Cryo- and radiofrequency cardiac ablation catheters for the treatment of atrial fibrillation

Report Part 1:

Rapid Review of high-level clinical evidence

29 October 2018

Disclaimer:

This Rapid Review reports on a targeted assessment of a purposive sample of high-level clinical evidence chosen to address specific questions posed by the Commonwealth Department of Health. The clinical evidence is drawn from existing systematic reviews, meta-analyses and economic evaluations. As it has been prepared using pragmatic methodology, the current review cannot be viewed as a comprehensive review or critical appraisal of all literature of potential relevance to the topic area.

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ABBREVIATIONS

AAD	antiarrhythmic drug
AF	atrial fibrillation
AHRQ	Agency for Healthcare Research and Quality
AMSTAR	Assessing the Methodological Quality of Systematic Reviews
AT	atrial tachyarrhythmia
CA	cardiac/catheter ablation
CB	cryoballoon
CBA	cryoballoon ablation
HF	heart failure
HRQoL	health-related quality of life
HTA	health technology assessment
INAHTA	International Network of Agencies for Health Technology Assessment
LV	left ventricular
LVEF	left ventricular ejection fraction
MBS	Medicare Benefits Schedule
NICE	National Institute for Health and Care Excellence
PICO	population, intervention, comparator, outcome
PLAC	Prostheses List Advisory Committee
PNP	phrenic nerve palsy
PVI	pulmonary vein isolation
QoL	quality of life
RCT	randomised controlled trial
RF	radiofrequency
RFCA	radiofrequency catheter ablation
SR	systematic review
TIA	transient ischaemic attack
UK	United Kingdom
USA	United States of America
WSHCA	Washington State Health Care Authority

Key findings

Is there sufficient clinical evidence to demonstrate the superiority of cardiac ablation over treatment with anti-arrhythmic medication? If not, what are the gaps?

The key findings relating to the assessment of **cardiac ablation compared with medical therapy** are summarised in Table 1, taken from the best available evidence. For further details, see Table 14 in Section 2.5.1. Please note that as this is a rapid review, the strength of evidence is based on our informal judgement of the evidence rather than a formal assessment (e.g. using GRADE methods).

Table 1 Summary of key findings and strength of evidence: cardiac ablation (CA) vs. medical therapy (MT)

Outcome	Population	No. of studies	Strength of evidence[a]	Statistical significance
All-cause mortality	Any AF	10 RCT (NR)	**Low**	**Favours CA**
	Paroxysmal AF	2 RCT (N=408)	**Low**	**No difference**
	Persistent AF	3 RCT (N=559)	**Low**	**No difference**
Stroke	Any AF	7 RCT, 10 OBS (NR)	**Low**	**Favours CA**
	Paroxysmal AF	2 RCT (N=194)	**Insufficient**	**No difference**
	Persistent AF	1 RCT (N=146)	**Insufficient**	**No difference**
Freedom from arrythmia recurrence	Any AF	11 RCT (N=1481)	**Moderate**	**Favours CA**
	Paroxysmal AF	3 RCT (N=619)	**Moderate**	**Favours CA**
	Persistent AF	3 RCT (N=559)	**Moderate**	**Favours CA**
Repeat ablation	Any AF	8 RCT (N=430)	**Insufficient**	Definitive conclusions not possible.
	Paroxysmal AF	4 RCT (N=337)	**Insufficient**	Definitive conclusions not possible.
	Persistent AF	5 RCT (N=246)	**Insufficient**	Definitive conclusions not possible.
Cardiac hospitalisation/ re-admission	Any AF	4 RCT (N=629)	**Low**	**Favours CA**
	Paroxysmal AF	2 RCT (N=361)	**Insufficient**	**Favours CA**
	Persistent AF	2 RCT (N=349)	**Insufficient**	**Favours CA**
Pulmonary vein stenosis	Any AF	6 RCT (N=1109)	**Low**	**No difference**
	Paroxysmal AF	5 RCT (N=544)	**Insufficient**	Definitive conclusions not possible.
	Persistent AF	2 RCT, 1 OBS (N=295)	**Insufficient**	Definitive conclusions not possible.
Pericardial effusion	Any AF	5 RCT, 1 OBS (N=930)	**Insufficient**	Definitive conclusions not possible.
	Paroxysmal AF	3 RCT (N=519)	**Insufficient**	Definitive conclusions not possible.
	Persistent AF	1 RCT, 1 OBS (N=274)	**Insufficient**	Definitive conclusions not possible.
Cardiac tamponade	Any AF	8 RCT, 2 OBS (N=1056)	**Insufficient**	Definitive conclusions not possible.
	Paroxysmal AF	4 RCT, 1 OBS (N=597)	**Insufficient**	Definitive conclusions not possible.
	Persistent AF	3 RCT, 1 OBS (N=231)	**Insufficient**	Definitive conclusions not possible.
Major bleeding	Any AF	7 RCT (N=811)	**Low**	**Favours MT**
	Paroxysmal AF	1 RCT (N=67)	**Insufficient**	Definitive conclusions not possible.
	Persistent AF	1 OBS (N=412)	**Insufficient**	Definitive conclusions not possible.

Abbreviations: AF, atrial fibrillation; CA, cardiac ablation; MT, medical therapy; OBS, observational study; RCT, randomised controlled trial.
a Strength of evidence has been judged informally by the authors of the Rapid Review.

In summary, there is moderate evidence that radiofrequency (RF) ablation is superior to medical therapy for enhancing patient freedom from recurrence of atrial arrhythmias in both the short and long term regardless of type of atrial fibrillation (AF), but re-ablation is common. Cardiac ablation has a beneficial impact on all-cause mortality in patients with AF; however, this benefit appears to be largely driven by the

inclusion of patients with heart failure. Evidence from observational studies suggests that cardiac ablation may decrease the risk of stroke compared with medical therapy, but this benefit is not seen in randomised controlled trials (RCTs), which are likely underpowered for this outcome. Evidence comparing cryoballoon ablation with medical therapy is insufficient to draw firm conclusions regarding efficacy or safety.

The key findings relating to the assessment of **RF ablation compared with cryoablation** are summarised in Table 2, taken from the best available evidence. For further details see Table 15 in Section 2.5.2.

