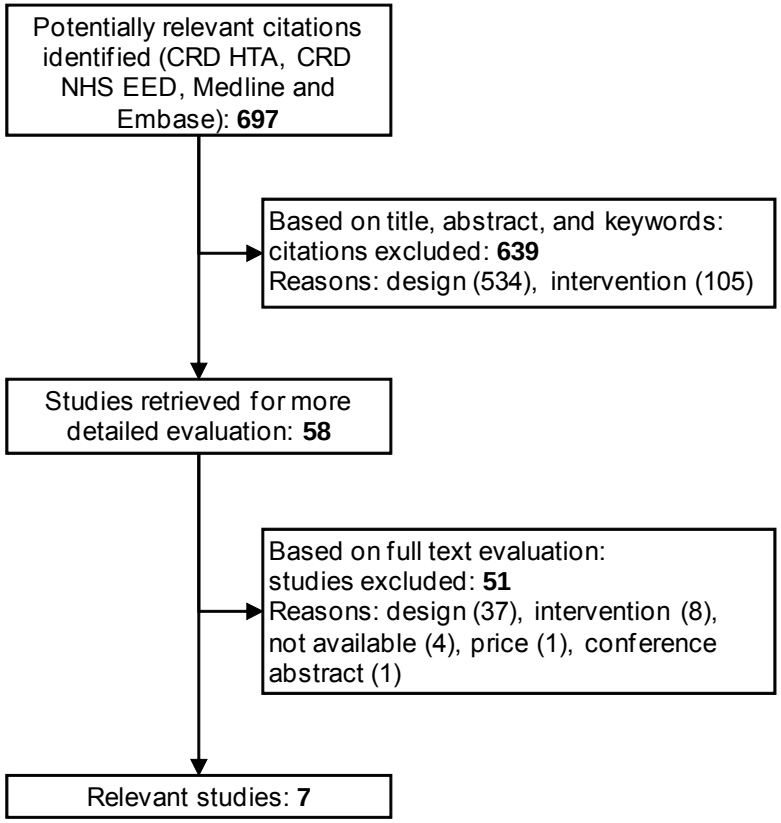
All retrieved references were assessed against pre-defined selection criteria, in terms of population, intervention, comparator, and design (Table 21). Several choices were made when setting up these criteria. The population was not restricted to a specific type of atrial fibrillation. Both paroxysmal, persistent and permanent AF populations were eligible. The intervention was open to catheter ablation. It is expected that the retrieved economic evaluations will focus on radiofrequency CA since the evidence is mainly restricted to this type of intervention. The comparator explicitly excludes other types of catheter ablation than with radiofrequency or catheter ablation during surgery. The design is restricted to full economic evaluations, i.e. studies comparing at least two alternative treatments in terms of costs and outcomes. Before/after cost analyses were excluded from this overview (see discussion 7.3.1).

Table 21 – Economic evaluation selection criteria

	Inclusion criteria	Exclusion criteria
Population	Patients with atrial fibrillation	Other populations
Intervention	(Radiofrequency) catheter ablation	Other interventions
Comparator	Rate or rhythm control	Other types of catheter ablation or surgical procedures
Design	Full economic evaluations	Other designs such as cost calculations

The selection of relevant articles was performed in a two-step procedure: initial assessment of the title, abstract, and keywords, followed by a full-text assessment of the selected references. When no abstract was available and the citation was unclear or ambiguous, consideration of the citation was directly made on the basis of a full-text assessment. Reference lists of the selected studies were checked for additional relevant citations. Figure 11 provides the flow chart of this process. In the end, seven relevant studies were selected (Table 22). These full economic evaluations were then summarized in an in-house data extraction sheet (see Table 43 in appendix). These data extraction sheets are working documents that provide the basis to make summary tables which are provided and discussed in part 1.1.

Figure 11 – Selection of relevant articles



CRD: Centre for Reviews and Dissemination; EED: Economic Evaluation Database; HTA: Health Technology Assessment; NHS: National Health System.

Table 22 – List of selected economic evaluations

References
Assasi N, Blackhouse G, Xie F, Gaebel K, Robertson D, Hopkins R, et al. Ablation procedures for rhythm control in patients with atrial fibrillation: clinical and cost-effectiveness analyses. Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH), 2010.[28]
Chan PS, Vijan S, Morady F, Oral H. Cost-effectiveness of radiofrequency catheter ablation for atrial fibrillation. Journal of the American College of Cardiology 2006;47(12):2513-2520.[77]
Eckard N, Davidson T, Walfridsson H, Levin LA. Cost-effectiveness of catheter ablation treatment for patients with symptomatic atrial fibrillation. Journal of Atrial Fibrillation 2009;1(8):461-470.[78]
McKenna C, Palmer S, Rodgers M, Chambers D, Hawkins N, Golder S, et al. Cost-effectiveness of radiofrequency catheter ablation for the treatment of atrial fibrillation in the United Kingdom. Heart 2009;95(7):542-549.[79]
Ollendorf D, Silverstein M, Bobo T, Pearson S. Atrial fibrillation management options. Boston: Institute for Clinical and Economic Review (ICER), 2010.[20]
Reynolds MR, Zimetbaum P, Josephson ME, Ellis E, Danilov T, Cohen DJ. Cost-effectiveness of radiofrequency catheter ablation compared with antiarrhythmic drug therapy for paroxysmal atrial fibrillation. Circulation: Arrhythmia and Electrophysiology 2009;2(4):362-369.[80]
Rodgers M, McKenna C, Palmer S, Chambers D, Van Hout S, Golder S, et al. Curative catheter ablation in atrial fibrillation and typical atrial flutter: systematic review and economic evaluation: NIHR Health Technology Assessment programme, 2008:1-220.[81]

Remark: the article of McKenna et al.[79] is based on the full HTA report of Rodgers et al.[81]. In the overview, these two publications will be treated as one.

7.2. Overview of economic evaluations

First of all, we provide an overview of the retrieved economic evaluations. A critical appraisal of these evaluations is provided in the discussion (see part 1.1).

An overview of the general characteristics of the economic evaluations is presented in Table 23. All studies were published between 2006 and 2010. They were performed for Canada,[28] the US,[20, 77, 80] Sweden[78] and the UK.[79, 81] All studies performed a cost-utility analysis (CUA) based on a Markov model with in some cases a decision tree modelling the events during the first year. The time horizon was 5 years or lifetime. Studies with a 5-year time horizon included a longer-term scenario analysis and vice versa. The discount rate for costs and health outcomes reflected national guidelines. The perspective is a payer or societal perspective. However, in the latter case, productivity and travel costs are not included and the analyses rather reflect the payer perspective.

The populations were different across studies (Table 23). Most of the studies include (mainly) male patients with paroxysmal AF who are unsuccessfully treated with an AAD. However, some analysis also model first-line CA[20, 77] or include persistent AF patients.[20, 78] Some studies explicitly mention to include (moderately to highly) symptomatic patients.[20, 78] Age and stroke risks also differ across studies. Reflecting the selection criteria, the assessed intervention was radiofrequency catheter ablation for treatment of atrial fibrillation. In all cases, AAD was the comparator. The study of Chan et al.[77] assessing first-line CA also included both rate control and rhythm control with AAD as a comparator.

Costs applied in the original articles for the initial intervention, complications, comparator and/or supportive treatments are presented in Table 24 to Table 26. For simplicity and in order not to overload the tables with information, we preferred to present only the original costs and not to transpose these numbers to euro-values in a common year. Table 24 provides an overview of the costs for the initial procedure, the average number of procedures (1.25 - 1.4), and both probabilities and costs of procedural complications. Some models include a general cost for procedure complications,[20, 77, 78] while other models make a distinction between different types of complications.[28, 79-81]

Table 25 presents the costs for AAD, rate control and anti-coagulation. The differences reflect not only price differences of drugs, but also differences in the elements included in the cost estimate (e.g. whether or not hospitalizations are included in the AAD cost estimate). Two studies mention costs for rate control,[20, 77] which are lower than those for AAD treatment. Assumptions relating to the use of anticoagulation treatment is somewhat different across studies: Assassi et al.[28] assume that AF ablation patients discontinue warfarin three months after their procedure; Chan et al.[77] assume patients with restored sinus rhythm continue warfarin therapy for six more months before transitioning to the use of aspirin; the other studies mention anticoagulation depends on the stroke risk,[78] or would continue as appropriate regardless of whether AF had recurred,[20] with equivalent practices in all treatment groups.[80]

Table 26 provides an overview of stroke costs and other costs such as those for bleeding or drug toxicity. The probabilities of these events are shown in Table 27 and Table 28. Half of the models assume that the annual stroke risk is lower with a normal sinus rhythm.[28, 77, 79, 81] The other half did not assume a reduction in stroke in their base case analysis.[20, 78, 80] Furthermore, based on a secular trend, Ollendorf et al.[20] adapted the risk of stroke associated with a particular CHADS2 score (Table 27). The bleed and toxicity risks also differ in most studies depending on the drugs taken (Table 27 and Table 28). Differences in mortality risk between the intervention and control arm is modelled indirectly, e.g. through the different stroke risks (Table 28). Only Reynolds et al.[80] explicitly mention the projected all-cause mortality was equivalent between both groups.

Table 29 provides an overview of the modelled efficacy in both the ablation arm and for the comparators. The model inputs of first-line treatments[20, 77] are incomparable with those after unsuccessful AAD treatment. A normal sinus rhythm was achieved in 74%[79, 81] up to 90%[80] with catheter ablation. For non-first line AAD treatment this was between 9%[78] and 37%[79, 81] at one year. In the models including first-line treatments,[20, 77] patients under rate control are assumed to convert spontaneously to a normal sinus rhythm in 38% of cases. The annual probability of AF recurrence after the first year is not always explicitly mentioned. In the 2nd-line treatment models of Assasi et al.[28] and Rodgers et al.,[79, 81] it is lower than 4% in the ablation arm.

Utility values were modelled indirectly through several assumptions. Most models start from age- and gender-specific general population utility values and take into account a (dis)utility for certain health states (e.g. normal sinus rhythm or AF) and events (e.g. stroke or procedure complications).[20, 28, 78-81] In contrast to all other models, Chan et al.[77] assign a utility value of 1 to patients in normal sinus rhythm. We refer to Table 30 for details on the assumed (dis)utility for health states and events. The evidence base for these values is weak and will be discussed in part 1.1.

Table 31 presents the results of the base case analyses and a selection of the most important sensitivity analyses. The base case average incremental cost-effectiveness ratios (ICERs) range from less than £8 000 per QALY for different CHADS2 scores,[79, 81] up to about $60 000 for a CHADS2-score of 2 in paroxysmal AF patients.[28] In our discussion, based on current knowledge, we will show why these results are probably overoptimistic. In patients with persistent AF, the results are less favorable.[20] The table also provides a selection of results of the sensitivity analyses. More details on these and other analyses are available in the original articles. The results show that the most determining variables are: the difference in utility between the intervention and comparator group, the applied time horizon, and the impact on stroke. Shorter time horizons and/or smaller utility differences easily increased the average ICERs to more than $100 000 per QALY.[28, 80] The analysis of Rodgers and McKenna[79, 81] indicate stroke risk doesn't have much influence on results, while other models provide better results for high-risk patients.[28, 77, 78] This is of course dependent on the initial modelling assumptions and the baseline stroke risk.

Table 32 shows the authors' conclusions of the retrieved economic evaluations. Some authors are very confirmative in considering CA a cost-effective intervention.[78, 80] Others refer to the uncertainty surrounding decisive variables: e.g. "if sufficiently high CA efficacy rates in restoring sinus rhythm translate into lower morbidity",[77] or "it requires that the QoL benefits are maintained for more than 5 years and/or that normal sinus rhythm has prognostic value in preventing the risk of stroke."[79, 81] The report of Ollendorf et al.[20] mentions there is a high certainty of a small benefit only for secondary catheter ablation in paroxysmal patients. However, no explicit conclusion on the intervention's cost-utility is stated.

Table 23 – General information on economic evaluations

Reference	Assasi et al., 2010	Chan et al., 2006	Eckard et al., 2009	Ollendorf et al., 2010	Reynolds et al., 2010	Rodgers et al., 2008 McKenna et al., 2009
Country	Canada	US	Sweden	US	US	UK
Currency	Canadian dollar (2010)	US dollar (2004)	US dollar (2006)	US dollar (2010)	US dollar (2001-2006)	UK pounds sterling (2006)
Conflict of interest	Yes	Not reported	Not reported	Not reported	Yes	Not reported
Population	65-year-old males Paroxysmal AF Unsuccessfull AAD CHADS2 score of 2	55- and 65-year-old AF First-line treatment Moderate/low stroke risk	Symptomatic patients Paroxysmal/persistent AF Unsuccessfull AAD	Moderately to highly symptomatic atrial fibrillation, first-line or after AAD failure: - 60, male, paroxysmal AF - 65, male, long-standing persistent AF and HF - 75, male, hypertension and diabetes mellitus and persistent AF.	60-year-old males Paroxysmal AF Unsuccessfull AAD Without severe structural heart disease	Mean age 52, 80% male AF (majority paroxysmal) Unsuccessfull AAD
Intervention	Radiofrequency ablation	Radiofrequency ablation	Radiofrequency ablation	Radiofrequency ablation	Radiofrequency ablation with/without AAD	Radiofrequency ablation without long-term AAD
Comparator	AAD (amiodarone)	AAD (amiodarone) or rate control therapy	AAD	AAD	AAD	AAD (amiodarone)
Type of analysis	CUA	CUA	CUA	CUA	CUA	CUA
Design	One-year decision tree and a longer-term Markov model	Markov model	One-year decision tree and a longer-term Markov model	Markov model	Markov model	One-year decision tree and a longer-term Markov model
Time horizon	5 years	Lifetime	Lifetime	Lifetime	5 years	Lifetime
Discount rate	5% for both costs and health outcomes	3% for both costs and health outcomes	3% for both costs and health outcomes	3% for both costs and health outcomes	3% for both costs and health outcomes	3.5% for both costs and health outcomes
Perspective	Publicly funded health care system	Societal perspective	Societal perspective	Public payer perspective	Societal perspective	Perspective of the NHS and Personal Social Services (PSS)

For abbreviations: see list of abbreviations at the beginning of the document.
One of the models has a strange design. Reynolds et al.[80] mention to include patients refractory to one or more AADs. However, referring to their model, the authors state that "patients initially receive a first-line drug (sotalol or flecainide) and enter the "well 1st drug" state. In the event of toxicity or therapeutic failure, they proceed to treatment with amiodarone ("well amio" state), and in the event of amiodarone failure are treated with rate control ("RC/AC")." It is important in modelling incremental costs and effects that both the intervention and control group start at the same, i.e. in this case after AAD failure.