Table 2 Summary of key findings and strength of evidence: RF ablation vs. cryoablation

Outcome	Population	No. of studies	Strength of evidence[a]	Conclusion
All-cause mortality	Any AF	0 studies	-	-
	Paroxysmal AF	1 OBS (N=396)	Insufficient	**No difference**
	Persistent AF	0 studies	-	-
Stroke	Any AF	NR (N= 4058)	Low	**No difference**
	Paroxysmal AF	0 studies	-	-
	Persistent AF	0 studies	-	-
Arrythmia recurrence	Any AF	5 RCT (N=1306)	Moderate	**No difference**
	Paroxysmal AF	NR (N=6055)	Moderate	**No difference**
	Persistent AF	0 studies	-	-
Repeat ablation	Any AF	5 RCT (N=1306)	Moderate	**No difference**
	Paroxysmal AF	1 RCT (N=50)	Insufficient	**Favours RFA**
	Persistent AF	0 studies	-	-
Cardiac hospitalisation/ re-admission	Any AF	0 studies	-	-
	Paroxysmal AF	0 studies	-	-
	Persistent AF	0 studies	-	-
Pericardial effusion	Any AF	3 RCT, 10 OBS (N=7117)	Low	**Favours CBA**
	Paroxysmal AF	11 studies (N=5821)	Low	**Favours CBA**
	Persistent AF	0 studies	-	-
Pericardial tamponade	Any AF	2 RCT, 6 OBS (N=5120)	Low	**Favours CBA**
	Paroxysmal AF	7 studies (N=5020)	Low	**Favours CBA**
	Persistent AF	0 studies	-	-
Pulmonary vein stenosis	Any AF	3 OBS (N=4295)	Low	**No difference**
	Paroxysmal AF	2 OBS (N=4171)	Low	**No difference**
	Persistent AF	0 studies	-	-
Major vascular complications	Any AF	7 studies (NR)	Low	**No difference**
	Paroxysmal AF	0 studies	-	-
	Persistent AF	0 studies	-	-

Abbreviations: AF, atrial fibrillation; CBA, cryoballoon ablation; OBS, observational study; RCT, randomised controlled trial; RFA, radiofrequency ablation.
a Strength of evidence has been judged informally by the authors of the Rapid Review.

In summary, there was no significant difference between groups with regards to freedom from atrial tachyarrhythmia (AT) in a follow up of at least 12 months; post-procedural phrenic nerve palsy was significantly more common in the cryoballoon group, although the overwhelming majority resolved within 1 year (data not shown in this report); the incidence of pericardial effusion and cardiac tamponade was higher with RF ablations; and non-AF AT during follow-up were less frequent in the cryoballoon group.

Are the clinical outcomes different in different age groups?

No systematic reviews were identified that focus on the effect of age on clinical outcomes for cardiac ablation. *AHRQ 2015* also concluded that there were no studies that provide evidence as to how age modifies the effects of the interventions.

However, one systematic review (*Barra* 2018) performed a meta-regression to assess the individual impact of moderator variables on the effectiveness of cardiac ablation. The analysis showed that for studies with a higher mean patient age, cardiac ablation had a more pronounced benefit in the reduction of all-cause mortality and stroke (see **Appendix G**).

Other relevant information

Recent findings from the highly anticipated CABANA trial

Findings from the *Catheter ABlation vs ANtiarrhythmic Drug Therapy in Atrial Fibrillation* (CABANA) trial are yet to be formally published but have recently been reported in a conference presentation.[1] In this landmark trial, 2,204 patients from 10 countries were randomised to receive cardiac ablation or current state-of-the-art pharmacologic therapy. Approximately 36% of patients had Class II or III heart failure at baseline. Based on intention-to-treat (ITT) analyses at median follow up of approximately four years, there was no significant difference between the two arms in the primary endpoint of the trial (the composite of all-cause mortality, disabling stroke, serious bleeding, or cardiac arrest) or the individual components of the primary endpoint. However, one secondary outcome, the rate of death or cardiovascular hospitalisation, was significantly lower in the cardiac ablation arm (hazard ratio [HR] 0.83; 95% CI 0.74, 0.93; P=0.001). Consistent with previous trials, cardiac ablation was associated with a significant reduction in recurrence of AF (HR 0.53; 95% CI 0.46, 0.61; P<0.0001). It is expected that future subgroup analyses may demonstrate the groups of patients who benefit more from ablation.

Interpretation of the findings of CABANA has been controversial because the trial was only single-blinded, there was heterogeneity in the drug therapy (which included both rate and various rhythm control strategies), and there were high rates of patient crossover between arms (9.2% crossover from ablation to medical therapy and 27.5% crossover from medical therapy to ablation). Placebo-controlled sham trials are now being planned to confirm the findings.

Recent Australian guidance on management of AF

The National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand have recently published *Australian Clinical Guidelines for the Diagnosis and Management of Atrial Fibrillation* (2018).[2] The recommendations in relation to percutaneous catheter AF ablation are as follows:

- Catheter ablation should be considered for symptomatic paroxysmal or persistent AF refractory or intolerant to at least one Class I or III antiarrhythmic medication *[GRADE quality of evidence: High; GRADE strength of recommendation: Strong]*
- Catheter ablation can be considered for symptomatic paroxysmal or persistent AF before initiation of antiarrhythmic therapy *[GRADE quality of evidence: Moderate; GRADE strength of recommendation: Strong]*
- Catheter ablation can be considered for symptomatic paroxysmal or persistent AF in selected patients with heart failure with reduced ejection fraction *[GRADE quality of evidence: Moderate; GRADE strength of recommendation: Strong]*

The guideline advises that AF ablation is an effective procedure for appropriately selected patients with symptomatic AF. The procedure is considered applicable to patients who have failed or are intolerant to

[1] Study rationale and design Preliminary findings available at Cabana trial Accessed 11 October 2018.
[2] Guideline available at Heart and lung circulation Accessed 22 October 2018.

antiarrhythmic drugs, or for some patients who decline medical therapy. The guideline notes that in patients with recently diagnosed AF, ablation can be deferred until the natural history in that individual patient becomes apparent, as some patients might have only infrequent episodes for many years or could have AF that is responsive to well-tolerated medical therapy. Certain patient characteristics can be used to define patients in whom a lower success rate or a higher complication rate is likely. According to the guideline, these characteristics include the presence of concomitant heart disease, obesity, sleep apnoea, left atrial size, patient age and frailty, as well as the duration of time the patient has been in continuous AF. It is also noted that outcomes are better when experienced operators are performing the procedure in high-volume centres.