Table 24 – Information on costs (part 1: CA procedure and complications)

Reference	Assasi et al., 2010	Chan et al., 2006	Eckard et al., 2009	Ollendorf et al., 2010	Reynolds et al., 2010	Rodgers et al., 2008 McKenna et al., 2009
AF ablation cost per procedure	$9590	$16 500	$9860	$11 231 (without complications)	$15 000	£9810
Average number of procedures	1.27	1.30	1.40	Not reported in overview table	1.25	1.30
Procedural complications	Stroke: 0.3% TIA: 0.2% Cardiac tamponade: 0.8% PV stenosis: 1.6%	Death: 0.1% Stroke: 0.8% Cardiac tamponade: 0.7% Atrio-esophageal fistula: 0.2% Other: 0.3%	Complications: 3% (Serious complications include: tamponade, bleeding, pulmonary vein stenosis, stroke and oesophageal fistulas)	Death: 0.1% Stroke: 0.4% Minor complications: 3.7% Major complications: 1.3%	Procedural death: 0.05% Stroke: 0.3% TIA: 0.4% Cardiac tamponade: 0.8% PV stenosis: 0.4% Vascular access: 1.2% Pneumothorax / hemothorax: 0.18% Phrenic nerve palsy: 0.1%	Operative death: 0.05% Stroke: 0.28% Cardiac tamponade: 1.22% PV stenosis: 0.74%
Cost procedure complications	Tamponade: $5842 PV stenosis: $8487 stroke: $14 872 TIA: $4296	Complications from ablation: $11 000 (an average of complication costs from tamponade and stroke) Atrioesophageal fistula: $50 000	$2190	AF ablation cost with complications: $17 024	Tamponade: $7500 PV stenosis: $7800 Stroke: $8200 TIA: $8200 Vascular access: $8000 Pneumothorax / hemothorax: $13 000	Tamponade: £815 PV stenosis: £3217

Table 25 – Information on costs (part 2: drugs)

Reference	Assasi et al., 2010	Chan et al., 2006	Eckard et al., 2009	Ollendorf et al., 2010	Reynolds et al., 2010	Rodgers et al., 2008 McKenna et al., 2009
Cost AAD	Total annual cost amiodarone: $433.	Annual care with amiodarone: $1200.	Annual cost: $1640 (This cost includes hospitalisation, AAD medication and consultation; hospitalization being the major cost driver for AAD)	Annual drug cost amiodarone: $434	Cost well on amiodarone: $3500	The base-case analysis assumed that amiodarone would be administered in an outpatient setting for all patients: £154. Amiodarone (200 mg daily): £32 per year.
Cost rate control	/	annual cost rate control: $400 (combination of digoxin and atenolol).	/	Annual drug cost: - digoxin: $263 - atenolol: $80	/	/
Cost anti-coagulation	- Proportion of patients taking warfarin in both treatment groups: 0.44. - Annual cost warfarin treatment and monitoring: $463 (5 mg per day: $75.30, monitoring cost: $387.54). - Based on treatment algorithms in the RCTs: assumed that AF ablation patients discontinue warfarin three months after their procedure, resulting in different bleeding risks between AF ablation patients and AAD-treated patients.	- Cost annual care aspirin: $13 - Cost annual care warfarin (including every 4-week monitoring): $600 - In all treatment arms, patients received antithrombotic or anticoagulant therapy. Patients at moderate risk of stroke received warfarin, whereas patients at low risk of stroke received either warfarin or aspirin. Patients with sinus rhythm restored continued warfarin therapy for six more months before transitioning to the use of aspirin.	Warfarin: $770 All AF patients with at least one risk factor for stroke (CHADS2) benefit from anticoagulation treatment to reduce thromboembolic events.	Annual drug cost: - aspirin: $23 - warfarin: $440 Anticoagulation would continue as appropriate regardless of whether AF had recurred.	- Long-term anticoagulation practices and related costs and complications are equivalent between groups. - Rate control/ anticoagulation: $2800/year.	- All patients receive anticoagulants and/or aspirin. Warfarin (5 mg daily): £19 per year. Aspirin (75 mg daily): £20 per year. (summary table mentions the following use: Warfarin 64.0%, Aspirin 27.3%, and None 8.7%)

Table 26 – Information on costs (part 3: stroke and other costs)

Reference	Assasi et al., 2010	Chan et al., 2006	Eckard et al., 2009	Ollendorf et al., 2010	Reynolds et al., 2010	Rodgers et al., 2008 McKenna et al., 2009
Cost stroke	1st year: - ischemic stroke: $61 413 - hemorrhagic stroke: $58 159 subsequent years: - ischemic stroke: $6801 - hemorrhagic stroke: $5843	Stroke: $8900	1st year: $19 180. Subsequent years: $4380 per year.	Acute cost (hospital care): - no disability: $7932 - mild disability: $10 075 - moderate/severe disability: $15 235 Annual cost: - mild disability: $2990 - moderate/severe disability: $26 450	Stroke: $8200	1st year: £9431. Subsequent years: £2488 per year.
Other costs	- Follow-up after CA: 1st year: $666 (three cardiologist consultations and CT scan). No follow-up costs after the first year. - acute cost of pulmonary toxicity: $22 434. - irreversible pulmonary toxicity: annual cost of $3799. - Major gastrointestinal bleed: $6023.	Single event - hospitalization: - Amiodarone pulmonary toxicity: $8600 - Intracranial bleed or stroke: No residual defects ($6400); Mild residual defects ($7830); Moderate to severe residual defects ($12 490) - Extracranial haemorrhage: $3730 Annual care: - Intracranial bleed or stroke: Mild disability ($2600); Moderate to severe disability ($23 000) - Pulmonary toxicity caused by amiodarone: $3500		Drug toxicity: - reversible: $100 - acute amiodarone pulmonary toxicity: $4250 - chronic amiodarone pulmonary toxicity: $4025 Haemorrhage & ICH: - haemorrhage, not ICH: $3750 - ICH, no disability: $4295 - ICH, mild disability: $6048 - ICH, moderate/severe disability: $9536 Annual costs: - mild disability: $2990 - moderate/severe disability: $26 450	- Well post ablation: 1st year: $1300, then $200/year. - Cost well on 1st line drug: $4000 - Drug toxicity 1st line drug: Fatal: $10 000, Nonfatal: $5100. - Amiodarone toxicity: Fatal: $10 000, Nonfatal: $5000.	- Costs of community and hospital-based care related to AF, including general practitioner consultations, anticoagulation visits and hospital costs. An annual amount of £646 was estimated for these costs. - Toxic event: £1497. - Reversale toxicity: £0.43 per day. - Irreversible toxicity: £158 per year. - Major bleed: £1573 per year. - Minor bleed: £87 per year.

Table 27 – Risk information (part 1: stroke and bleeding risk)

Reference	Assasi et al., 2010	Chan et al., 2006	Eckard et al., 2009	Ollendorf et al., 2010	Reynolds et al., 2010	Rodgers et al., 2008 McKenna et al., 2009
Risk stroke	Annual probability of stroke by CHADS2 score: 0: 0.019 1: 0.028 2: 0.040 3: 0.059 4: 0.085 5: 0.125 6: 0.182 Stroke risk NSR = stroke risk AF x 0.625 (the inverse of 1.6).	Yearly stroke risk: - In sinus rhythm: Moderate risk: 0.9%, Low risk: 0.5% - Patients in AF: aspirin therapy: 2.3% and 1.1%, warfarin therapy: 1.3% and 0.7%, for moderate and low stroke risk, respectively. - Stroke risk first month after AAD: 0.27% - Stroke risk was adjusted linearly with a relative risk of 1.4 for each decade of age.	- AF: 1.5% - free from AF: 1.5%	- Annual incidence rate: 0.019 (CHADS2 score = 0, vary by CHADS2 score) - Reduced risk of stroke (secular trend): 0.315 - RRR stroke aspirin: 0.210 - RRR stroke warfarin: 0.680 - RR stroke after CA if NSR: 1.000 (0.15 in alternate scenario)	We assumed no benefit from ablation on stroke.	- Stroke risk for AF by CHADS2 score: 0: 1.9% 1: 2.8% 2: 4.0% 3: 5.9% - Stroke risk for NSR: Hazard ratio for AF relative to NSR: 1.60. - Stroke risk reduction with anticoagulation (RR): Warfarin vs placebo: 0.33, Warfarin vs aspirin: 0.59.
Bleed risk	without warfarin: 0.58% with warfarin: 1.28%	- Warfarin therapy: 1.8% (age<75), 3.2 % (age ≥75) '- Aspirin therapy: 1.2% (age<75), 1.5 % (age ≥75) - Bleed outcome: Non-intracranial (85 %) and Intracranial (15 %) (of which Fatal (20%), Mild disability (67%), Moderate to severe disability (17%)) - Relative risk for recurrent bleeding: 1.5.		- rate of major haemorrhage: 0.006 - rate of major haemorrhage with aspirin: 0.012 - rate of major haemorrhage with warfarin: 0.018		- Annual probability bleed on warfarin: 2.40% (major), 15.80% (minor). - Relative risk for bleeds comparing warfarin with aspirin: 0.58 (major), 0.45 (minor). - Relative risk for bleeds comparing warfarin with no anticoagulant (OAC): 0.45 (major), 0.46 (minor).

Table 28 – Risk information (part 2: toxicity and mortality risk)

Reference	Assasi et al., 2010	Chan et al., 2006	Eckard et al., 2009	Ollendorf et al., 2010	Reynolds et al., 2010	Rodgers et al., 2008 McKenna et al., 2009
Toxicity risk	- Annual probability of pulmonary toxicity while on AAD: 0.00832. - The proportion of irreversible cases: 0.25. - Probability of death after pulmonary toxicity: 0.091.	- Irreversible pulmonary toxicity: 0.5% - Death from pulmonary toxicity: 0.1% - Digitalis toxicity: 1.1%/year - Beta blocker toxicity: 0.2%/year		Amiodarone toxicity: - reversible toxicity: 0.104 - permanent disability from toxicity: 0.011 - fatal pulmonary toxicity: 0.000 Rate control toxicity (atenolol & digoxin): - digitalis toxicity: 0.011 - beta blocker toxicity per year: 0.002	- Toxicity on IC AAD / sotalol: Fatal: 0.5% year one, then 0.32% per year; Nonfatal: 9.5% year one, then 1.28% per year. - Toxicity on amiodarone: Fatal: 0.1% per year; Nonfatal: 9.9% year one, then 0.9% per year.	Side effects AADs: - General toxicity: In year 1: 12.50%; In subsequent years: 6.25%. - Withdrawal because of toxicity: In year 1: 10.00%, In subsequent years 5.00%. - Probability of pulmonary complication given withdrawal: 15.19%
(stroke) mortality	- Ischemic and hemorrhagic stroke mortality according to time (28 days, 1 year), age category and gender (see tables with full details in original text). - For post-stroke mortality after one year, the general population mortality was increased by a factor of 2.3.	- Stroke outcome (Fatal, Moderate to severe disability, Mild disability, No disability): different for aspirin vs. warfarin. - Relative risk for recurrent stroke: 2. - Mortality was modified by a relative risk of 1.3 and 2.3 in patients without and with moderate-to-severe disability (from stroke or intra-cranial bleed), respectively. - The model incorporated relative risk reductions of 17% and 33% in nonstroke vascular mortality by aspirin and warfarin, respectively. - AAD: Relative risk for non-cardiovascular mortality: 1.08.	The ´post stroke´ health state implies an elevated mortality risk.	- Probability of death due to stroke: 0.179 - RR of death with mild disability: 1.3 - RR of death with moderate/severe disability: 2.3 (probability mild or moderate/severe disability with stroke: 0.411 or 0.300) - RRR vascular death due to aspirin: 0.170 - RRR vascular death due to warfarin: 0.330 - Amiodarone: probability of death with cardioversion: 0.010	All patients face a background rate of mortality based on their age and sex. Based on the low estimates of fatality from procedural complications or drug toxicity, projected all-cause mortality was equivalent between groups (7.7% ablation versus 7.8% AAD).	- Probability of irreversible pulmonary toxicity given withdrawal for pulmonary complication: 25.00% - Mortality risk from stroke (RR): 1st year: 7.40, subsequent years: 2.30. - Probability of death given irreversible pulmonary toxicity: 20%.

Table 29 – Efficacy of intervention and comparator(s)

Reference	Assasi et al., 2010	Chan et al., 2006	Eckard et al., 2009	Ollendorf et al., 2010	Reynolds et al., 2010	Rodgers et al., 2008 McKenna et al., 2009
NSR						
CA	75.6% (Probability of AF ablation patients being in NSR at one year: 0.756 (2.93 x 0.258))	80% (Efficacy rate of 80%)	78% (Probability of AF free at 12 months: 0.780.)	Paroxysmal AF: 82.1% Persistent AF: 69.8%	90% (The model was calibrated to achieve a 10% overall failure rate with the ablation strategy. Recurrence after 1st ablation (6 months): 40%; AAD success post 1st ablation: 30%; Redo ablation 25%; Recurrence after 2nd ablation 50%; Success on drugs after 2nd ablation (6 months): 35%; Recurrence on IC AAD / sotalol (no ablation) (over 12 months): 75%.)	74 -84% (Probability of freedom from AF at 12 months: - Analysis 1 (RCT evidence): 0.8405 - Analysis 2 (RCT and case series evidence): 0.7404 - Analysis 3 (RCT and Cappato et al., 2005 evidence): 0.7867)
AAD	25.8% (Probability of AF ablation patients being in NSR at one year: 0.258)	85% (first line) (Overall cardioversion success: 85%)	9% (Probability of AF free at 12 months: 0.090)	83.3% (first line)	35% (Recurrence on amiodarone (no ablation) over 12 months: 65%)	24-37% (Probability of freedom from AF at 12 months: - Analysis 1: 0.3682 - Analysis 2: 0.2428 - Analysis 3: 0.3116)
rate control	/	38%	/	38%	/	/
AF recurrence						
CA	Annual probability of AF recurrence: 3.6%.	Annual relapse rate back to AF: 2%.	Risk ratio CA vs AAD: 0.1017.	Paroxysmal AF: 8.5% Persistent AF: 14.9%	See first row of this table	Annual rate of reversion to AF: 3.35%.
AAD	22.1%	30% in first 6 months, 5% yearly after 6 months	Rate of AF in AAD: 2.4423.	9.7%	No data in overview table after 12 months	28.83%
rate control	/	Annual relapse rate: 5%	/	9.7%	/	/

Table 30 – Utilities in the economic evaluations

Reference	Assasi et al., 2010	Chan et al., 2006	Eckard et al., 2009	Ollendorf et al., 2010	Reynolds et al., 2010	Rodgers et al., 2008 McKenna et al., 2009
Utilities	- NSR: age- and gender-specific general population utility values (going from 0.71 to 0.91, see details in original document). - AF: disutility of 0.046. - Stroke: 0.46 (post ischemic) and 0.28 (post hemorrhagic). - CA complications: disutility of 1.0 for seven days. - Pulmonary toxicity: disutility of 1.0 for duration of related hospitalization (mean 13 days). - Irreversible pulmonary toxicity: utility weight of 0.6 in each cycle.	a) Permanent quality-of-life adjustment: - Treatment strategy: Well in sinus rhythm (1.0), Aspirin (0.998), Warfarin (0.987), Amiodarone (0.987). - Stroke or intracranial bleed: Mild residual defect (0.76), Moderate to severe residual defect (0.39) - Persistent pulmonary toxicity (0.6) b) Short-term disutilities for clinical events (stroke, hemorrhage, drug toxicity, and complications for ablation): - Disutility value of 0.5 for the duration of the event.	- QALY-weights for males in normal population: Age >69: 0.830 Age 70-79: 0.800 Age 80<: 0.740 - Decrement for AF: 0.100. - Decrement for stroke: 0.250.	- Well in NSR (male, 60): 0.827 (varies by age & sex) - AF: -0.065 - Comorbidities: HF (-0.0635), diabetes (-0.0351), hypertension (-0.0250), previous stroke or TIA (-0.0524), QoL (short-term) morbidity (0.5) - procedure complications: -0.5 - cardioversion: -0.016 (3 days) - CA: -0.004 (2.7 days, 4.7 days with minor complication), with major complication: -0.010 - permanent disability: -0.049 - amiodarone, aspirin, digoxin/atenolol: -0.002 - warfarin: -0.013 - acute drug toxicity: -0.4 - amiodarone pulmonary toxicity: -0.043 (3 days) - ICH with mild or moderate/severe disability: -0.052 (10 days) or -0.305 (14 days) - Stroke mild or moderate/severe disability: -0.052 (10 days) or -0.305 (14 days)	a) Chronic States - Well after CA: 0.79 - Well on drugs: 0.79 - Rate control / anticoagulation: 0.725 - Post major stroke: 0.39 - Post minor stroke: 0.76 b) Disutility short term events - Nonfatal drug toxicity: 7 days - Telemetry admission: 3 days - Ablation complication: 4 days	- Reference point: utility of general population. - Decrement for NSR: CA 0.0000, AADs 0.0199. - Decrement for AF: CA 0.0034, AADs 0.0925. - Stroke: Non-disabled stroke (year 1 and post year 1) 0.74, Disabled stroke (year 1 and post year 1) 0.38, Combined stroke (assuming 30.9% disabled) 0.63. - Decrement pulmonary toxicity: 0.0329 - Decrement non-pulmonary toxicity (days of perfect health lost): 1 day. - Decrement bleeding event (days of perfect health lost): 1 day.