The Australian guideline acknowledges that patients frequently report a 'dramatic improvement' in quality of life with AF ablation, and that the procedure may have a mortality benefit in patients with heart failure. The CABANA trial is noted as an ongoing study awaiting publication.

1 Introduction

On 26 September 2018, the Department of Health engaged a contractor to provide the following services:

- Part 1 – A Rapid Review of high-level clinical evidence for cryo- and radiofrequency (RF) cardiac ablation catheters used to treat atrial fibrillation (AF).
- Part 2 – An assessment of cost-effectiveness, including a comparison against anti-arrhythmic medication.

This report describes the methods and findings for the review of the clinical evidence (Part 1). The assessment of cost-effectiveness (Part 2) will be described in a subsequent report.

1.1 BACKGROUND

On 10 October 2017 the Minister for Health requested that the PLAC provide advice by 31 December 2018 on options for including cardiac ablation catheters (including an assessment of comparative clinical and cost effectiveness) on the Prostheses List.

A key driver for this request was the claim by consumer groups that cardiac ablation procedures could be accessed only in the public hospital system, which is subject to waiting times. It is claimed that providing this procedure through the private health system would provide earlier access to treatment for appropriately insured patients. It is also claimed that increasing the availability of cardiac ablation treatment (a once-in-a-lifetime procedure) would provide savings to the health system offered via reduced rates of hospitalisation and stroke.

1.2 ATRIAL FIBRILLATION

AF is the major cause of ischemic stroke and is moderately associated with increased mortality from stroke, heart failure, and cardiovascular disease (Churgh et al 2014). Stroke prevention, therefore, is a major goal for the management of AF.

Treatment of AF involves rate control, rhythm control, prevention of thromboembolic events, and treating the underlying disease (e.g. hypertension) if applicable (AHRQ 2015). The primary reason for rate and rhythm control is to improve symptoms and quality of life, and the primary treatment is typically pharmacologic therapy. Anticoagulation treatment has been shown to reduce AF-related stroke; however, the use of anticoagulants is limited due to poor patient compliance and increased risk of bleeding complications.

For rhythm control, antiarrhythmic drug (AAD) therapy has been the cornerstone of medical management but some patients show resistance to AAD or need to discontinue treatment because of side effects. Adverse effects of AADs include thyroid toxicity, pulmonary toxicity, liver dysfunction, bradycardia, and a potential pro-arrhythmia effect. Selection of first-line AAD is largely driven by the presence or absence of structural heart disease (AHRQ 2015).

1.3 CARDIAC ABLATION PROCEDURE

Cardiac ablation for the treatment of AF is increasingly being performed on symptomatic patients as an alternative to medical management, or when medical management has been ineffective or not tolerated (AHRQ 2015). The goal of cardiac ablation for treatment of AF is to ablate or isolate triggers that mostly originate in the area of the pulmonary veins. Thus, the most commonly used and recommended cardiac ablation procedure to treat AF is pulmonary vein isolation (PVI). While other approaches may also be used,

typically in addition to PVI, there is uncertainty regarding additional benefits or harms of such approaches (AHRQ 2015).

Among methods and technologies used during the procedure, energy source is an important factor. There are currently two main types of cardiac ablation procedures, those that burn the target sites (RF ablation), and those that freeze the target sites (cryoablation).

RF cardiac ablation systems deliver RF energy between an electrode at the tip of the ablation catheter and a grounding patch on the patient's skin. This produces heat in the immediate vicinity of the ablation catheter tip, which has a small surface area. As a result, significant resistive heating occurs only at the catheter tip–tissue interface and in a small volume of surrounding tissue.

Cryoablation involves the insertion of a catheter with a balloon into the openings where the four pulmonary veins join the left atrium. This is commonly the site of origin of AF. When the balloon is inflated the opening is closed off, which stops blood flow from the vein. The balloon is then filled with liquid coolant, which destroys a ring of tissue. The resultant scarring prevents AF.

Complications arising from cardiac ablation include:

- device-related complications, causing injury to adjacent structures (e.g. transient or permanent phrenic nerve palsy);
- procedure-related complications, relating to vascular access (e.g. groin complications such as arteriovenous fistulae or femoral artery pseudoaneurysm) or cardiac perforation (e.g. pericardial effusion and tamponade); and
- energy-related complications (e.g. pulmonary vein stenosis; thromboembolic complications such as periprocedural stroke or transient ischaemic attack; oesophageal complications).

A high complication rate may result from an operator's inexperience with the system, the ablation system itself, and/or inadequate peri-procedural anticoagulation.

Imaging may be performed before or during the ablation procedure, including magnetic resonance imaging, computed tomography imaging, and transthoracic, trans-esophageal, and intra-cardiac echocardiography (AHRQ 2015). Mapping techniques vary greatly and continue to evolve. Evaluation of imaging and the mapping approach is beyond the scope of the current review.

1.4 PUBLIC FUNDING FOR THE PROCEDURE

There are currently three Medicare Benefits Schedule (MBS) items for services relating to catheter-based arrhythmia ablation:[3]

- Item 38287 – Ablation of arrhythmia circuit or focus or isolation procedure involving 1 atrial chamber;
- Item 38290 – Ablation of arrhythmia circuit or foci, or isolation procedure involving both atrial chambers and including curative procedures for atrial fibrillation;
- Item 38293 – Ventricular arrhythmia with mapping and ablation, including all associated electrophysiological studies performed on the same day.

These services have been on the MBS since 1998 and have not undergone formal assessment of comparative safety, clinical effectiveness and cost-effectiveness. Although there has been considerable growth in use of these items (see **Appendix A**), the MBS Review Taskforce's Cardiac Services Clinical Committee recently recommended leaving the items unchanged, claiming that growth in services is likely reflective of (i) the increasing number of electrophysiologists, which is improving access to services; and (ii)

[3] MBS Category 3 – Therapeutic Procedures, Group T8 – Surgical Operations, Subgroup 6 – Cardio-thoracic, Subheading 2 – Catheter Based Arrhythmia Ablation.

a change in clinical guidelines, which now identify ablation as a first-line treatment for a number of arrhythmias.[4]

[4] Report available at Health

2 Rapid Review of Clinical Evidence

2.1 RESEARCH QUESTIONS

The rapid review is intended to address the three research questions below:

1. Is there sufficient clinical evidence to demonstrate the superiority of cardiac ablation over treatment with anti-arrhythmic medication? If not, what are the gaps?
2. Are the clinical outcomes different in different age groups?
3. Is there sufficient data to establish that the devices are cost effective at the prices currently being paid in Australia?