Table 31 – Results of the economic evaluations

Reference	Assasi et al., 2010	Chan et al., 2006	Eckard et al., 2009	Ollendorf et al., 2010	Reynolds et al., 2010	Rodgers et al., 2008 McKenna et al., 2009
Base case analyses	The primary economic analysis found the incremental cost effectiveness of AF ablation compared to anti-arrhythmic medication to be $59 194 per quality-adjusted life year (QALY) in patients with a $CHADS_2$ risk score of two, and for whom at least one anti-arrhythmic medication had failed.	In 65-year-old subjects with AF at moderate stroke risk, relative reduction in stroke risk with an 80% CA efficacy rate for sinus rhythm restoration would need to be ≧42% and ≧11% to yield ICERs <$50 000 and $100 000 per QALY, respectively. Because amiodarone was both less effective and more costly, it was dominated by rate control therapy.	The RFA treatment strategy was associated with reduced costs ($25 460 vs $30 440) and an incremental gain in QALYs (9.46 QALYs vs 8.68 QALYs) compared to the AAD treatment strategy.	Secondary CA: - 60, male, Paroxysmal AF: $37 808 - 65, male, CHF and Persistent AF: $73 947 - 75, male, DM HT Persistent AF: $96 846 Primary CA: - 60, male, Paroxysmal AF: $22 172 - 65, male, CHF and Persistent AF: $60 804 - 75, male, DM HTN Persistent AF: $80 615	In the base case scenario, cumulative costs with the CA and AAD strategies were $26 581 and $19 898, respectively. Over 5 years, quality-adjusted life expectancy was 3.51 QALYs with CA versus 3.38 for the AAD group. The ICER for CA versus AAD was thus $51 431 per QALY.	There appears to be little variation across the different CHADS2 scores in terms of the ICER itself (ranging from £7763 to £7910 per additional QALY). At a threshold of £20 000 per QALY there is very little uncertainty surrounding the cost-effectiveness results. The probability that CA is cost-effective at this threshold varies from 0.981 to 0.992 across the separate risk groups.
Sensitivity	- No difference in utility between normal sinus rhythm and AF health states: $221 839/QALY. - Restoring normal sinus rhythm has no impact on stroke: $86 129/QALY. - 20-year time horizon: ablation becomes less costly and more effective than AAD. - $CHADS_2$: Score 0: $68 822/QALY; Score 4: $44 652/QALY.	- Higher and lower CA efficacy rates would require correspondingly lower and higher stroke risk reduction for equivalent ICER thresholds. - In patients at low stroke risk, CA was unlikely to be cost-effective.	The results were sensitive to whether long-term quality of life improvement is maintained for the RFA treatment strategy and the risk of stroke in the different atrial fibrillation health states.	Secondary CA: 5 years - 60, male, Paroxysmal AF: $193 272 - 65, male, CHF and Persistent AF: $267 261 - 75, male, DM HT Persistent AF: $294 599 Primary CA: 5 years - 60, male, Paroxysmal AF: $105 907 - 65, male, CHF and Persistent AF: $161 090 - 75, male, DM HT Persistent AF: $171 729 QoL: If no decrement in quality of life from AF: all strategies provide nearly identical total QALYs, pure rate control strategy is the most effective.	- The model results were most sensitive to the time horizon of the analysis, the cost of ablation, and to the relative utility weights of successful ablation versus unsuccessful drug therapy. - Time horizon: 3 years: $157 000/QALY; 10 years: <$1000/QALY. - Utility: ICER was $100 000/QALY with utility difference of 0.04 or greater. Larger differences resulted in quite favorable ICERs, whereas smaller differences yielded ICERs in the economically unattractive range.	Each of the different scenarios explored as part of the sensitivity analysis is then undertaken assuming a CHADS2 score of 1, considered to provide the most representative risk for this patient group: -Results of the 5-year analysis show that the ICER for CA is within the range of conventional thresholds in the NHS: CHADS2 score 0: £27 745/QALY; $CHADS_2$ score 3: £20 831/QALY. -No influence on stroke risk: lifetime analysis: £9237/QALY; 5-year analysis: £37 997/QALY

Table 32 – Conclusions of the economic evaluations

Reference	Assasi et al., 2010	Chan et al., 2006	Eckard et al., 2009	Ollendorf et al., 2010	Reynolds et al., 2010	Rodgers et al., 2008 McKenna et al., 2009
Conclusion	The primary economic evaluation using a five-year time horizon found the incremental cost per QALY of AF ablation compared with AAD to be $59 194. These findings were similar to those of other published economic evaluations. The cost-effectiveness of AF ablation was found to be more favourable when longer time horizons were used .	In patients with AF, LACA is unlikely to be cost-effective in patients at low risk for stroke. In moderaterisk patients, LACA may be cost-effective if sufficiently high LACA efficacy rates in restoring sinus rhythm translate into lower morbidity. Our analyses may help in designing future clinical trials that compare ablation with medical therapy by providing estimates for LACA efficacy and stroke risk reduction needed in order to demonstrate both clinical efficacy and cost-effectiveness.	In conclusion, the RFA treatment strategy was associated with reduced cost and an incremental gain in QALYs and was considered a cost-effective treatment strategy compared to the AAD in a lifetime perspective, despite higher initial intervention costs.	No explicit conclusion on the cost-utility of CA. Conclusion on the efficacy of CA: a) 60, male, paroxysmal AF: - secondary CA: high certainty of a small benefit. - primary CA: unproven with potential. b) 65, male, long-standing persistent AF and HF - primary/secondary CA: unproven with potential. c) 75, male, hypertension and diabetes mellitus and persistent AF - primary/secondary CA: insufficient	RFA with/without AAD for symptomatic, drug-refractory paroxysmal AF appears to be reasonably cost-effective compared with AAD therapy alone from the perspective of the US health care system, based on improved quality of life and avoidance of future health care costs.	The overall conclusions regarding the cost-effectiveness of RFCA appear to require that the QoL benefits are maintained for more than 5 years and/or that NSR has prognostic value in preventing the risk of stroke. If neither of these is considered to be realistic then the cost-effectiveness of RFCA remains highly uncertain.

For abbreviations: see list of abbreviations at the beginning of the document.

7.3. Discussion

7.3.1. Before/after cost analyses

Before/after cost analyses are difficult to interpret in the case of catheter ablation and were therefore excluded from our overview. For example, catheter ablation may be considered when a patient failed on AAD treatment. The costs of taking this drug disappear, together with hospitalization costs due to e.g. side effects and costs for regular GP visits. The 'before' period is also probably the worst period for the patient, i.e. the decision to perform ablation is taken because of e.g. too much side effects leading to hospitalizations and impacting on QoL. This means that also with an alternative approach (e.g. optimal pharmacologic treatment) the patient's costs and outcomes would have changed. The outcomes in the catheter ablation group should therefore be compared with the latter (i.e. patients that also failed on AAD treatment and receive the next best alternative treatment) and not with the 'before' outcomes. As a result, in order to have a view on incremental costs and effects with catheter ablation, only studies with a comparator group and both looking at costs and effects are included in this review.

7.3.2. Rate control

Most of the economic models include patients with paroxysmal AF unsuccessfully treated with AAD. Even though evidence on the effectiveness of first-line ablation to restore sinus rhythm or have an impact on patient-relevant outcomes is lacking, two studies also model the cost-effectiveness of first-line ablation. In the study of Chan et al.[77] amiodarone was both less effective and more costly, and thus dominated by rate control therapy (Table 31). Ollendorf et al.[20] concluded efficacy of primary catheter ablation is unproven but has potential (Table 32).

In an economic evaluation based on the AFFIRM study, "*a mean survival gain of 0.08 year (P = 0.10) was observed for rate control* in comparison with antiarrhythmic drugs (rhythm control)*. Patients in the rate-control group used fewer resources (hospital days, pacemaker procedures, cardioversions, and short-stay and emergency department visits). Rate control costs $5 077 less per person than rhythm control.*"[82] They concluded that "*Rate control is a cost-effective approach to the management of atrial fibrillation compared with maintenance of sinus rhythm* with AAD *in patients with atrial fibrillation similar to those enrolled in AFFIRM.*"[82] Reynolds et al.[80] assumed that patients were seeking rhythm control strategies because of dissatisfaction with rate control alone.

Based on current knowledge and economic considerations, the rational to support catheter ablation as first-line treatment are lacking and both rate/rhythm control should be considered first. Based on real-world Belgian data, it seems that this is not the case in up to 15% of the ablated patients (see 6.4.6).

7.3.3. Procedural complications

The bulk of published data on AF ablation comes from selected centres of excellence.[80] Data on complications from these centres may underestimate real-world complication rates. Data from real-world registers or surveys may provide more realistic values. Some studies[79-81] refer to the worldwide survey conducted by Cappato and colleagues.[61] Not all complications mentioned in this survey are included in the models. Whereas complications are estimated to be around 5% (see 5.1), all but one[20] of the models include only 3% or less complications. This difference might be explained by the fact that some of these complications occur during the initial hospitalization, and therefore, related costs are already included in those of the ablation procedure. If this is not the case, the underestimation of costs will favor the ablation group. Furthermore, the survey of Cappato et al. only had a 23% response rate. As mentioned by Rodgers,[81] the findings of this survey have a clear potential for bias, most likely in favor of ablation, i.e. by overestimating success rates and/or underestimating complications. Some of the experts remarked that not filling in the survey might be related to other factors (e.g. time constraints). Increased experience and/or concentration of the procedure in the most experienced centres may lead to lower rates of complications than those reported by Cappato.

7.3.4. Use of drugs

The economic evaluations make several assumptions towards the use of drugs. One study[28] assumed that AF ablation patients discontinue warfarin three months after their procedure. This results in different costs and bleeding risks between AF ablation patients and AAD-treated patients. However, this does not reflect reality and favors the ablation group. Reynolds et al.[80] assume that ablation patients would not be treated with amiodarone after failed ablation. The Belgian data (see 6.4.4) show this is not the case. In fact, these data show that overall AAD drug use after ablation is higher in Belgium than in the economic evaluations. Whatever the reason might be, it has an impact on costs and effects. First, costs will be higher in the ablation group. Second, the modelled adverse events linked to these drugs (e.g. bleeding and pulmonary toxicity) are thus underestimated in the ablation group. This leads to overoptimistic results for catheter ablation in the economic evaluations.

7.3.5. Stroke and mortality

Several models focus on the impact of ablation on stroke.[28, 77, 79, 81] However, there is no direct hard evidence from RCTs to support this assumption. At the KCE expert meeting, it was mentioned that this can be difficult to prove. It would probably demand a very large study since the absolute benefit is limited. This is due to both a small relative impact on stroke (if existing) and/or the low baseline risk of stroke. Unless evidence from ablation therapy on stroke is provided in a well-performed RCT with optimal treatment in the control group, results of models that assume a major impact on stroke remain questionable.

The evidence does not suggest that ablation is associated with increased mortality.[81] However, the opposite is also true. Nevertheless, an impact on mortality is modelled through assuming a different stroke risk and including an immediate stroke mortality and an increased mortality risk afterwards (Table 28). If the impact on stroke is not supported by hard evidence, then an indirect impact through stroke on mortality should also be regarded with caution.

All models mention to perform a cost-utility analysis. However, with the exception of one study, no results are presented in life-years gained. Therefore it is not possible to separately assess the modelled impact of mortality and QoL on results. Only one study provided such information. Through their base case assumption that ablation had a small procedure-related stroke risk and did not impact the long-term stroke risk, ablation was estimated to be more expensive and provide less life-years than rhythm control.[20] Reynolds[80] also mentioned the projected all-cause mortality was equivalent between groups (7.7% ablation versus 7.8% AAD) (Table 28). It is not clear whether or not other models included a large impact on mortality. If this would be the case, then this would be questionable since no hard evidence is available to support an increased/decreased stroke and/or mortality risk.

7.3.6. Quality of life

There is evidence from RCTs that ablation improves QoL in the short-term, measured with the generic profile SF-36 instrument. Unfortunately, none of the RCTs measured QoL with a generic utility instrument and information on the long-term impact on QoL is lacking (see Chapter 4.5). Notwithstanding, all models include an impact on QoL and assume such a long-term impact. Some assumptions make the results of the economic evaluations rather optimistic or subject to large uncertainty.

With the exception of one study,[20] none of the economic evaluations include a utility loss for the initial ablation procedure (Table 30). Although this impact might be relatively small, it is applicable to all patients in the ablation group.

Chan et al.[77] apply a utility of 1 for patients well in sinus rhythm, and values close to 1 for healthy patients taking aspirin, warfarin or amiodarone (Table 30). However, the utility of an average healthy population is not equal to 1, which is shown in the other models that use age- and gender-specific general population values. As a result, the modelled incremental effect is very probably too large in the study of Chan et al.

The RCTs have not measured QoL with a generic utility instrument. Consequently, all models try to rely on best available data to include the incremental impact on quality-adjusted life years. For example, Reynolds et al.[80] derived utilities for 3 separate populations of patients with AF to estimate the likely changes that might be observed after successful ablative or drug therapy. For drug-treated patients, SF-12 data from the FRACTAL registry[83] were transformed to utilities. For ablation patients, SF-36 data from a prospective cohort of patients undergoing catheter ablation at a medical centre were transformed to utilities. And finally, utilities were

calculated using SF-36 data for patients enrolled in the A4 trial[33] to estimate the comparative changes in utility for patients treated with drugs versus ablation. However, this study had a 67% rate of crossover to ablation in the AAD group. In general, indirect estimation of utilities, based on different studies, measured with different instruments, and transformed to utilities through mapping is prone to very large uncertainty and should be regarded with caution.

Most studies include utility decrements for specific health states or events. The evidence base for these decrements is most of the time lacking. In the UK study[79, 81] a different decrement is included for the same health state after ablation versus AADs, while decrements for adverse events are modelled separately. For example, the decrement for atrial fibrillation is 0.0034 in the ablation group, while this is 0.0925 in the AAD group. This is in favor of the ablation group. The impact on QoL is also modelled through the impact on stroke. Again, it is very important to have hard evidence on this stroke endpoint in order to allow reliable cost-effectiveness calculations.

Disutilities are also modelled for drug related events. However, the real-world Belgian data indicate that a large part of the ablation group still takes one or more of these drugs after the intervention. Not taking this into account underestimates the adverse events and impact on QoL and thus is in favor of the ablation intervention.

It is stated that "*it should be recognised that the QoL estimates applied in the model remain highly uncertain.*"[81] This applies to all identified models. Even so, the results and sensitivity analyses show that the impact on QoL is a determinant factor for the cost-effectiveness of ablation. Therefore, it is desirable to have better data to support these economic evaluations. In future research, QoL should be measured with a generic utility instrument (such as the EQ-5D) in a properly performed RCT.

7.3.7. Time horizon

Most analyses use a lifetime horizon in their base case analysis (Table 23). Evidence for longer-term benefits of ablation is lacking. Extrapolating potential benefits reported over shorter time horizons is standard in economic evaluations. Nevertheless, the reliability of results becomes increasingly uncertain, especially in this case of ablation where both short and long-term evidence on the catheter ablation impact on mortality, stroke, and quality of life (utilities) is lacking. Comparing input variables from the models with more recent published data also indicates that extrapolations are probably too optimistic. For example, the annual probability of AF recurrence is less than 4% in several studies (Table 29).[28, 77, 79, 81] According to experts, this should be rather between 6% and 9%.[1] In Belgium, a redo during the second year after the index ablation was performed in about 9%. A 90% success rate (Table 29) also seems rather optimistic in comparison with data from the medical review (see Chapter 1.1.1). Other assumptions, such as not allowing for repeat ablation procedures after the first 12 months[79, 81] are not in accordance with reality. These assumptions are clearly in favor of the ablation arm, especially in models with a longer time horizon.

7.4. Conclusion

The published economic evaluations indicate that the most determining input variables for a cost-effectiveness assessment of catheter ablation of AF are the impact on utility and/or stroke, and the duration of these effects. However, it now appears that there are no good utility data, especially not in the long-term, and that evidence on stroke impact is lacking. Long-term extrapolations without hard short-term evidence on these endpoints is even more uncertain. In combination with one or more other factors (e.g. higher yearly recurrence of AF or higher real-world use of other drugs in the ablation arm) the modelled outcomes therefore seem to be optimistic.

Based on current knowledge, it is difficult to assess whether catheter ablation represents efficient use of limited resources. It is a certainty that catheter ablation is associated with higher initial costs and certain complications. Atrial fibrillation catheter ablation's cost-effectiveness depends on the belief one places on longer-term outcomes. Modelling is hardly ever without assumptions. However, having no hard evidence for the most important variables is rather a disappointment. We preferred not to model ourselves the cost-effectiveness of catheter ablation. Our calculations would be prone to the same uncertainty as all previous models. This is in line with the 2010 SBU (The Swedish Council on Health Technology Assessment) report that concluded that "The scientific evidence is insufficient for drawing conclusions about the cost-effectiveness of the method since its long-term effects are uncertain."[29]

In the SBU report, insufficient evidence means that no conclusions can be drawn when there are no studies that meet the criteria for quality.[29] We fully agree with that.

Key points

- **There are significant upfront costs with catheter ablation. The procedure is also associated with infrequent but severe complications.**
- **Existing economic evaluations are mainly based on assuming an impact on stroke and/or long-term quality of life. However, no direct hard evidence supports these assumptions.**
- **Based on current knowledge, it is difficult to assess catheter ablation's cost-effectiveness. There is no hard evidence supporting the most determining variables, being: incremental impact on short- and long-term QoL measured with a generic utility instrument, impact on stroke (if any) and impact on mortality (if any).**
- **Better evidence in the medium-term (1-5 years) is necessary before extrapolating to very long-term outcomes (after 5 years).**

8. PATIENT ISSUES

AF is a condition with potentially serious consequences, among which stroke and death. At this moment in time, there is not one single study that demonstrates that a successful ablation reduces the risk of these hard endpoints. The indication to use antithrombotic medication for life is not altered by a successful ablation. Based on current scientific knowledge, catheter ablation should only be considered for people who continue to suffer symptoms of AF, in spite of adequate rate control and provided antiarrhythmic agents have proven to be ineffective.

According to the results of RCTs, the chance of a patient remaining free from AF one year after an ablation is expected to be 65 to 90% in cases of paroxysmal AF, and at 55 to 80% in cases of persistent AF. Short term success rates reported in observational studies are on average inferior to those from RCTs.

How long patients remain free from AF beyond that period of one year is not properly known. From observational data, experts estimate that beyond one year after the index procedure, 6 to 9% of patients relapse each year. There are almost no data on the effectiveness of the procedure beyond more than 5 years after the index procedure. This is not a trivial issue since catheter ablation has an intended benefit extending over several decades.

Based on 2008 Belgian data, we estimate that after 1 year, AF recurs in 37.3 to 59.8% of patients. After two years, these figures are 49.9 to 65.9%.

The procedure entails a risk of serious complications. The reported risk of cardiac tamponade ranges between 1 and 3%, the risk of dying ranges between 0 and 2 per 1000 ablations, the risk of suffering a severe stroke ranges between 1 and 3 per 1000. There is also an additional risk of up to 5% less severe complications, some of which requiring hospitalisation or surgical correction. During the procedure, patients are exposed to X-rays for a protracted period of time, up to 1000 times longer than if they were having a classic chest roentgenogram taken. Experts estimate that every ablation is accompanied by a delayed risk of contracting a fatal cancer of 0.2 to 2.1 in 1000.

Patients must be clearly told that the fact that an instrument has been given a European seal of approval (CE mark) does not mean that it is effective and/or safe. If the electrophysiologist uses a new instrument that has not yet been proven to be reliable in at least 1 well-performed RCT, he should inform the patient that he will be using an experimental technique which may not necessarily be as effective and safe as mentioned above.

It should be contemplated to write down the abovementioned information in a patient leaflet and include it as a mandatory part of the discussion with patients before proceeding to the intervention.[t]

9. REGULATORY AND ORGANISATIONAL ISSUES

9.1. Belgian legislation

In 1999, so-called “care programs” (“zorgprogramma’s”, “programmes de soins”) have been installed by the Belgian federal government. They are related to a variety of hospital services such as geriatrics, paediatrics, oncology, reproductive health and cardiology. Further in this text, the latter will be referred to as “cardiac care program (CCP)”. Several distinct CCPs have been defined: A, B, P, E, T, and C. Virtually all acute hospitals can have a CCP “A” certification allowing for clinical cardiology without limitations as far as non-invasive diagnosis or non-invasive treatment is concerned. To obtain a higher level of CCP a hospital needs to adhere to a number of qualitative and quantitative criteria that have recently been adapted by Royal Decree (June 112, 2012). Hospitals with a CCP “P” (P=pacemaker) are accredited to provide PM therapy. CCP “T”, relating to heart- and lung transplantation, and CCP “C” relating to congenital heart disease, are beyond the scope of the present report.

In order to obtain a CCP “E” (electrophysiology) qualification, a hospital must have a CCP “B” and a CCP “P” accreditation in addition to a number of quantitative requirements, such as a minimum number of electrophysiology procedures and the number of cardiologists affiliated with the hospital. These requirements have been further specified in a Royal Decree of July 15, 2004. In order to receive a CCP E accreditation, centres had to have performed at least 50 electrophysiology procedures per year. To maintain the accreditation, 80 procedures have to be performed yearly. In November 2007, the nomenclature related to electrophysiology has drastically changed by introducing a separate reimbursement of devices and by introducing a series of nomenclature codes related to the ablation of specific arrhythmias. The legislation that defines the requirements for CCP E accreditation has not yet taken into account the new nomenclature and is still referring to the older codes.

[t] http://www.nice.org.uk/nicemedia/live/11964/42872/42872.pdf

All care programs must be submitted to an internal and an external quality appraisal, to be organised and controlled by the College of Physicians. More specifically, the responsibility for the quality control of the CCP "P" lies with the College of Physicians – Cardiac Pathology – Section Pacing and Electrophysiology. In practice however, this obligation has never been enforced, and hospitals have only been encouraged to contribute data to the Belgian Heart Rhythm Association (BeHRA) pacemaker register.[u] These data are not publicly available.

It is not fully clear how many hospitals currently have a CCP "E" accreditation. Based on information obtained from Belgian experts, it is estimated that there are 44 CCP E centres. We obtained data on clinical electrophysiology activities in Belgian hospitals from the 3 major sickness funds, representing 90% of the Belgian population. It appeared that over 2009-2011, 30 Belgian hospitals performed at least one CA-AF. In the year 2011, 25 hospitals performed at least 25 AF ablations, 18 did at least 50, and 6 did more than 100 such procedures in 2011.

9.2. Belgian catheter ablation registration

The Belgian Heart Rhythm Association (BeHRA), formerly the Belgian Working Group on Cardiac Pacing and Electrophysiology, is a working group of the Belgian Society of Cardiology, established in 1980 (www.behra.be). The BeHRA collects the Belgian clinical electrophysiology activity based on data that are voluntarily provided by its members on web-based forms. The structure of this database was changed by the end of 2007 in response to the new nomenclature that was then adopted. Unfortunately, it does not report follow-up data. Upon our request, BeHRA provided us some aggregated data related to the years 2008-2011. These will be included in the chapter on Belgian practice.

9.3. European and US regulation

We have previously documented that high-risk medical devices very often receive market approval for clinical use in Europe years before they got approval for clinical use in the U.S.[84] This also holds true for catheters that are used for CA-AF. Several devices for catheter ablation that are routinely used in Europe still have studies ongoing in order to enter the US market.

In order for devices to get marketed in Europe, "device performance" and "safety" has to be demonstrated, whereas in the US also clinical effectiveness needs to be demonstrated (as is the case for pharmaceuticals both in Europe and the US). To these ends, different trial designs are to be used. In Europe a small case series ("device performance trial") will often be judged sufficient data by the Notified Body requested by the company to judge whether the product can be CE marked. In the US, the FDA typically requires evidence of clinical effectiveness based on a randomised controlled trial, and this takes time and resources to conduct. Results of such RCT will be made public as part of the FDA assessment, provided the company continues to seek marketing authorisation. Unfortunately, and despite the Declaration of Helsinki, results of such "device performance trials" that are used for granting market approval of a device in Europe are rarely made public. Yet, transparency is required to allow physicians to practice evidence-based medicine and patients to make an informed decision.

Compared with patients in the US, patients in Europe can thus have an earlier access to an innovative device, but at the risk of inadequately documented efficacy and safety. This has been amply demonstrated earlier in the present report in relation with Medtronic's Ablation Frontiers Cardiac Ablation System® (TTOP study), the HD Mesh Ablator®, marketed by C.R. Bard Inc (MACPAF study) and the high-intensity focused ultrasound (HIFU) balloon catheter ablation (ProRhythm Inc.).

---

u http://www.health.belgium.be/eportal/Healthcare/Consultativebodies/Doctorscolleges/CardiacPathology/index.htm

In 2007, the existing medical device directives were amended by Directive 2007/47/EC, which became effective in March 2010.[v] It states that, in the case of implantable devices, clinical investigations shall be performed unless relying on existing clinical data is duly justified. The guidance document (December 2010, MEDDEV 2.7/4 guidelines) does not provide any specific requirement on the depth and extent of the premarketing clinical evaluations.[w] The remaining variation in the stringency of clinical review both at the level of Notified Bodies and the Competent Authority level is still not optimal to guarantee patient safety in a uniform way for EU citizens.[85]

9.4. Volume outcome relationship

CA-AF is one of the most technically challenging procedures in the field of interventional electrophysiology.[86] It has been shown that hospital experience is independently related to outcome in terms of procedural complications and re-hospitalisations. Shah et al. analysed administrative data from more than 4000 adult patients who underwent their first CA-AF in California from 2005 to 2008. Hospital yearly procedural experience varied between 7.0±4.4 in the lowest quartile to 139.9±27.8 in the highest. A 57% increase in the odds of complications was calculated in the lowest compared with the highest quartile.[62]

In a worldwide survey the success rate off-AADs ($p<0.001$) and the overall success rate ($p<0.05$) significantly increased as the number of procedures per centre increased.[61] This has been confirmed in an update of this survey on 16,000 patients treated between 2003 and 2006, where success rates off-AADs increased with centre experience (odds ratio 1.04 per experience increase by 30 procedures; 95%CI 1.01-1.06).[44] These data have to be interpreted with caution since they originate from statistics, voluntary provided by only a quarter of invited centres (n=777 in the first survey [61] and n=52 in the second[44]).

In a recently published consensus statement, no formal recommendations are made as to the minimal number of CA-AF a given centre should perform in order to be considered “technically competent”. It is however stated that trainees who intend to perform CA-AF independently, should have performed 50 such procedures during training.[19]

---

[v] Available from: http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:247:0021:01:EN:HTML

[w] http://ec.europa.eu/consumers/sectors/medical-devices/files/meddev/2_7_4_en.pdf

10. DISCUSSION

Clinical trials have revealed that the chance of selected patients remaining free from AF one year after a single radiofrequency or cryoablation ablation ranges between 55 and 90%. The success rate is highest in patients suffering from paroxysmal AF with no or only minimal underlying cardiac pathology. How long the procedure remains successful in the long run is not known. Experts estimate that beyond one year after the index procedure, 6 to 9% of patients relapse each year. There are almost no data on the effectiveness of the procedure beyond more than 5 years after the index procedure.

At this moment in time, there is no hard evidence showing that other problems associated with AF, such as the risk of stroke and the need to take anticoagulant drugs, are affected by a successful ablation.

In as yet unpublished RCTs the clinical effectiveness of catheter ablation is lower than in the earlier trials. This may be due to patient selection that became less stringent than in earlier clinical trials. Some of those studies included patients at higher risk for stroke, whilst others included patients that went not through a tryout with drugs before proceeding to ablation. There have also been serious problems with some newly developed ablation devices which, notwithstanding their CE labelling, ultimately turned out to perform poorly, both in terms of safety as in terms of efficacy.

From administrative data, we used 3 parameters to estimate the effectiveness of AF ablation: redo of the procedure and the need for electric cardioversion or antiarrhythmic drugs afterwards. We estimated AF to recur after a single ablation in 37.3 to 59.8% of patients within one year, and in 49.9 to 65.9% after two years. These performance estimates are poorer than those observed in RCTs, but they are contained within the wide estimates of AF recurrences as reported in observational studies.

In the Belgian AF ablation population, almost a quarter of patients had non-paroxysmal AF, an estimated 15% of them did not go through a tryout with drugs before the ablation, and 12 out of 30 centres perform less than 50 AF ablation procedures per year (2011).

The chance that patients become asymptomatic following an ablation must be weighed against the potential complications of the procedure. This is all the more important since ablation is currently advocated in patients with AF at low risk for complications from this arrhythmia. The risk of cardiac tamponade ranges between 1 and 3%, the risk of major stroke ranges between 1 and 3 per 1000 and the risk of death ranges between 0 and 2 per 1000 ablations. There is also an additional risk of up to 5% of less severe complications, some of which requiring hospitalisation or surgical correction. Furthermore, there is a delayed 0.2 to 2.1 per 1000 risk of patients developing a fatal cancer due to the prolonged X-ray exposure.

The lack of hard data on the impact of catheter ablation on relevant endpoints such as quality of life, mortality, and stroke preclude a reliable calculation of its cost-effectiveness. This is reflected in the long series of unresolved questions listed in the 2012 Consensus Statement, originating from the major European, US and Asian cardiologic societies:[19]

1. What is the long-term impact of CA-AF on stroke risk, the development of heart failure, and major morbidity and mortality?
2. Has the concept of “slowing progression of AF” any clinical value in the context of AF ablation?
3. Is there a comparative effectiveness advantage to catheter based vs. surgical interventions?
4. What are the comparative success rates of various ablative techniques in differing patient populations, particularly persistent and longstanding persistent AF?
5. What is the benefit of AF ablation in patients not well represented in clinical trials of AF ablation, including the elderly, women, those with heart failure, African Americans, and those with longstanding persistent AF?
6. Is there an age limit to successful ablative intervention?
7. Are there patients in whom oral anticoagulation can be safely discontinued following ablation, and what is the impact of direct thrombin inhibitors and factor Xa inhibitors on anticoagulation strategies prior to, during and following AF ablation?
8. Is there acceptable rationale for ablation applied as first line therapy for AF?
9. Is ablative intervention cost-effective or is drug therapy more economically efficient?

10. Beyond placebo effect, what is the relative quality of life benefit of ablation vs. drug therapy?
11. What are the safety and efficacy outcomes of newer ablation technologies such as cryoballoon and laser balloon ablation?
12. Can useful, robust performance measures characterising outcomes of ablation be developed?
13. What are the very long-term outcomes (>5 years) of CA-AF?