Questions 1 and 2 are addressed in this report. Question 3 will be addressed in Report 2, which will follow.

PICO criteria have been developed to assist with evidence selection for each research question. These criteria define the following four elements in detail:

P – the target population

I – the intervention being considered

C – the appropriate comparator

O – the outcome of interest

The PICO criteria for the Rapid Review are defined below.

Table 3 PICO criteria for the Rapid Review

PICO criterion	Description
Population	Patients with symptomatic AF • paroxysmal • non-paroxysmal (persistent or permanent)
Intervention	Cardiac catheter ablation (alone or in combination with anti-arrhythmic medication) for the treatment or prevention of AF • RF ablation • Cryoablation
Comparators	• Medical management with anti-arrhythmic medication • Other type of cardiac ablation (i.e. RF ablation versus cryoablation)
Outcomes	• All-cause mortality • Stroke (fatal or non-fatal) • Recurrence of AF/AT • Periprocedural complications and other safety outcomes (pericardial effusion, major vascular complications, pericardial tamponade and pulmonary vein stenosis) • Cardiac hospitalisation/re-admission • Repeat ablation • Cost/cost-effectiveness[5]

[5] The cost and cost-effectiveness of cardiac ablation catheters will be addressed in Report 2.

PICO criterion	Description
Additional considerations	• Patient age • Comorbidities (e.g. heart failure) • Type of AF (paroxysmal or non-paroxysmal) • Definition of persistent/permanent AF • Type of catheter (e.g. RF, cryoballoon, irrigated, non-irrigated) • Line of therapy (first-line or after failed medical therapy) • Newer generation technology (first or second generation?) • Operator experience • Duration of patient follow up

Abbreviations: AF, atrial fibrillation; AT, atrial tachyarrhythmia; RF, radiofrequency.

2.2 RESEARCH METHODS

2.2.1 Literature search

A search for high level clinical evidence (systematic reviews and health technology assessments [HTAs]) was conducted on 26 September 2018 using the following databases:

- **Epistemonikos** –meta-database of systematic reviews relevant for health decision-making. The database is populated through daily to weekly searching of 18 different sources, including the Cochrane Database of Systematic reviews, Pubmed, EMBASE, CINAHL, PsychINFO, Database of Abstracts of Reviews of Effects, The Campbell Collaboration online library, Joanna Briggs Institute (JBI) Database of Systematic Reviews and Implementation Reports, and EPPI-Centre Evidence Library.
- **HTA Database** (maintained by University of York Centre for Reviews and Dissemination) – repository of ongoing and completed HTAs submitted by 52 members of the International Network of Agencies for Health Technology Assessment (INAHTA) and 20 other international HTA organisations.
- **NHS Evidence** (created by the National Institute for Health and Care Excellence, NICE) – provides access to synthesised high quality, authoritative evidence-based information and best practice advice.

The literature search strategy is provided in **Appendix B**.

2.2.2 Inclusion and exclusion criteria

Studies that met the criteria in Table 4 were considered potentially eligible for inclusion in this Rapid Review. The primary focus is on the comparative safety and efficacy/effectiveness of cardiac ablation versus medical therapy. A secondary focus is to compare the safety and efficacy/effectiveness of RF ablation with cryoablation. As this is a Rapid Review, studies focusing on hybrid ablation or particular types of cardiac ablation (e.g. contact-force-sensing; robotic; irrigated) were considered out-of-scope, as were studies focusing on particular medical populations (e.g. patients with heart failure or diabetes).

Table 4 Inclusion and exclusion criteria

Criteria	Inclusion	Exclusion
Time period	• published 2012 onwards	• published before 2012
Type of publication	• full text journal articles • Cochrane reviews • health technology assessments	• conference abstracts • letters and editorials • opinion pieces and commentaries • primary studies (RCTs, observational studies, etc.) • unpublished studies
Type of study	• systematic reviews • meta-analyses • economic evaluations (Australian only)	• narrative systematic reviews • non-Australian economic evaluations
Study language	• English	• non-English
Population	• as per PICO in Table 3	• patients with other types of supraventricular tachyarrhythmia, such as atrial flutter or supraventricular tachycardia • studies focussing on CA in patients with a particular comorbidity (e.g. HF; diabetes)
Intervention	• as per PICO in Table 3	• intraoperative ablation or ablation as an adjunct to surgery (hybrid ablation) • studies focusing on periprocedural anticoagulation in patients undergoing CA • studies focusing on robotic ablation or comparing robotic to manual ablation • studies comparing CA guidance techniques • studies focussing on particular types of CA (e.g. comparison of contact-force-sensing catheter ablation vs. no contact-force-sensing catheter ablation) • studies focussing broadly on interventions for the treatment of AF
Comparator	• as per PICO in Table 3	• non-pharmacological comparators such as surgical procedures or cardioversion alone (in the absence of medical therapy)
Outcomes	• as per PICO in Table 3	• any outcome not listed in the PICO • non-Australian cost or cost-effectiveness data

Abbreviations: AF, atrial fibrillation; CA, cardiac ablation; HF, heart failure; RCT, randomised controlled trial.

2.3 RESULTS OF LITERATURE SEARCH

2.3.1 Included systematic reviews

Twenty-three systematic reviews (including two Cochrane Reviews) and three HTAs met the eligibility criteria for the Rapid Review. Due to the large body of high-level evidence, key reviews were selected purposefully on the basis of:

- recency – date that the literature search was conducted;
- comprehensiveness – number and type of primary studies, populations, interventions and outcomes included, analyses conducted; and
- quality – risk of bias assessed using the Assessing the Methodological Quality of Systematic Reviews version 2 (AMSTAR 2) critical appraisal tool for systematic reviews (Shea et al 2017).

Appendix C provides evidence matrices showing a list of the primary studies included in each systematic review and HTA that met the eligibility criteria for the Rapid Review. Across all systematic reviews and HTAs, there are approximately 76 RCTs and 93 non-randomised observational studies. As expected, the overlap in included primary studies varies considerably between reviews depending on the literature search date, the AF populations and ablation catheters of interest, study types included, and other study eligibility criteria such as the duration of patient follow up and review focus (e.g. contemporary/second-generation devices; first-line treatment; etc.).