In August 2012, an update of the guidelines for the management of AF has been issued by the European Society of Cardiology (ESC). It attributes a “class I - level A” indication for catheter ablation for symptomatic paroxysmal AF in drug-refractory patients, indicating that the intervention “is recommended” in such patients and that the evidence for this recommendation is derived from “multiple RCTs or meta-analyses”. However the efficacy of catheter ablation as observed in those RCTs has not been reproduced in observational studies, including the present study on Belgian practice. Furthermore, the procedure has an intended benefit for patients extending over several decades but its effect beyond 5 years remains completely unknown. Therefore, we feel this ESC recommendation being overenthusiastic.

In the same document, the ESC attributes a “class IIA - level B” indication for catheter ablation as a first line therapy in selected patients. This indicates that, based on “data derived from a single RCT or from large non-randomised studies”, the procedure “should be considered”. Data from terminated but as yet unpublished RCTs have shown that the effectiveness of catheter ablation as a first-line treatment for AF is much less prominent than in the earlier trials where the ablation was performed in patients with symptomatic recurrences on antiarrhythmic drug therapy. Again, according to our analysis of the available scientific data, conclusive data are lacking to consider catheter ablation as a first line therapy for AF in everyday clinical practice.

The two abovementioned clinical guidelines do not take into account cost considerations.

APPENDIX

1. LITERATURE SEARCH (CLINICAL EFFECTIVENESS)

1.1. HTA reports

In a first step, HTA reports previously issued by other agencies were looked for. This search was accomplished between November 2011 and January 2012. First, the CRD database was searched. Next, the website of each INAHTA member was searched and reports that were not identified via CRD were retrieved. Finally the EUnetHTA POP database was checked for ongoing projects. HTA reports published in 2010 and 2011 were retrieved for detailed assessment.

1.1.1. CRD database

Search term: “atrial fibrillation”

- CADTH Sep 2010: Ablation Procedures for Rhythm Control in Patients with Atrial Fibrillation: Clinical and Cost-Effectiveness Analyses[28]
- ICER (Institute for Clinical and Economic Review) Sep 2010: Rhythm Control and Stroke Prevention Strategies for Patients with Atrial Fibrillation[20]
- 3 HTAs from Hayes: Radiofrequency Ablation of the Pulmonary Veins for the Treatment of Atrial Fibrillation; Cardio ablation systems (Medtronic Inc) for atrial fibrillation; Sensei X robotic system (Hansen Medical Inc.) for treatment of atrial fibrillation. These documents are not freely available and were not considered in the present report.
- A 2010 “Alert Report”, originating from the Swedish Council on Health Technology Assessment (SBU). This is a 16-page document written in Swedish including a two pages English summary.[29]

1.1.2. Individual HTA agencies from INAHTA database

Search terms: “atrial fibrillation”, complemented by “ablation” or “catheter ablation” in agencies where “atrial fibrillation” as a single lemma led to a high number of hits

- NICE June 2011: Interventional procedure overview (= rapid review of medical literature) of percutaneous endoscopic catheter laser balloon pulmonary vein isolation for atrial fibrillation.[x] This is a provisional document.

1.1.3. EUnetHTA POP (planned and ongoing) database

Search terms: “atrial fibrillation”, “ablation”

- Percutaneous HIFU balloon ablation for AF: NICE, planned (“being monitored”)[y]
- NICE Interventional procedures Programme (IP950), October 2011: Percutaneous cryo-ablation for AF.[z] This is interim report that contains no formal conclusions yet. (Its final version with corresponding guidance was issued in May 2012 and was incorporated in the discussion of the current report.)

1.2. Systematic reviews

1.2.1. CRD database

Search for systematic reviews (SR) on January 12, 2012 (“atrial fibrillation” AND “ablation”, limited to 2010-2011) resulted in 4 papers[30, 31, 87, 88].

1.2.2. Cochrane Database of Systematic Reviews

No 2010-2011 Cochrane reviews on this subject were identified.

In April 2012, during the preparation of the present report, a Cochrane Review on CA was published.[42] Its literature search extended to August 2009 and as such, it did not include additional information to that provided by the SRs that were published in 2010-2011 (Table 1).

1.2.3. PubMed

A Medline search was executed via PubMed on Jan 5, 2012, using the following MeSH terms: “atrial fibrillation”; “catheter ablation” (includes *electrical* and *radiofrequency*); “cryosurgery” (includes *cryo-ablation*, but obviously focused on surgery); “pulmonary veins”; “High-Intensity Focused Ultrasound Ablation”. No language restrictions were applied. The following search string was entered:

("Atrial Fibrillation"[Mesh] AND ("Catheter Ablation"[Mesh] OR "Cryosurgery"[Mesh] OR "Pulmonary Veins"[Mesh] OR "High-Intensity Focused Ultrasound Ablation"[Mesh])) AND ((Clinical Trial[ptyp] OR Meta-Analysis[ptyp] OR Randomized Controlled Trial[ptyp] OR Review[ptyp]) AND ("2010/01/01"[PDAT] : "3000"[PDAT]))

This resulted in 210 hits that were screened for systematic reviews and randomised controlled trials. The aim was to identify RCTs (and systematic reviews of RCTs) that compared CA-AF with AAD treatment.

After reviewing title and abstract, five SRs were retrieved.[30, 43, 88-90] These were subjected to a full-text evaluation. Wilton,[88] was rejected because it only compared patients with and those without left ventricular dysfunction. Brooks,[89] was rejected because it compared different ablation techniques. Viles-Gonzalez,[43] and Nault[90] were narrative reviews. Bonanno’s[30] is a formal systematic review.

1.2.4. EMBASE

An EMBASE search was executed on Jan 9, 2012, making use of the Emtree terms: “heart atrial fibrillation”; “ablation therapy”; “catheter ablation”; “high intensity focused ultrasound”; “laser surgery”; “pulmonary vein isolation”; “radiofrequency ablation” in the following search string:

'heart atrium fibrillation'/exp AND ('ablation therapy'/exp OR 'catheter ablation'/exp OR 'electrosurgery'/exp OR 'high intensity focused ultrasound'/exp OR 'laser surgery'/exp OR 'pulmonary vein isolation'/exp) AND [embase]/lim AND ([cochrane review]/lim OR [controlled clinical trial]/lim OR [meta analysis]/lim OR [randomized controlled trial]/lim OR [systematic review]/lim) AND [2010-2012]/py. No language restrictions were applied.

This resulted in 112 hits that were screened for systematic reviews and randomised controlled trials.

---

x http://guidance.nice.org.uk/IPG399/DraftGuidance

y http://www.nice.org.uk/guidance/index.jsp?action=byID&o=13434

z http://www.nice.org.uk/nicemedia/live/13475/57679/57679.pdf

After reviewing title and abstract, five SRs were retrieved.[30, 31, 88, 91, 92]: Dagres; Andrade: Parkash; Garikipati; Wilton; Bonanno. Four of these were not identified by PubMed and were subjected to a full-text evaluation. Dagres[92] was rejected because it focused on left ventricular function and included only 1 RCT[35] in its analysis. Andrade,[91] was rejected because it included only 1 RCT and was limited to cryo-ablation. Parkash,[31] represents a formal SR.

1.3. Randomised controlled trials

RCTs comparing CA-AF with AAD treatment that were published before 2010 were searched for in the HTA reports and SRs mentioned above, and through hand searching. RCTs published in 2010-2011 were systematically searched applying the abovementioned search strings in PubMed and EMBASE.

1.3.1. PubMed

3 RCTs recorded in 2010-2011: Wilber,[40] Reynolds,[55] MacDonald[35] The latter included only a limited number of patients (22 CA-AF and 19 controls) and was atypical as compared to the other RCTs in that it enrolled only patients with advanced heart failure and its primary endpoint was a change in left ventricular ejection fraction.

1.3.2. EMBASE

3 RCTs in 2010-2011: Hunter (congress abstract) and Reynolds[55] and Wilber[40] These studies were identified by PubMed as well.

2. QUALITY APPRAISAL OF HEALTH TECHNOLOGY ASSESSMENT REPORTS

The quality of HTA reports were assessed by using the INAHTA 2007 checklist.[aa]

[aa] http://inahta.episerverhotell.net/HTA/Checklist/

2.1. Canadian Agency for Drugs and Technologies in Health (CADTH, Sep 2010).[28]

Item	Yes	Partly	No
Preliminary			
1. Appropriate contact details for further information?	X		
2. Authors identified?	X		
3. Statement regarding conflict of interest?	X		
4. Statement on whether report externally reviewed?	X		
5. Short summary in non-technical language?			X
Why?			
6. Reference to the policy question that is addressed?		X	
7. Reference to the research question(s) that is/are addressed?	X		
8. Scope of the assessment specified?			
9. Description of the assessed health technology?		X	
How?			

10. Details on sources of information and literature search strategies provided?

Search strategy	Databases	Year range	Language restriction	Primary data	Other kind of information resources
X	X	X	X	X	X

Complete reference list of included studies	List of excluded studies	Inclusion criteria	Exclusion criteria
X	X	X	X

11. Information on basis for the assessment and interpretation of selected data and information?				
Method of data extraction described?	Critical appraisal method (for quality assessment of the literature) described?	Method of data synthesis described?	Results of the assessment clearly presented, e.g. in the form of evidence tables?	
X	X	X	X	
Context? (may or may not apply to each HTA)				
(Medico-) legal implications considered?	Economic analysis provided?	Ethical implications considered?	Social implications considered?	Other perspectives (stakeholders, patients, consumers) considered?
X	X	O	O	O

What then?	**Yes**	**Partly**	**No**
12. Findings of the assessment discussed?	X		
13. Conclusions from assessment clearly stated?	X		
14. Suggestions for further action?	X		

2.2. Institute for Clinical and Economic Review (ICER, Sep 2010).[20]

Item	Yes	Partly	No
Preliminary			
1. Appropriate contact details for further information?	X		
2. Authors identified?	X		
3. Statement regarding conflict of interest?			X
4. Statement on whether report externally reviewed?	X		
5. Short summary in non-technical language?			X
Why?			
6. Reference to the policy question that is addressed?	X		
7. Reference to the research question(s) that is/are addressed?	X		
8. Scope of the assessment specified?	X		
9. Description of the assessed health technology?	X		
How?			

10. Details on sources of information and literature search strategies provided?

Search strategy	Databases	Year range	Language restriction	Primary data	Other kind of information resources
X	X	X	X (English only)	X	X

Complete reference list of included studies	List of excluded studies	Inclusion criteria	Exclusion criteria

X	X	X	X
11. Information on basis for the assessment and interpretation of selected data and information?			
Method of data extraction described?	Critical appraisal method (for quality assessment of the literature) described?	Method of data synthesis described?	Results of the assessment clearly presented, e.g. in the form of evidence tables?
X	X	X	X
Context? (may or may not apply to each HTA)			

(Medico-) legal implications considered?	Economic analysis provided?	Ethical implications considered?	Social implications considered?	Other perspectives (stakeholders, patients, consumers) considered?
O	X	O	O	X

What then?	**Yes**	**Partly**	**No**
12. Findings of the assessment discussed?	X		
13. Conclusions from assessment clearly stated?	X		
14. Suggestions for further action?	X		

3. QUALITY APPRAISAL OF SYSTEMATIC REVIEWS[bb]

3.1. Parkash et al.[31]

Approach to the Catheter Ablation Technique of Paroxysmal and Persistent Atrial Fibrillation: A Meta-Analysis of the Randomized Controlled Trials.

Parkash R, Tang AS, Sapp JL, Wells G. J Cardiovasc Electrophysiol 2011;22(7):729-38.

Patients: paroxysmal or persistent AF

Intervention: radiofrequency ablation of AF

Control: anti-arrhythmic drugs (or other types of catheter ablation that were omitted in the present HTA report)

Outcome: freedom from AF after a single radiofrequency procedure

METHODEN

1. Is de vraagstelling adequaat geformuleerd?

[√] Ja

[ ] Nee

[ ] Te weinig informatie in het artikel om dit te beantwoorden

2. Is de zoekactie adequaat uitgevoerd?

[√] Ja

[ ] Nee

[ ] Te weinig informatie in het artikel om dit te beantwoorden

3. Is de selectieprocedure van artikelen adequaat uitgevoerd?

[√] Ja

[ ] Nee

[ ] Te weinig informatie in het artikel om dit te beantwoorden

4. Is de kwaliteitsbeoordeling adequaat uitgevoerd?

[√] Ja

[ ] Nee

[ ] Te weinig informatie in het artikel om dit te beantwoorden

5. Is adequaat beschreven hoe data-extractie heeft plaatsgevonden?

[√] Ja

[ ] Nee

[ ] Te weinig informatie in het artikel om dit te beantwoorden

6. Zijn de belangrijkste kenmerken van de oorspronkelijke onderzoeken beschreven?

[√] Ja

[ ] Nee

[ ] Te weinig informatie in het artikel om dit te beantwoorden

7. Is adequaat omgegaan met klinische en statistische heterogeniteit van de onderzoeken?

[ ] Ja

[√] Nee

[ ] Te weinig informatie in het artikel om dit te beantwoorden

8. Is statistische pooling op een correcte manier uitgevoerd?

[√] niet van toepassing (vanwege heterogeniteit)

[ ] Nee

[ ] Te weinig informatie in het artikel om dit te beantwoorden

[bb] Dutch Cochrane instrument for the quality appraisal of a systematic review of RCTs.

ALGEMEEN OORDEEL

9. Zijn de resultaten van de systematische review valide en toepasbaar?

[ ] Voldoende valide en toepasbaar

[√] Twijfelachtig

[ ] Onvoldoende valide en toepasbaar

3.2. Bonanno et al.[30]

Efficacy and safety of catheter ablation versus antiarrhythmic drugs for atrial fibrillation: A meta-analysis of randomized trials.

Bonanno C, Paccanaro M, La Vecchia L, Ometto R, Fontanelli A. J Cardiovasc Med (Hagerstown) 2010;11(6):408-18.

Patients: AF

Intervention: radiofrequency ablation of AF

Control: anti-arrhythmic drugs

Outcomes: (1) freedom from AF and (2) safety

METHODEN

1. Is de vraagstelling adequaat geformuleerd?

[√] Ja

[ ] Nee

[ ] Te weinig informatie in het artikel om dit te beantwoorden

2. Is de zoekactie adequaat uitgevoerd?

[√] Ja

[ ] Nee

[ ] Te weinig informatie in het artikel om dit te beantwoorden

3. Is de selectieprocedure van artikelen adequaat uitgevoerd?

[√] Ja

[ ] Nee

[ ] Te weinig informatie in het artikel om dit te beantwoorden

4. Is de kwaliteitsbeoordeling adequaat uitgevoerd?

[√] Ja

[ ] Nee

[ ] Te weinig informatie in het artikel om dit te beantwoorden

5. Is adequaat beschreven hoe data-extractie heeft plaatsgevonden?

[ ] Ja

[√] Nee

[ ] Te weinig informatie in het artikel om dit te beantwoorden

6. Zijn de belangrijkste kenmerken van de oorspronkelijke onderzoeken beschreven?

[√] Ja

[ ] Nee

[ ] Te weinig informatie in het artikel om dit te beantwoorden

7. Is adequaat omgegaan met klinische en statistische heterogeniteit van de onderzoeken?

[ ] Ja

[√] Nee

[ ] Te weinig informatie in het artikel om dit te beantwoorden

8. Is statistische pooling op een correcte manier uitgevoerd?

[√] niet van toepassing (vanwege heterogeniteit)

[ ] Nee

[ ] Te weinig informatie in het artikel om dit te beantwoorden

ALGEMEEN OORDEEL

9. Zijn de resultaten van de systematische review valide en toepasbaar?

[ ] Voldoende valide en toepasbaar

[√] Twijfelachtig (efficacy)

[√] Onvoldoende valide en toepasbaar (safety)

4. LITERATURE SEARCH (QUALITY OF LIFE)

A quick search for quality-of-life data was performed in Medline and Embase. After removing duplicates, 59 references were identified.