Appendix D provides the citation details, authors' conclusions, and rationale for each systematic review and HTA that met the eligibility criteria for the Rapid Review (Table App 4 lists reviews that compare cardiac ablation with medical therapy, and Table App 5 lists reviews that compare RF ablation with cryoablation).

Appendix E provides the AMSTAR 2 risk of bias assessment for selected systematic reviews/HTAs.

Appendix F provides a list of 17 systematic reviews that are considered out-of-scope for this Rapid Review because they focus on cardiac ablation in particular medical subpopulations.

Based on the selection criteria above, four recent systematic reviews and one HTA were selected for further assessment (see Table 5 below). The need for multiple reviews was due to differences in the included study types, AF populations, interventions, outcomes and analyses conducted. None of the selected systematic reviews were by Australian authors.[6]

Table 5 List of selected systematic review and HTAs

Study ID [Country of authors]	Title	Risk of bias[a]
Barra 2018 [UK/France]	Association of catheter ablation for atrial fibrillation with mortality and stroke: A systematic review and meta-analysis.	Low
Chen 2018 [China]	Catheter ablation versus medical therapy for patients with persistent atrial fibrillation: a systematic review and meta-analysis of evidence from randomized controlled trials.	Low
Khan 2018 [USA]	The clinical benefits and mortality reduction associated with catheter ablation in subjects with atrial fibrillation: a systematic review and meta-analysis.	Low
Cardoso 2016 [USA]	Cryoballoon versus radiofrequency catheter ablation in atrial fibrillation: a meta-analysis.	Low
AHRQ 2015 [USA]	Catheter ablation for treatment of atrial fibrillation: Technology Assessment Report. Agency for Healthcare Research and Quality.	Low

a Risk of bias assessed using the AMSTAR 2. See **Appendix E** for further details.

2.3.2 Characteristics of included studies

The key characteristics of the selected systematic reviews and HTAs are provided in Table 6 (cardiac ablation versus medical therapy) and Table 7 (RF ablation versus cryoablation). Three of the published reviews (*Barra 2018*; *Cardoso 2016*; *AHRQ 2015*) included RCTs and non-randomised observational studies. Although observational studies are prone to treatment selection bias, they provide 'real world' assessment of uncommon events, such as death, stroke and serious complications.

The risk of bias of the individual (primary) studies included in the selected reviews has not been formally assessed as part of this Rapid Review. Rather, it was captured as reported in the published reviews. All included RCTs in the systematic reviews published in 2018 were judged by the authors of the reviews to be at low risk of bias or of good quality. However, the HTA for the Agency for Healthcare Research and Quality

[6] One systematic review from Australian authors (Kabunga et al 2016) had a literature search date of December 2014. This review of contemporary ablation strategies was not selected for inclusion in the Rapid Review because there are more recent and comprehensive reviews available.

(*AHRQ 2015*) considered only one RCT to be of high quality; all other RCTs were rated as insufficient, low or moderate quality.

Table 6 Characteristics of selected systematic reviews/HTAs: cardiac ablation vs. medical therapy

Study ID *Risk of bias*[a]	Study aim	Search dates Study eligibility	No. of included studies *Risk of bias*[b]	Intervention Comparator	Outcomes of interest	Analyses
Khan 2018 *Low*	To compare the efficacy and safety of CA with those of MT for the treatment of AF.	Search: 1966 – Feb 2018 Inclusion • RCTs of CA vs. MT (rhythm or rate-control medications) • adult patients with AF • studies report ≥1 event for outcomes of interest	17 RCTs (2,272 patients) *Low RoB*	Intervention Any type of ablation Comparator MT including; optimal HF treatment +/- digoxin or warfarin; rate control drugs (beta blockers, digitalis, calcium antagonist) and/or antiarrhythmic agents.	• all-cause mortality • stroke • recurrence of atrial arrythmia • cardiac hospitalisation • major bleeding • pulmonary vein stenosis • pericardial complications	• with and without HF • RCTs only
Chen 2018 *Low*	To perform a meta-analysis of RCTs to assess the clinical outcomes of CA compared with MT in persistent AF patients.	Search: no restriction to Oct 2017 Inclusion • RCTs of CA vs. MT (rhythm or rate-control medications) • patients with persistent AF • follow up duration of ≥6 months • sample size >10 Exclusion • non-English studies • prior ablation • restoration of the SR by surgical ablation • rate control via atrioventricular node ablation	8 RCTs (809 patients) *Low RoB*	Intervention Any type of ablation Comparator medical rhythm control or medical rate control strategy	• all-cause mortality • recurrence of atrial arrythmia • cardiac hospitalisation	• RCTs only

Study ID ***Risk of bias***[a]	**Study aim**	**Search dates** **Study eligibility**	**No. of included studies** ***Risk of bias***[b]	**Intervention** **Comparator**	**Outcomes of interest**	**Analyses**
Barra 2018 *Low*	To determine whether AF ablation is associated with a reduction in all-cause mortality and stroke compared with MT alone	Search: no restriction to Aug 2017 Inclusion • CA (+/- electrical cardioversion) and MT (+/- electrical cardioversion) • patients with AF • follow up duration of ≥6 months • longitudinal studies Exclusion • non-English studies	19 RCTs, 11 non-RCTs (78,966 patients) *Good study quality*[7]	Intervention PVI (+/- additional substrate ablation) Comparator MT	• all-cause mortality • stroke	• age • co-morbidities
AHRQ 2015 *Low*	To evaluate the comparative efficacy, effectiveness, and safety of CA and MT for the treatment of AF.	Search: 2005 – Nov 2014 Inclusion • CA vs MT or different CA energy sources • adults with paroxysmal, persistent or permanent AF • RCTs and comparative observational with ≥100 patients Exclusion • non-English studies	15 RCTs, 9 non-RCTs *1 RCT high quality, all others rated as insufficient, low or moderate*	Intervention Any type of ablation Comparator MT, RF ablation or cryoballoon ablation	• all-cause mortality • freedom from recurrence of arrhythmia • repeat ablation • cardiac hospitalisation/ re-admission • major bleeding • pulmonary vein stenosis • pericardial tamponade • pericardial effusion	• type of AF • type of catheter • duration of patient follow-up • age • comorbidities • operator experience • line of treatment

Abbreviations: AF, atrial fibrillation; AT, atrial tachyarrhythmia; CA, cardiac ablation; HF, heart failure; MT, medical therapy; PVI, pulmonary vein isolation; RCT, randomised controlled trial; RF, radiofrequency; RoB, risk of bias.
a Risk of bias for systematic reviews was assessed using the AMSTAR 2. See **Appendix E** for further details.
b Risk of bias for individual (primary) studies is captured as reported in included systematic reviews.