Table 33 – Search strategy and results for Medline (OVID)

Date	**4 July 2012**		
Date covered	1996 to June Week 3 2012		
Search strategy	1	exp "Quality of Life"/	84784
	2	EQ-5D.mp.	1781
	3	SF-6D.mp.	257
	4	SF-36.mp.	9705
	5	Health Utility Index.mp.	81
	6	HUI.mp.	422
	7	5 or 6	474
	8	quality of well-being.mp.	227
	9	QWB.mp.	121
	10	8 or 9	244
	11	exp Atrial Fibrillation/	20868
	12	exp Catheter Ablation/	16491
	13	1 and 11 and 12	127
	14	2 or 3 or 4 or 7 or 10	11821
	15	13 and 14	**24 references**
Note	Including the instruments in the search terms with or without a hyphen does not make a difference. E.g searching ‘EQ 5D’ as keyword provides the same number of hits as searching ‘EQ-5D’.		

Table 34 – Search strategy and results for EMBASE

Date	**4 July 2012**		
Date covered	All		
Search Strategy	1	'quality of life'/exp	208367
	2	'eq-5d'	3288
	3	'sf-6d'	438
	4	'sf-36'/exp OR 'sf-36'	18040
	5	'health utility index'	132
	6	'quality of well-being'	300
	7	'qwb'	177
	8	#6 OR #7	327
	9	'heart atrium fibrillation'/exp	61249
	10	'catheter ablation'/exp	17848
	11	#1 AND #9 AND #10	359
	12	#2 OR #3 OR #4 OR #5 OR #8	21199
	13	#11 AND #12	**50 references**
Note	Including the instruments in the search terms with or without a hyphen does not make a difference. E.g searching 'EQ 5D' as keyword provides the same number of hits as searching 'EQ-5D'.		

5. NOMENCLATURE CODES

Below are the nomenclature codes used by RIZIV-INAMI. They can be consulted online[cc]

Code or pseudo-code	Creation date	Valid until	Label
212111-212122	01/11/2007	-	Défibrillation électrique du coeur en cas d'arrêt circulatoire et/ou électrostimulation du coeur par pacemaker externe, y compris le contrôle électrocardiographique, en dehors des interventions à thorax ouvert et des prestations 229110-229121, 475930-475941, 475952-475963, 475974-475985, 475996-476000
			Elektrische defibrillatie van het hart in geval van circulatiestilstand en/of elektrostimulatie van het hart door uitwendige hartprikkelaar, inclusief de elektrocardiografische controle, buiten de ingrepen met open thorax en de verstrekkingen 229110-229121, 475930-475941, 475952-475963, 475974-475985, 475996-476000
229600	01/09/1996	-	Opération sur le coeur ou les gros vaisseaux intrathoraciques qui comporte la plastie ou la mise en place d'une valve artificielle, avec circulation extracorporelle
			Operatie op het hart of op de grote intrathoracale bloedvaten die de plastiek of het plaatsen van een kunstklep omvat, met extracorporele circulatie
475016-475020	01/11/2007	-	** Défibrillation électrique du coeur, y compris le contrôle électrocardiographique pendant l'intervention
			** Electrische defibrillatie van het hart, inclusief electrocardiografische controle tijdens bewerking
476276-476280	01/01/1992	-	Examen électrophysiologique approfondi sans ablation en vue de l'éveil et de l'arrêt de tachycardies au moyen de trois cathéters ou plus, y compris la prise d'échantillons de sang, les contrôles radioscopiques et électrocardiographiques, l'administration de produits pharmaceutiques et opacifiants, avec protocole et tracés
			Uitgebreid elektrofysiologisch onderzoek zonder ablatie voor het opwekken en beëindigen van tachycardieën met behulp van drie of meer catheters,inclusief afname van bloedstalen, radioscopische en electrocardiografische controles, toediening van farmaca en contraststoffen, met protocol en tracés
476291-476302	01/01/1992	-	Examen électrophysiologique restreint sans ablation en vue de l'étude de la fonction du noeud sino-auriculaire et de la conduction atrioventriculaire au moyen d'un ou de plusieurs cathéters, y compris les enregistrements électrocardiographiques

[cc] http://inami.fgov.be/care/fr/nomenclature/ (French) and http://inami.fgov.be/care/nl/nomenclature/ (Dutch)

			Beperkt elektrofysiologisch onderzoek zonder ablatie tot studie van de sinusknoopfunctie en van de atrioventriculaire geleiding met behulp van een of meerdere catheters met inbegrip van de electrocardiografische opnamen
554573	01/11/2007	-	Temps de thromboplastine (temps de prothrombine), y compris l'éventuel calcul du fibrinogène (Maximum 1) (Règle de cumul 54) (Règle diagnostique 95)
			Tromboplastinetijd (prothrombinetijd), inclusief de eventuele berekening van fibrinogeen (Maximum 1) (Cumulregel 54) (Diagnoseregel 95)
554595	01/11/2007	-	Temps de thromboplastine partielle (Maximum 1) (Règle de cumul 107)
			Gedeeltelijke thromboplastinetijd (Maximum 1) (Cumulregel 107)
554654	01/11/2007	-	Temps de thromboplastine (thrombotest, normotest, K-test ou PPS-test) (Maximum 1)(Règle de cumul 54)
			Thromboplastinetijd (thrombotest, normotest, K-test of PPS-test) (Maximum 1)(Cumulregel 54)
589315-589326	01/01/1992	31/10/2007	Ablation percutanée par énergie électrique ou radiofréquence du système de conduction atrioventriculaire et/ou d'un foyer arythmique atrial et/ou ventriculaire, y compris les contrôles électrocardiographiques et radioscopiques et les cathéters utilisés
			Percutane ablatie met electrische of radiofrequente energie van het atrioventriculaire geleidingssysteem en/of van een atriale en/of ventriculaire arytmiefocus, inclusief electrocardiografische en radioscopische controles en de gebruikte catheters
589492-589503	01/11/2007	-	Examen électrophysiologique et ablation percutanée pour le traitement d'une tachycardie auriculo-ventriculaire par réentrée nodale, d'une tachycardie auriculo-ventriculaire par réentrée par faisceau accessoire de Kent ou d'une tachycardie auriculaire ectopique droite, par ablation spécifique du circuit ou du foyer d'arythmie
			Elektrofysiologisch onderzoek en percutane ablatie ter behandeling van een atrioventriculaire nodale re-entry tachycardie, een atrioventriculaire re-entry tachycardie (over Kent-bundel) of een rechter atriale ectopische tachycardie door gerichte ablatie van het aritmiecircuit of van de aritmiefocus
589514-589525	01/11/2007	-	Examen électrophysiologique et ablation percutanée pour le traitement d'un flutter auriculaire droit par ablation spécifique du circuit d'arythmie
			Elektrofysiologisch onderzoek en percutane ablatie ter behandeling van een rechter atriale flutter door gerichte ablatie van het aritmiecircuit
589536-589540	01/11/2007	-	Examen électrophysiologique et ablation percutanée pour le traitement d'arythmies ventriculaires par ablation spécifique du circuit ou du foyer d'arythmie

			Elektrofysiologisch onderzoek en percutane ablatie ter behandeling van ventriculaire aritmieën door gerichte ablatie van het aritmiecircuit of van de aritmiefocus
589551-589562	01/11/2007	-	Examen électrophysiologique et ablation percutanée pour le traitement d'un flutter auriculaire gauche (par ablation spécifique du circuit ou du foyer d'arythmie) ou d'une fibrillation auriculaire (par isolation ou ablation circonférentielle des veines pulmonaires)
			Elektrofysiologisch onderzoek en percutane ablatie ter behandeling van een linker atriale flutter (door gerichte ablatie van het aritmiecircuit of van aritmiefocus) of atriale fibrillatie (door isolatie of circumferentiële ablatie van de pulmonaalvenen)
589573-589584	01/11/2007	-	Examen électrophysiologique et ablation percutanée du faisceau de His
			Elektrofysiologisch onderzoek en percutane His bundel ablatie
697572-697583	01/11/2007	-	Ensemble des cathéters et accessoires utilisés lors de la prestation 589492-589503
			Geheel van katheters en toebehoren gebruikt naar aanleiding van de verstrekking 589492-589503
697594-697605	01/11/2007	-	Ensemble des cathéters et accessoires utilisés lors de la prestation 589514-589525
			Geheel van katheters en toebehoren gebruikt naar aanleiding van de verstrekking 589514-589525
697616-697620	01/11/2007	-	Ensemble des cathéters et accessoires utilisés lors de la prestation 589536-589540
			Geheel van katheters en toebehoren gebruikt naar aanleiding van de verstrekking 589536-589540
697631-697642	01/11/2007	-	Ensemble des cathéters et accessoires utilisés lors de la prestation 589551-589562
			Geheel van katheters en toebehoren gebruikt naar aanleiding van de verstrekking 589551-589562
697653-697664	01/11/2007	-	Cathéter supplémentaire utilisé pour un système de navigation en 3D remplaçant partiellement la fluoroscopie, lors des prestations 589536-589540 et 589551-589562
			Bijkomende katheter gebruikt voor een driedimensioneel navigatiesysteem dat fluoroscopie deels vervangt, tijdens verstrekkingen 589536-589540 en 589551-589562

6. COSTS DESCRIPTION

In the report, expenses per procedure are only presented for the interventions with a match for the 100% per diem hospital price. For the non-matched procedures, expenses for the other cost categories are show in Table 35.

Table 35 – Expenses per procedure for three of the four cost categories

Procedure (nomenclature codes: 589551-589562)

Variable	N	Mean	25th Pctl	Median	75th Pctl	Std Dev	5th Pctl	95th Pctl
Total costs	734	2 341.15	2 152.00	2 367.20	2 367.20	276.29	2 152.00	2 492.44
Total costs before	2	2 259.60	2 152.00	2 259.60	2 367.20	152.17	2 152.00	2 367.20
Total costs after	734	2 334.99	2 152.00	2 367.20	2 367.20	251.55	2 152.00	2 492.44

Material (nomenclature codes: 697631-697642, 697653-697664)

Variable	N	Mean	25th Pctl	Median	75th Pctl	Std Dev	5th Pctl	95th Pctl
Total costs	719	3 565.48	3 584.64	3 584.64	3 584.64	430.74	2 817.86	3 610.84
Total costs before	2	3 936.87	3 584.64	3 936.87	4 289.10	498.13	3 584.64	4 289.10
Total costs after	719	3 554.53	3 584.64	3 584.64	3 584.64	386.18	2 817.86	3 584.64

Others

Variable	N	Mean	25th Pctl	Median	75th Pctl	Std Dev	5th Pctl	95th Pctl
Total costs	734	2 245.49	1 416.81	1 869.37	2 314.32	2 559.84	513.30	4 161.15
Total costs before	341	979.92	746.74	840.61	967.61	1 239.87	592.23	1 390.17
Total costs after	734	1 790.24	1 078.31	1 468.31	1 963.72	2 290.18	328.52	3 260.95

(n=734, no daily hospitalization fee matching found)

7. LITERATURE SEARCH (COST-EFFECTIVENESS)

In February 2012, the websites of HTA institutes (Table 36) and following databases were searched: Medline, Embase and Centre for Reviews and Dissemination (CRD) databases (NHS Economic Evaluation Database (NHS EED) and Health Technology Assessments (HTA)). Table 37 up to Table 41 provide an overview of the applied search strategies. In June 2012, the databases were searched again using the same search strategies in order to identify recent published studies. The number of additional citations retrieved during this 4-month period is mentioned separately in the tables.

Table 36 – List of INAHTA member websites searched for HTA reports

Abbreviation	Institute	Country
AETMIS	Agence d´Évaluation des Technologies et des Modes d´Intervention en Santé	Canada
AETS	Agencia de Evaluación de Tecnologias Sanitarias	Spain
AETSA	Andalusian Agency for Health Technology Assessment	Spain
AGENAS	The Agency for Regional Healthcare	Italy
AHRQ	Agency for Healthcare Research and Quality	USA
AHTA	Adelaide Health Technology Assessment	Australia
AHTAPol	Agency for Health Technology Assessment in Poland	Poland
ASERNIP-S	Australian Safety and Efficacy Register of New Interventional Procedures -Surgical	Australia
AVALIA-T	Galician Agency for Health Technology Assessment	Spain
CADTH	Canadian Agency for Drugs and Technologies in Health	Canada
CAHIAQ	Catalan Agency for Health Information, Assessment and Quality (formerly CAHTA)	Spain
CDE	Center for Drug Evaluation	Taiwan
CEDIT	Comité d'Évaluation et de Diffusion des Innovations Technologiques	France
CENETEC	Centro Nacional de Excelencia Tecnológica en Salud Reforma	Mexico
CMERC	Department of Internal Medicine	South Africa
CNHTA	Committee for New Health Technology Assessment	Korea
CRD	Centre for Reviews and Dissemination	United Kingdom
CVZ	College voor Zorgverzekeringen	The Netherlands
DACEHTA	Danish Centre for Evaluation and Health Technology Assessment	Denmark
DAHTA @DIMDI	German Agency for HTA at the German Institute for Medical Documentation and Information	Germany
DECIT-CGATS	Secretaria de Ciëncia, Tecnologia e Insumos Estratégicos, Departamento de Ciência e Tecnologia	Brazil

DSI	Danish Institute for Health Services Research	Denmark
ETESA	Department of Quality and Patient Safety of the Ministry Health of Chile	Chile
FinOHTA	Finnish Office for Health Care Technology Assessment	Finland
G-ba	The German Health Care System and the Federal Joint Committee	Germany
GÖG	Gesundheit Österreich	Austria
GR	Gezondheidsraad	The Netherlands
HAS	Haute Autorité de Santé	France
HIQA	Health Information and Quality Authority	Ireland
HIS	Healthcare Improvement Scotland	United Kingdom
HITAP	Health Intervention and Technology Assessment Program	Thailand
HSAC	Health Services Assessment Collaboration	New Zealand
HTA-HSR/DHTA	HTA & Health Services Research	Denmark
IECS	Institute for Clinical Effectiveness and Health Policy	Argentina
IHE	Institute of Health Economics	Canada
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen	Germany
KCE	Belgian Federal Health Care Knowledge Centre	Belgium
LBI of HTA	Ludwig Boltzmann Institut für Health Technology Assessment	Austria
MaHTAS	Health Technology Assessment Section at Ministry of Health of Malaysia	Malaysia
MAS	Medical Advisory Secretariat	Canada
MTU-SFOPH	Medical Technology Unit - Swiss Federal Office of Public Health	Switzerland
NCCHTA	National Coordinating Centre for Health Technology Assessment	United Kingdom
NECA	National Evidence-based healthcare Collaboration Agency	Korea