[7] The overall study quality was good, as seven randomized controlled studies had ≥6 Delphi criteria and 8 cohort studies had a Newcastle-Ottawa score of ≥7.

Table 7 Characteristics of selected systematic reviews/HTAs: RF ablation vs. cryoablation

Study ID *Risk of bias*[a]	Study aim	Search dates Study eligibility	No. of included studies *Risk of bias*[b]	Intervention Comparator	Outcomes of interest	Analyses
Cardoso 2016	To present an updated meta-analysis comparing the efficacy and safety of CB versus RF ablations in AF.	Search: no restriction to April 2016 Inclusion • cryoablation to irrigated RFCA • patients with AF • mean or median follow up duration of ≥12 months Exclusion • no control group • overlapping patient populations • patients who had received a previous CA for AF • investigational devices or techniques	22; 5 RCTs, 17 non-RCTs (8,668 patients) *RCTS; low RoB* *Non-RCTs: low and moderate RoB*	Intervention Cryoablation Comparator Irrigated RFCA	Outcomes • freedom from recurrent AT • major vascular complications • pericardial effusion • pericardial tamponade	• study type • paroxysmal AF • second-generation CB

Abbreviations: AF, atrial fibrillation; AT, atrial tachyarrhythmia; CA, cardiac ablation; CB, cryoballoon; RCT, randomised controlled trial; RF, radiofrequency; RFCA, radiofrequency cardiac ablation; RoB, risk of bias.
a Risk of bias for systematic reviews was assessed using the AMSTAR 2. See **Appendix E** for further details.
b Risk of bias for individual (primary) studies is captured as reported in included systematic reviews.

2.3.3 Results of selected systematic reviews

All-cause mortality

Barra 2018 included the largest number of studies and found that cardiac ablation was associated with lower mortality risk, in both randomised (P=0.001) and observational studies (P<0.001). In the randomised studies, the pooled benefit was mostly attributable to two studies, namely the AATAC trial (Di Biase et al 2016) and the CASTLE-AF trial (Marrouche et al 2017). Both studies enrolled patients with heart failure and significant left ventricular (LV) systolic dysfunction. The mortality benefit was robustly noted in observational studies, even when restricting the analysis to studies with propensity score matching, although even such matching strategies cannot completely eliminate bias inherent to observational studies. As such, the extent of mortality benefit noted from observational studies, while encouraging, needs to be interpreted with caution, particularly given the substantial heterogeneity.

Consistent with the findings from *Barra 2018*, a second SR, *Khan 2018,* found a statistically significant mortality benefit for cardiac ablation compared with medical therapy in RCTs of patients with heart failure (P<0.001), but no significant difference was observed in RCTs of patients without heart failure (P=0.81).

The *AHRQ 2015* HTA reported that in the general population, evidence on the long-term efficacy of RF ablation compared with medical therapy for reducing mortality was 'low' (i.e. limited confidence) for paroxysmal AF. However, the HTA did not include key studies published from 2015 onwards.

There is insufficient evidence to make a statement regarding any differential effect of RF ablation versus cryoablation on mortality.

Table 8 Results from selected systematic reviews – All-cause mortality

Study ID *Risk of bias*[a]	Population (follow up)	Analysis subgroup (no. studies)	Intervention n/N (%)	Comparator n/N (%)	Risk estimate (95% CI)	Heterogeneity P-value; I^2
Cardiac ablation vs. medical therapy						
Khan 2018 *Low*	Any AF (mean 19 months, range 6-60 months)	CA vs. MT with HF (4 RCTs)	33/333 (9.9%)	65/337 (19.3%)	RD -0.06 (-0.13, 0.01) P=0.09	P=NR; I^2=NR
					RR 0.52 (0.36, 0.76) P < 0.001	P=NR; I^2=0%
		CA vs. MT without HF (4 RCTs)	6/373 (1.6%)	7/337 (2.1%)	RD -0.00 (-0.02, 0.02) P=0.99	P=0.NR; I^2=NR
					RR 0.88 (0.29, 2.61) P=0.81	P=NR; I^2=0%
Barra 2018 *Low*	Any AF (6-53 months)	CA vs. MT (10 RCTs, 8 non-RCTs)	n/N NR (5.7%)	n/N NR (17.9%)	RR 0.44 (0.32, 0.62) P<0.001	P=NR; I^2=88% *High*[8]
		CA vs. MT (10 RCTs)	n/N NR (4.2%)	n/N NR (8.9%)	RR 0.55 (0.39, 0.79) P=0.001	P=0.001; I^2=0%[8] *Low*[8]
		CA vs. MT (8 non-RCTs)	n/N NR (6.1%)	n/N NR (18.3%)	RR 0.39 (0.26, 0.59) P<0.001	P=NR, I^2=95% *High*[8]
Chen 2018 *Low*	Persistent AF (6-24 months)	CA vs. AAD (3 RCTs)	9/338 (2.7%)	18/221 (8.1%)	RR 0.47 (0.22, 1.02) P=0.05	P=0.45, I^2=0%

[8] I^2 < 25 % considered low, I^2 > 25 % considered high and in between considered moderate.

Study ID *Risk of bias*[a]	Population (follow up)	Analysis subgroup (no. studies)	Intervention n/N (%)	Comparator n/N (%)	Risk estimate (95% CI)	Heterogeneity P-value; I^2
AHRQ 2015 *Low*	Any AF[9] (12 months)	RFA vs. MT (7 RCTs)	4/551 (0.7%)	6/427 (1.4%)	NR	NR
	Paroxysmal AF (12 months)	RFA vs. MT (3 RCTs)	1/187 (0.54%)	2/146 (1.37%)	NR	P=0.357; I^2=0%
	Paroxysmal AF (24 months)	RFA vs. MT >30 days (2 RCTs)	2/206 (0.97%)	4/202 (2.0%)	NR	NR
	Persistent AF (12 months)	RFA vs. MT (3 RCTs)	2/201 (1.0%)	0/143 (0%)	NR	P=0.962; I^2=0%
	Persistent AF (mean 60 months)	RFA vs. MT >30 days (1 non-RCT)	2/153 (1.3%)	5/259 (1.9%)	NR P=0.71	NR
	Mixed AF (mean 16-69 months)	RFA vs. MT >30 days (2 non-RCTs)	3/231 (1.3%)	35/290 (12.1%)	NR	NR
	Mixed AF[10] (12 months)	Cryoablation vs MT (1 RCT)	1/163 (0.6%)	0/79 (0%)	NR	NA
RF ablation vs. cryoablation						
AHRQ 2015 *Low*	Paroxysmal AF (mean 23 months)	Cryoballoon vs. RFA Second-line (1 non-RCT)	0/136 (0%)	3/260 (1.2%)	NR	NA