NHSC	National Horizon Scanning Center	United Kingdom
NOKC	Norwegian Knowledge Centre for Health Services	Norway
OSTEBA	Basque Office for Health Technology Assessment	Spain
SBU	Swedish Council on Technology Assessment in Health Care	Sweden
UCEETS	The National Coordination Unit of Health Technology Assessment and Implementation	Argentina
UETS	Unidad de evaluacíon Technologias Santarias	Spain
UVT	HTA Unit in A. Gemelli University Hospital	Italy
VASPVT	State Health Care Accreditation Agency under the Ministry of Health of the Republic of Lithuania	Lithuania
VATAP	VA Technology Assessment Program	USA
ZonMw	The Medical and Health Research Council of The Netherlands	The Netherlands
AETMIS	Agence d´Évaluation des Technologies et des Modes d´Intervention en Santé	Canada
AETS	Agencia de Evaluación de Tecnologias Sanitarias	Spain
AETSA	Andalusian Agency for Health Technology Assessment	Spain
AGENAS	The Agency for Regional Healthcare	Italy
AHRQ	Agency for Healthcare Research and Quality	USA
AHTA	Adelaide Health Technology Assessment	Australia
AHTAPol	Agency for Health Technology Assessment in Poland	Poland
ASERNIP-S	Australian Safety and Efficacy Register of New Interventional Procedures -Surgical	Australia
AVALIA-T	Galician Agency for Health Technology Assessment	Spain
CADTH	Canadian Agency for Drugs and Technologies in Health	Canada

Table 37 – Search strategy and results for CRD: HTA

Date	**7 February 2012**	
Date covered	All	
Search Strategy	MeSH DESCRIPTOR atrial fibrillation EXPLODE ALL TREES IN HTA	**56 references**
Note	Potentially relevant references were not detected if the previous MeSH was combined with the following MeSH: “MeSH DESCRIPTOR catheter ablation EXPLODE ALL TREES IN HTA”.	
Update	The update was performed on 14 August 2012: 9 extra references were identified. One of them was potentially relevant. However, it was only accessible by paying a substantial fee. We decided not to purchase this report.	65 references

Table 38 – Search strategy and results for CRD: NHS EED

Date	**7 February 2012**	
Date covered	All	
Search Strategy	MeSH DESCRIPTOR atrial fibrillation EXPLODE ALL TREES IN NHSEED	**66 references**
Note	Potentially relevant references were not detected if the previous MeSH was combined with the following MeSH: “MeSH DESCRIPTOR catheter ablation EXPLODE ALL TREES IN NHSEED”	
Update	The update was performed on 14 August 2012: 16 extra references were identified. None of them was an economic evaluation of radiofrequency catheter ablation of atrial fibrillation.	82 references

Table 39 – Search strategy and results for Medline (OVID) (part I)

Date	**8 February 2012**		
Date covered	1996 to January Week 4 2012		
Search Strategy	1	economics/	5669
	2	exp "Costs and Cost Analysis"/	100942
	3	Value of Life/ec [Economics]	211
	4	Economics, Dental/	166
	5	exp Economics, Hospital/	9178
	6	Economics, Medical/	1618
	7	Economics, Nursing/	488
	8	Economics, Pharmaceutical/	1931
	9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	111472
	10	(econom$ or cost$ or pric$ or pharmacoeconomic$).tw.	276978
	11	(expenditure$ not energy).tw.	9936
	12	(value adj1 money).tw.	9
	13	budget$.tw.	9608
	14	10 or 11 or 12 or 13	286504
	15	9 or 14	330366
	16	letter.pt.	424617
	17	editorial.pt.	208148
	18	historical article.pt.	110775

	19	16 or 17 or 18	734264
	20	15 not 19	313245
	21	Animals/	2302985
	22	human/	6353103
	23	21 not (21 and 22)	1509379
	24	20 not 23	286544
	25	(metabolic adj cost).ti,ab,sh.	439
	26	((energy or oxygen) adj cost).ti,ab,sh.	1337
	27	24 not (25 or 26)	285191
	28	Atrial Fibrillation/	19922
	29	27 and 28	607
	30	Catheter Ablation/	15779
	31	Cryosurgery/	3054
	32	High-Intensity Focused Ultrasound Ablation/	210
	33	30 or 31 or 32	18488
	34	29 and 33	**83 references**
Update	The update was performed on 14 August 2012: 4 extra references were identified. None of them were considered relevant.		87 references

Table 40 – Search strategy and results for Medline (OVID) (part II)

Date	**8 February 2012**		
Date covered	In process & other non-indexed citations		
Search Strategy	1	cost$.mp.	19887
	2	economic$.mp.	8611
	3	budget$.mp.	1408
	4	expenditure$.mp.	1425
	5	1 or 2 or 3 or 4	28538
	6	atrial fibrillation {Including Related Terms}	2350
	7	5 and 6	63
	8	catheter ablation {Including Related Terms}	308
	9	cryosurgery {Including Related Terms}	175
	10	High-Intensity Focused Ultrasound Ablation {Including Related Terms}	1356
	11	8 or 9 or 10	1630
	12	7 and 11	**5 references**
Update	The update was performed on 14 August 2012: 7 references were identified of which 4 references were new. None of them were selected for further review.		7 references

Table 41 – Search strategy and results for EMBASE

Date	**8 February 2012**		
Date covered	All		
Search Strategy	1	'socioeconomics'/exp	145626
	2	'cost benefit analysis'/exp	58529
	3	'cost effectiveness analysis'/exp	78549
	4	'cost of illness'/exp	12028
	5	'cost control'/exp	40787
	6	'economic aspect'/exp	974090
	7	'financial management'/exp	254033
	8	'health care cost'/exp	171367
	9	'health care financing'/exp	10622
	10	'health economics'/exp	529838
	11	'hospital cost'/exp	22027
	12	'finance'/exp	8749
	13	'funding'/exp	12097
	14	fiscal	5789
	15	financial	292542
	16	#12 OR #13 OR #14 OR #15	301737
	17	'cost minimization analysis'/exp	2005
	18	estimate*:de,cl,ab,ti	562171
	19	cost*:de,cl,ab,ti	545421

	20	variable*:de,cl,ab,ti	532925
	21	unit:de,cl,ab,ti	343707
	22	'#19' NEAR/4 '#18' OR '#18' NEAR/4 '#19'	720208
	23	'#19' NEAR/4 '#20' OR '#20' NEAR/4 '#19'	704575
	24	'#19' NEAR/4 '#21' OR '#21' NEAR/4 '#19'	51790
	25	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #16 OR #17 OR #22 OR #23 OR #24	2398652
	26	'heart atrium fibrillation'/exp	57541
	27	#25 AND #26	5785
	28	'catheter ablation'/exp	17057
	29	'cryosurgery'/exp	9737
	30	'high intensity focused ultrasound'/exp	1672
	31	#28 OR #29 OR #30	28154
	32	#27 AND #31	**537 references**
Update	The update was performed on 14 August 2012:44 extra references were identified. None of them were selected for further review.		581 references

After removal of all duplicates, a total of 697 papers were identified (Table 42).

Table 42 – Results of search strategy

Database	References identified	
	February 2012	Update August 2012 Total
CRD HTA	56	65
CRD NHS EED	66	82
Medline	83	87
Medline In-Process & Other	5	7
Embase	537	581
Total (incl. duplicates)	747	822*
Duplicates	50	/
Total (excl. duplicates)	697	/

* The new identified references were checked for relevance.

8. DATA EXTRACTION SHEET

Table 43 – Data extraction sheet

1	Reference (including all authors)
2	Conflict of interest and/or study funding
3	Country
4	Study question
5	Type of analysis (analytic technique) - e.g. cost-effectiveness analysis, cost-utility analysis, …
6	Design - e.g. Markov model, decision tree, …
7	Population
8	Intervention
9	Comparator
10	Time horizon
11	Discount rate - For costs and/or effects
12	Perspective
13	Costs - Cost items included - Measurement of resource use - Valuation of resource use - Data sources - Currency and cost year

	- Other aspects…
14	Outcomes - Endpoints taken into account and/or health states - Valuation of health states - Treatment effect and Extrapolation - Utility assessment (Quality of Life) - Data sources for outcomes - Other aspects…
15	Uncertainty - Scenario analysis - Sensitivity analysis
16	Assumptions
17	Results - Cost-effectiveness and/or cost-utility (base case) - Scenario analysis - Sensitivity analysis - Other aspects…
18	Conclusions - The conclusion of the authors (which can be discussed in the actual critical appraisal)
19	Remarks - e.g. limitations of the study

REFERENCES

1. Wazni O, Wilkoff B, Saliba W. Catheter ablation for atrial fibrillation. N Engl J Med. 2011;365(24):2296-304.
2. Camm AJ, Kirchhof P, Lip GYH, Schotten U, Savelieva I, Ernst S, et al. Guidelines for the management of atrial fibrillation. Europace. 2010;12(10):1360-420.
3. Wilber DJ. Pursuing sinus rhythm in patients with persistent atrial fibrillation: when is it too late? J Am Coll Cardiol. 2009;54(9):796-8.
4. Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation-executive summary: A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients with Atrial Fibrillation). European Heart Journal. 2006;27(16):1979-2030.
5. Cain ME. Atrial fibrillation--rhythm or rate control. N Engl J Med. 2002;347(23):1822-3.
6. Kirchhof P, Eckardt L. Atrial fibrillation: Ablation of atrial fibrillation: for whom and how? Heart. 2010;96(16):1325-30.
7. Wann LS, Curtis AB, January CT, Ellenbogen KA, Lowe JE, Estes NA, 3rd, et al. 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (Updating the 2006 Guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2011;57(2):223-42.
8. Lafuente-Lafuente C, Mouly S, Longas-Tejero MA, Bergmann JF. Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation. Cochrane Database Syst Rev. 2007(4):CD005049.
9. Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med. 2002;347(23):1825-33.

10. Van Gelder IC, Hagens VE, Bosker HA, Kingma JH, Kamp O, Kingma T, et al. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. N Engl J Med. 2002;347(23):1834-40.
11. de Denus S, Sanoski CA, Carlsson J, Opolski G, Spinler SA. Rate vs rhythm control in patients with atrial fibrillation: a meta-analysis. Arch Intern Med. 2005;165(3):258-62.
12. Testa L, Biondi-Zoccai GG, Dello Russo A, Bellocci F, Andreotti F, Crea F. Rate-control vs. rhythm-control in patients with atrial fibrillation: a meta-analysis. Eur Heart J. 2005;26(19):2000-6.
13. Thrall G, Lane D, Carroll D, Lip GY. Quality of life in patients with atrial fibrillation: a systematic review. Am J Med. 2006;119(5):448 e1-19.
14. Carlsson J, Miketic S, Windeler J, Cuneo A, Haun S, Micus S, et al. Randomized trial of rate-control versus rhythm-control in persistent atrial fibrillation: the Strategies of Treatment of Atrial Fibrillation (STAF) study. J Am Coll Cardiol. 2003;41(10):1690-6.
15. Gronefeld GC, Lilienthal J, Kuck KH, Hohnloser SH. Impact of rate versus rhythm control on quality of life in patients with persistent atrial fibrillation. Results from a prospective randomized study. Eur Heart J. 2003;24(15):1430-6.
16. Hagens VE, Ranchor AV, Van Sonderen E, Bosker HA, Kamp O, Tijssen JG, et al. Effect of rate or rhythm control on quality of life in persistent atrial fibrillation. Results from the Rate Control Versus Electrical Cardioversion (RACE) Study. J Am Coll Cardiol. 2004;43(2):241-7.
17. Ogawa M, Tan AY, Song J, Kobayashi K, Fishbein MC, Lin SF, et al. Cryoablation of stellate ganglia and atrial arrhythmia in ambulatory dogs with pacing-induced heart failure. Heart Rhythm. 2009;6(12):1772-9.
18. Kobayashi Y, Fujiki A, Aonuma K. Learning from clinical randomized trials individualized therapy is important in the management of atrial fibrillation. Circulation Journal. 2009;73(2):229-30.
19. Calkins H, Kuck KH, Cappato R, Brugada J, Camm AJ, Chen SA, et al. 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: Recommendations for Patient Selection, Procedural Techniques, Patient Management and Follow-up, Definitions, Endpoints, and Research Trial Design: A report of the Heart Rhythm Society (HRS) Task Force on Catheter and Surgical Ablation of Atrial Fibrillation. Developed in partnership with the European Heart Rhythm Association (EHRA), a registered branch of the European Society of Cardiology (ESC) and the European Cardiac Arrhythmia Society (ECAS); and in collaboration with the American College of Cardiology (ACC), American Heart Association (AHA), the Asia Pacific Heart Rhythm Society (APHRS), and the Society of Thoracic Surgeons (STS). Endorsed by the governing bodies of the American College of Cardiology Foundation, the American Heart Association, the European Cardiac Arrhythmia Society, the European Heart Rhythm Association, the Society of Thoracic Surgeons, the Asia Pacific Heart Rhythm Society, and the Heart Rhythm Society. Europace. 2012;14(4):528-606.
20. Ollendorf D, Silverstein M, Bobo T, Pearson S. Atrial fibrillation management options. Report. Boston: Institute for Clinical and Economic Review (ICER); 2010. Available from: http://www.icer-review.org/index.php/a-fib-appraisal-1209.html
21. Haissaguerre M, Jais P, Shah DC, Takahashi A, Hocini M, Quiniou G, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med. 1998;339(10):659-66.
22. Shah D. A critical appraisal of cardiac ablation technology for catheter-based treatment of atrial fibrillation. Expert Rev Med Devices. 2011;8(1):49-55.
23. Siklody CH. Fully equipped to defeat the pulmonary vein potentials: on the quest for sinus rhythm. Europace. 2011;13(9):1213-4.
24. Hussein AA, Saliba WI, Martin DO, Bhargava M, Sherman M, Magnelli-Reyes C, et al. Natural history and long-term outcomes of

ablated atrial fibrillation. Circ Arrhythm Electrophysiol. 2011;4(3):271-8.

25. Deneke T, Mugge A, Balta O, Horlitz M, Grewe PH, Shin DI. Treatment of persistent atrial fibrillation using phased radiofrequency ablation technology. Expert Review of Cardiovascular Therapy. 2011;9(8):1041-9.

26. Reddy VY, Neuzil P, d'Avila A, Laragy M, Malchano ZJ, Kralovec S, et al. Balloon catheter ablation to treat paroxysmal atrial fibrillation: what is the level of pulmonary venous isolation? Heart Rhythm. 2008;5(3):353-60.

27. Haeusler KG, Koch L, Ueberreiter J, Endres M, Schultheiss HP, Heuschmann PU, et al. Stroke risk associated with balloon based catheter ablation for atrial fibrillation: Rationale and design of the MACPAF Study. BMC Neurol. 2010;10:63.

28. Assasi N, Blackhouse G, Xie F, Gaebel K, Robertson D, Hopkins R, et al. Ablation procedures for rhythm control in patients with atrial fibrillation: clinical and cost-effectiveness analyses. Report. Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH); 2010. Available from: http://www.cadth.ca/media/pdf/H0491_Ablation_Procedures_with_Atrial_Fibrillation_tr_e.pdf

29. Blomström Lundqvist C, Liliemark J, Eckerlund I. Catheter ablation for atrial fibrillation (update). Report. Stockholm: The Swedish Council on Health Technology Assessment (SBU); 2010. Available from: www.sbu.se/201006e

30. Bonanno C, Paccanaro M, La Vecchia L, Ometto R, Fontanelli A. Efficacy and safety of catheter ablation versus antiarrhythmic drugs for atrial fibrillation: A meta-analysis of randomized trials. Journal of Cardiovascular Medicine. 2010;11(6):408-18.

31. Parkash R, Tang AS, Sapp JL, Wells G. Approach to the catheter ablation technique of paroxysmal and persistent atrial fibrillation: a meta-analysis of the randomized controlled trials. Journal of Cardiovascular Electrophysiology. 2011;22(7):729-38.

32. Forleo GB, Mantica M, De Luca L, Leo R, Santini L, Panigada S, et al. Catheter ablation of atrial fibrillation in patients with diabetes mellitus type 2: results from a randomized study comparing pulmonary vein isolation versus antiarrhythmic drug therapy. Journal of Cardiovascular Electrophysiology. 2009;20(1):22-8.