Abbreviations: AAD, antiarrhythmic drugs; AF, atrial fibrillation; CA, cardiac ablation; CI, confidence interval; HF, heart failure; MT, medical therapy; NA, not applicable; NR, not reported; RD, risk difference; RF, radiofrequency; RFA, radiofrequency ablation; RCT, randomised control trial; RR, risk ratio.

a Risk of bias assessed using the AMSTAR 2. See **Appendix E** for further details.

Stroke

Barra 2018 included the largest number of studies (7 randomised and 10 non-randomised) and found that patients who received cardiac ablation had a lower risk of cerebrovascular events (stroke and transient ischaemic events [TIA]), but this effect was only seen in observational studies (P<0.001). The authors commented that any potential benefit of cardiac ablation in the reduction of long-term stroke risk is possibly counterbalanced against the peri-procedural risk of stroke, which remains a significant complication of AF ablation but was not consistently reported in the observational studies. No stroke reduction was noted in the pooled analysis of randomised trials (P=0.87), although none of the RCTs were sufficiently powered for this outcome. Adequately powered RCTs addressing this endpoint are needed to clarify whether ablation can be of benefit for stroke reduction.

Khan 2018 found no significant difference between cardiac ablation and medial therapy on risk of stroke in three RCTs in patients with heart failure. Due to paucity of data, *Khan 2018* did not assess stroke risk in patients without heart failure.

The *AHRQ 2015* HTA reported that data on stroke are sparse for patients with paroxysmal AF, and no long-term RCT data were found for those with persistent AF.

There is insufficient evidence to make a statement regarding any differential effect of RF ablation versus cryoablation on risk of stroke.

[9] Studies with any type of AF patients.

[10] Studies which include both persistent and paroxysmal AF patients.

Table 9 Results from selected systematic reviews – Stroke

Study ID *Risk of bias*[a]	Population (follow up)	Analysis subgroup (no. studies)	Intervention n/N (%)	Comparator n/N (%)	Risk estimate (95% CI)	Heterogeneity P-value; I^2
Cardiac ablation vs. medical therapy						
Khan 2018 *Low*	Any AFs (mean 19 months, range 6-60 months)	CA vs. MT with HF (3 RCTs)	7/351 (2.0%)	11/358 (3.1%)	RR 0.72 (0.24, 2.21) P=0.57	NR
Barra 2018[11] *Low*	Any AF (6-53 months)	CA vs. MT (7 RCTs, 10 non-RCTs)	n/N NR (2.3%)	n/N NR (5.5%)	RR 0.57 (0.46, 0.70) P < 0.001	P=NR, I^2=62% *High*[8]
		CA vs. MT (7 RCTs)	n/N NR (2.2%)	n/N NR (2.1%)	RR 0.94 (0.46, 1.94) P=0.87	P=NR, I^2=0% *Low*[8]
		CA vs. MT (10 non-RCTs)	n/N NR (2.3%)	n/N NR (5.5%)	RR 0.54 (0.43, 0.68) P<0.001	P=NR, I^2=75% *High*[8]
AHRQ 2015 *Low*	Paroxysmal AF (12-24 months)	RFA vs. MT >30 days, First-line (2 RCT)	0/98 (0%)	0/96 (0%)	NR	NA
	Persistent AF (12 months)	RFA vs. MT >30 days, Second-line (1 RCT)	0/98 (0%)	0/48 (0%)	NR	NA
	Mixed AF & diabetes (12 months)	RFA vs. MT >30 days, Second-line (1 RCT)	0/35 (0%)	0/35 (0%)	NR	NA
	Mixed AF (mean 16-69 months)	RFA vs. MT >30 days (2 non-RCTs)	0/231 (0%)	7/290 (2.4%)	NR	NR
	Mixed AF (12 months)	Cryoablation vs MT >30 days (1 RCT)	3/163 (1.8%)	0/79 (0%)	NR	NA
RF ablation vs. cryoablation						
Cardoso 2016 *Low*	Any AF (≥12 months)	Cryoablation vs. RFA (NR)	3/1422 (0.2%)	8/2636 (0.3%)	NR P=0.63	NR

Abbreviations: AF, atrial fibrillation; CA, cardiac ablation; CI, confidence interval; HF, heart failure; MT, medical therapy; NA, not applicable; NR, not reported; RD, risk difference; RFA, radiofrequency ablation; RCT, randomised control trial; RR, risk ratio.
a Risk of bias assessed using the AMSTAR 2. See **Appendix E** for further details.

Arrythmia recurrence

All reviews reporting the outcome of arrhythmia recurrence (*Khan 2018*) or conversely freedom from recurrence of arrhythmia (*Chen 2018*; *AHRQ 2015*) found statistically significant benefits of cardiac ablation compared with medical therapy.

AHRQ 2015 reported that moderate strength evidence indicates that for patients with either paroxysmal AF or persistent AF, RF ablation is effective in the short term (≤12 months) for preventing recurrence of atrial arrhythmias compared with medical therapy. While this appears to be sustained over a longer term in patients with paroxysmal AF, there was insufficient evidence for this in patients with persistent AF.

Cardoso 2016 and *AHRQ 2015* found no statistically significant difference between irrigated RF ablation and cryoablation in freedom from recurrence of arrhythmia.