33. Jais P, Cauchemez B, Macle L, Daoud E, Khairy P, Subbiah R, et al. Catheter ablation versus antiarrhythmic drugs for atrial fibrillation: the A4 study. Circulation. 2008;118(24):2498-505.

34. Krittayaphong R, Raungrattanaamporn O, Bhuripanyo K, Sriratanasathavorn C, Pooranawattanakul S, Punlee K, et al. A randomized clinical trial of the efficacy of radiofrequency catheter ablation and amiodarone in the treatment of symptomatic atrial fibrillation. J Med Assoc Thai. 2003;86 Suppl 1:S8-16.

35. MacDonald MR, Connelly DT, Hawkins NM, Steedman T, Payne J, Shaw M, et al. Radiofrequency ablation for persistent atrial fibrillation in patients with advanced heart failure and severe left ventricular systolic dysfunction: a randomised controlled trial. Heart. 2011;97(9):740-7.

36. Oral H, Pappone C, Chugh A, Good E, Bogun F, Pelosi Jr F, et al. Circumferential pulmonary-vein ablation for chronic atrial fibrillation. New England Journal of Medicine. 2006;354(9):934-41.

37. Pappone C, Augello G, Sala S, Gugliotta F, Vicedomini G, Gulletta S, et al. A randomized trial of circumferential pulmonary vein ablation versus antiarrhythmic drug therapy in paroxysmal atrial fibrillation: the APAF Study. J Am Coll Cardiol. 2006;48(11):2340-7.

38. Stabile G, Bertaglia E, Senatore G, De Simone A, Zoppo F, Donnici G, et al. Catheter ablation treatment in patients with drug-refractory atrial fibrillation: a prospective, multi-centre, randomized, controlled study (Catheter Ablation For The Cure Of Atrial Fibrillation Study). Eur Heart J. 2006;27(2):216-21.

39. Wazni OM, Marrouche NF, Martin DO, Verma A, Bhargava M, Saliba W, et al. Radiofrequency ablation vs antiarrhythmic drugs

as first-line treatment of symptomatic atrial fibrillation: a randomized trial. JAMA. 2005;293(21):2634-40.

40. Wilber DJ, Pappone C, Neuzil P, De Paola A, Marchlinski F, Natale A, et al. Comparison of antiarrhythmic drug therapy and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: a randomized controlled trial. JAMA. 2010;303(4):333-40.
41. Pappone C, Vicedomini G, Augello G, Manguso F, Saviano M, Baldi M, et al. Radiofrequency catheter ablation and antiarrhythmic drug therapy: a prospective, randomized, 4-year follow-up trial: the APAF study. Circ Arrhythm Electrophysiol. 2011;4(6):808-14.
42. Chen HS, Wen JM, Wu SN, Liu JP. Catheter ablation for paroxysmal and persistent atrial fibrillation. Cochrane Database Syst Rev. 2012;4:CD007101.
43. Viles-Gonzalez JF, Fuster V, Halperin J, Calkins H, Reddy VY. Rhythm control for management of patients with atrial fibrillation: balancing the use of antiarrhythmic drugs and catheter ablation. Clinical Cardiology. 2011;34(1):23-9.
44. Cappato R, Calkins H, Chen SA, Davies W, Iesaka Y, Kalman J, et al. Updated worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. Circ Arrhythm Electrophysiol. 2010;3(1):32-8.
45. Weerasooriya R, Khairy P, Litalien J, Macle L, Hocini M, Sacher F, et al. Catheter ablation for atrial fibrillation: are results maintained at 5 years of follow-up? J Am Coll Cardiol. 2011;57(2):160-6.
46. Ouyang F, Tilz R, Chun J, Schmidt B, Wissner E, Zerm T, et al. Long-term results of catheter ablation in paroxysmal atrial fibrillation: lessons from a 5-year follow-up. Circulation. 2010;122(23):2368-77.
47. Katritsis D, Wood MA, Giazitzoglou E, Shepard RK, Kourlaba G, Ellenbogen KA. Long-term follow-up after radiofrequency catheter ablation for atrial fibrillation. Europace. 2008;10(4):419-24.
48. Medi C, Sparks PB, Morton JB, Kistler PM, Halloran K, Rosso R, et al. Pulmonary vein antral isolation for paroxysmal atrial fibrillation: results from long-term follow-up. Journal of Cardiovascular Electrophysiology. 2011;22(2):137-41.
49. Hunter RJ, Berriman TJ, Diab I, Baker V, Finlay M, Richmond L, et al. Long-term efficacy of catheter ablation for atrial fibrillation: impact of additional targeting of fractionated electrograms. Heart. 2010;96(17):1372-8.
50. Gaita F, Caponi D, Scaglione M, Montefusco A, Corleto A, Di Monte F, et al. Long-term clinical results of 2 different ablation strategies in patients with paroxysmal and persistent atrial fibrillation. Circ Arrhythm Electrophysiol. 2008;1(4):269-75.
51. Bhargava M, Di Biase L, Mohanty P, Prasad S, Martin DO, Williams-Andrews M, et al. Impact of type of atrial fibrillation and repeat catheter ablation on long-term freedom from atrial fibrillation: results from a multicenter study. Heart Rhythm. 2009;6(10):1403-12.
52. Sorgente A, Tung P, Wylie J, Josephson ME. Six year follow-up after catheter ablation of atrial fibrillation: a palliation more than a true cure. Am J Cardiol. 2012;109(8):1179-86.
53. Nakagawa H, Antz M, Wong T, Schmidt B, Ernst S, Ouyang F, et al. Initial experience using a forward directed, high-intensity focused ultrasound balloon catheter for pulmonary vein antrum isolation in patients with atrial fibrillation. Journal of Cardiovascular Electrophysiology. 2007;18(2):136-44.
54. Neven K, Schmidt B, Metzner A, Otomo K, Nuyens D, De Potter T, et al. Fatal end of a safety algorithm for pulmonary vein isolation with use of high-intensity focused ultrasound. Circ Arrhythm Electrophysiol. 2010;3(3):260-5.
55. Reynolds MR, Walczak J, White SA, Cohen DJ, Wilber DJ. Improvements in symptoms and quality of life in patients with paroxysmal atrial fibrillation treated with radiofrequency catheter ablation versus antiarrhythmic drugs. Circ Cardiovasc Qual Outcomes. 2010;3(6):615-23.
56. Pappone C, Rosanio S, Augello G, Gallus G, Vicedomini G, Mazzone P, et al. Mortality, morbidity, and quality of life after circumferential pulmonary vein ablation for atrial fibrillation:

outcomes from a controlled nonrandomized long-term study. J Am Coll Cardiol. 2003;42(2):185-97.

57. Fichtner S, Deisenhofer I, Kindsmuller S, Dzijan-Horn M, Tzeis S, Reents T, et al. Prospective assessment of short- and long-term quality of life after ablation for atrial fibrillation. Journal of Cardiovascular Electrophysiology. 2012;23(2):121-7.

58. Arbelo E, Brugada J, Hindricks G, Maggioni A, Tavazzi L, Vardas P, et al. ESC-EURObservational Research Programme: the Atrial Fibrillation Ablation Pilot Study, conducted by the European Heart Rhythm Association. Europace. 2012.

59. Sacher F, Monahan KH, Thomas SP, Davidson N, Adragao P, Sanders P, et al. Phrenic nerve injury after atrial fibrillation catheter ablation: characterization and outcome in a multicenter study. J Am Coll Cardiol. 2006;47(12):2498-503.

60. Calkins H, Reynolds MR, Spector P, Sondhi M, Xu Y, Martin A, et al. Treatment of atrial fibrillation with antiarrhythmic drugs or radiofrequency ablation: two systematic literature reviews and meta-analyses. Circ Arrhythm Electrophysiol. 2009;2(4):349-61.

61. Cappato R, Calkins H, Chen SA, Davies W, Iesaka Y, Kalman J, et al. Worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. Circulation. 2005;111(9):1100-5.

62. Shah RU, Freeman JV, Shilane D, Wang PJ, Go AS, Hlatky MA. Procedural complications, rehospitalizations, and repeat procedures after catheter ablation for atrial fibrillation. J Am Coll Cardiol. 2012;59(2):143-9.

63. Bohnen M, Stevenson WG, Tedrow UB, Michaud GF, John RM, Epstein LM, et al. Incidence and predictors of major complications from contemporary catheter ablation to treat cardiac arrhythmias. Heart Rhythm. 2011;8(11):1661-6.

64. Baman TS, Jongnarangsin K, Chugh A, Suwanagool A, Guiot A, Madenci A, et al. Prevalence and predictors of complications of radiofrequency catheter ablation for atrial fibrillation. Journal of Cardiovascular Electrophysiology. 2011;22(6):626-31.

65. Hoyt H, Bhonsale A, Chilukuri K, Alhumaid F, Needleman M, Edwards D, et al. Complications arising from catheter ablation of atrial fibrillation: temporal trends and predictors. Heart Rhythm. 2011;8(12):1869-74.

66. Schrickel JW, Lickfett L, Lewalter T, Mittman-Braun E, Selbach S, Strach K, et al. Incidence and predictors of silent cerebral embolism during pulmonary vein catheter ablation for atrial fibrillation. Europace. 2010;12(1):52-7.

67. Gaita F, Leclercq JF, Schumacher B, Scaglione M, Toso E, Halimi F, et al. Incidence of silent cerebral thromboembolic lesions after atrial fibrillation ablation may change according to technology used: comparison of irrigated radiofrequency, multipolar nonirrigated catheter and cryoballoon. Journal of Cardiovascular Electrophysiology. 2011;22(9):961-8.

68. Herrera Siklody C, Deneke T, Hocini M, Lehrmann H, Shin DI, Miyazaki S, et al. Incidence of asymptomatic intracranial embolic events after pulmonary vein isolation: comparison of different atrial fibrillation ablation technologies in a multicenter study. J Am Coll Cardiol. 2011;58(7):681-8.

69. Koch L, Haeusler KG, Herm J, Safak E, Fischer R, Malzahn U, et al. Mesh ablator vs. cryoballoon pulmonary vein ablation of symptomatic paroxysmal atrial fibrillation: results of the MACPAF study. Europace. 2012.

70. Rogers DP, England F, Lozhkin K, Lowe MD, Lambiase PD, Chow AW. Improving safety in the electrophysiology laboratory using a simple radiation dose reduction strategy: a study of 1007 radiofrequency ablation procedures. Heart. 2011;97(5):366-70.

71. Lickfett L, Mahesh M, Vasamreddy C, Bradley D, Jayam V, Eldadah Z, et al. Radiation exposure during catheter ablation of atrial fibrillation. Circulation. 2004;110(19):3003-10.

72. Macle L, Weerasooriya R, Jais P, Scavee C, Raybaud F, Choi KJ, et al. Radiation exposure during radiofrequency catheter ablation for atrial fibrillation. Pacing & Clinical Electrophysiology. 2003;26(1 Pt 2):288-91.

73. Knight BP, Oral H, Chugh A, Scharf C, Lai SW, Pelosi F, Jr., et al. Effects of operator experience on the outcome and duration of pulmonary vein isolation procedures for atrial fibrillation. Am J Cardiol. 2003;91(6):673-7.

74. Picano E. Sustainability of medical imaging. BMJ. 2004;328(7439):578-80.

75. Fitton A, Sorkin EM. Sotalol. An updated review of its pharmacological properties and therapeutic use in cardiac arrhythmias. Drugs. 1993;46(4):678-719.

76. Wann LS, Curtis AB, January CT, Ellenbogen KA, Lowe JE, Estes NA, 3rd, et al. 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (updating the 2006 guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2011;123(1):104-23.

77. Chan PS, Vijan S, Morady F, Oral H. Cost-effectiveness of radiofrequency catheter ablation for atrial fibrillation. Journal of the American College of Cardiology. 2006;47(12):2513-20.

78. Eckard N, Davidson T, Walfridsson H, Levin LA. Cost-effectiveness of catheter ablation treatment for patients with symptomatic atrial fibrillation. Journal of Atrial Fibrillation. 2009;1(8):461-70.

79. McKenna C, Palmer S, Rodgers M, Chambers D, Hawkins N, Golder S, et al. Cost-effectiveness of radiofrequency catheter ablation for the treatment of atrial fibrillation in the United Kingdom. Heart. 2009;95(7):542-9.

80. Reynolds MR, Zimetbaum P, Josephson ME, Ellis E, Danilov T, Cohen DJ. Cost-effectiveness of radiofrequency catheter ablation compared with antiarrhythmic drug therapy for paroxysmal atrial fibrillation. Circulation: Arrhythmia and Electrophysiology. 2009;2(4):362-9.

81. Rodgers M, McKenna C, Palmer S, Chambers D, Van Hout S, Golder S, et al. Curative catheter ablation in atrial fibrillation and typical atrial flutter: systematic review and economic evaluation. HTA Technology Assessment Report. NIHR Health Technology Assessment programme; 2008. 12(34) Available from: http://www.hta.ac.uk/1539

82. Marshall DA, Levy AR, Vidaillet H, Fenwick E, Slee A, Blackhouse G, et al. Cost-effectiveness of rhythm versus rate control in atrial fibrillation. Annals of Internal Medicine. 2004;141(9):653-61.

83. Reynolds MR, Lavelle T, Essebag V, Cohen DJ, Zimetbaum P. Influence of age, sex, and atrial fibrillation recurrence on quality of life outcomes in a population of patients with new-onset atrial fibrillation: the Fibrillation Registry Assessing Costs, Therapies, Adverse events and Lifestyle (FRACTAL) study. Am Heart J. 2006;152(6):1097-103.

84. Vinck I, Hulstaert F, Van Brabandt H, Neyt M, Stordeur S. Market introduction of innovative high risk medical devices: towards a recast of the directive concerning medical devices. Eur J Health Law. 2011;18(5):477-89.

85. Hulstaert F, Neyt M, Vinck I, Stordeur S, Huić M, Sauerland S, et al. The pre-market clinical evaluation of innovative high-risk medical devices. Brussels: 2011. KCE Report 158C. D/2011/10.273/31.

86. Haines DE. Atrial fibrillation ablation in the real world. J Am Coll Cardiol. 2012;59(2):150-2.

87. Jeevanantham V, Ntim W, Navaneethan SD, Shah S, Johnson AC, Hall B, et al. Meta-analysis of the effect of radiofrequency catheter ablation on left atrial size, volumes and function in patients with atrial fibrillation. Am J Cardiol. 2010;105(9):1317-26.

88. Wilton SB, Fundytus A, Ghali WA, Veenhuyzen GD, Quinn FR, Mitchell LB, et al. Meta-analysis of the effectiveness and safety of catheter ablation of atrial fibrillation in patients with versus without left ventricular systolic dysfunction. Am J Cardiol. 2010;106(9):1284-91.

89. Brooks AG, Stiles MK, Laborderie J, Lau DH, Kuklik P, Shipp NJ, et al. Outcomes of long-standing persistent atrial fibrillation ablation: a systematic review. Heart Rhythm. 2010;7(6):835-46.

90. Nault I, Miyazaki S, Forclaz A, Wright M, Jadidi A, Jais P, et al. Drugs vs. ablation for the treatment of atrial fibrillation: the

evidence supporting catheter ablation. European Heart Journal. 2010;31(9):1046-54.

91. Andrade JG, Khairy P, Guerra PG, Deyell MW, Rivard L, Macle L, et al. Efficacy and safety of cryoballoon ablation for atrial fibrillation: a systematic review of published studies. Heart Rhythm. 2011;8(9):1444-51.

92. Dagres N, Varounis C, Gaspar T, Piorkowski C, Eitel C, Iliodromitis EK, et al. Catheter ablation for atrial fibrillation in patients with left ventricular systolic dysfunction. A systematic review and meta-analysis. J Card Fail. 2011;17(11):964-70.