[11] Outcomes reported as cerebrovascular event, which includes stroke or TIA

Table 10 Results from selected systematic reviews – Arrythmia recurrence

Study ID *Risk of bias*[a]	Population (follow up)	Analysis subgroup (no. studies)	Intervention n/N (%)	Comparator n/N (%)	Risk estimate (95% CI)	Heterogeneity P-value; I^2
Cardiac ablation vs. medical therapy						
Recurrence of atrial arrythmia						
Khan 2018 *Low*	Any AF (mean 19 months, range 6-60 months)	CA vs. MT with HF (6 RCTs)	113/385 (29.4%)	284/395 (71.9%)	RR 0.44 (0.31, 0.61) P<0.001	P=NR; I^2=56 *High*[12]
		CA vs. MT without HF (11 RCTS)	212/785 (27.0%)	444/696 (63.8%)	RD -0.40 (-0.52, -0.29) P<0.001	NR
					RR 0.40 (0.31, 0.52) P<0.001	P=NR; I^2=73% *High*[12]
Freedom from recurrence of any arrythmia						
Chen 2018 *Low*	Persistent AF (6-24 months)	CA vs. AAD (3 RCTs)	207/338 (61.2%)	67/221 (30.3%)	RR 2.08 (1.67, 2.58) P<0.00001	P=1.00, I^2=0%
	Persistent AF without AADs after CA (6-24 months)	CA vs. AAD (3 RCTs)	182/338 (53.9%)	67/221 (30.3%)	RR 1.82 (1.33, 2.49) P=0.0002	P=0.16, I^2=46%
AHRQ 2015 *Low*	Any AF (12 months)	RFA vs. MT (9 RCTs)	425/590 (72.0%)	140/492 (28.5%)	RR 2.62 (1.19, 3.96)	P=0.0001 I^2=84.2% *High*[13]
	Paroxysmal AF Short term (12 months)	RFA vs. MT (4 RCTs)	226/286 (79%)	64/245 (26.1%)	RR 3.06 (2.35, 3.90)	P=0.381; I^2=2.2%
	Paroxysmal AF Long term (24-48 months)	RFA vs. MT (3 RCTs)	226/311 (72.6%)	178/308 (57.8%)	RR 1.24 (1.11, 1.47)	P=0.388; I^2=0%
	Persistent AF Short term (12 months)	RFA vs. MT (3 RCTs)	133/201 (66.2%)	55/143 (38.5%)	NR	P=0.001; I^2=85% *High*[13]
RF ablation vs. cryoablation						
Freedom from recurrence						
Cardoso 2016[14] *Low*	Any AF (12-40 months)	Cryoablation vs. RFA (5 RCTs, 14 non-RCTs)	2223/3218 (69.1%)	2648/4193 (63.2%)	OR 1.12 (0.97, 1.29) P=0.13	P=0.11; I^2=30% *High*[15]
		Cryoablation vs. RFA (5 RCTs)	406/651 (62.4%)	400/655 (61.1%)	OR 1.00 (0.65, 1.56) P=0.99	P=0.04; I^2=60% ***High***[15]
	Paroxysmal AF (12-40 months)	Cryoablation vs. RFA (NR)	1569/2365 (66.3%)	2294/3690 (62.1%)	OR 1.08 (0.94, 1.26) P=0.28	NR
AHRQ 2015 *Low*	Paroxysmal AF (12 months)	Cryoablation vs. RFA Second-line (1 RCT)	12/25 (48.0%)	17/25 (68.0%)	RR 0.71 (0.43, 1.14) P=0.15	NA
	Mixed AF (12 months)	Cryoablation vs. RFA Second-line (1 RCT)	20/30 (66.7%)	26/30 (86.7%)	RR 1.1 (0.76, 1.5) P=0.68	NA

[12] I^2 > 50% considered high
[13] I^2 > 75% considered high
[14] Data refer to freedom from recurrent AT.
[15] I^2 >25% considered high.

Study ID *Risk of bias*[a]	Population (follow up)	Analysis subgroup (no. studies)	Intervention n/N (%)	Comparator n/N (%)	Risk estimate (95% CI)	Heterogeneity P-value; I^2
	Paroxysmal AF (mean 12-28 months)	Cryoablation vs. RFA Second-line (3 non-RCTs)	193/277 (69.7%)	215/364 (59.1%)	NR	NS

Abbreviations: AAD, anti-arrhythmic drug; AF, atrial fibrillation; AT, atrial tachyarrhythmia; CA, cardiac ablation; CI, confidence interval; HF, heart failure; MT, medical therapy; NA, not applicable; NR, not reported; NS, not statistically significant; OR, odds ratio; RD, risk difference; RFA, radiofrequency ablation; RCT, randomised control trial; RR, risk ratio.
a Risk of bias assessed using the AMSTAR 2. See **Appendix E** for further details.

Repeat ablation

Repeat ablation is only relevant for patients who received initial cardiac ablation. As such, risk estimates are only shown in the table below when comparing RF ablation with cryoablation. Rates of repeat ablation varied considerably across studies from 0% to 54%.

Cardoso 2016 found no statistically significant difference in rates of repeat ablation in patients treated with RF catheter (irrigated) versus cryoballoon.

Table 11 Results from selected systematic reviews – Repeat ablation

Study ID *Risk of bias*[a]	Population (follow up)	Analysis subgroup (no. studies)	Intervention n/N (%)	Comparator n/N (%)	Risk estimate (95% CI)	Heterogeneity P-value; I^2
Cardiac ablation vs. medical therapy[16]						
AHRQ 2015 *Low*	Any AF (6-12 months)	RFA vs. MT (8 RCTs)	NR/430 Range 0-53.8%	NA	NR	NR
	Paroxysmal AF (12 months)	RFA vs. MT (3 RCTs)	NR/184 Range 0-43.3%	NA	NR	NR
	Paroxysmal AF (12-48 months)	RFA vs. MT (4 RCTs)	NR/337 Range 12.5-49.2%	NA	NR	NR
	Persistent AF (6-12 months)	RFA vs. MT (5 RCTs)	NR/246 Range 8.1-53.8%	NA	NR	NR
	Persistent AF with HF (6-12 months)	RFA vs. MT (3 RCTs)	25/71 (35.2%)	NA	NR	NR
	Persistent AF (mean 60 months)	RFA vs. MT (1 non-RCT)	28/153 (18.3%)	NA	NR	NA
	Paroxysmal AF (12 months)	RFA vs. MT (1 non-RCT)	10/82 (12.2%)	NA	NR	NA

[16] n/N for medical therapy group has not been reported as repeat ablation is not a possible outcome.

Study ID *Risk of bias*[a]	Population (follow up)	Analysis subgroup (no. studies)	Intervention n/N (%)	Comparator n/N (%)	Risk estimate (95% CI)	Heterogeneity P-value; I^2
RF ablation vs. cryoablation						
Cardoso 2016 *Low*	Any AF (12-40 months)	Cryoablation vs. RFA[17] (8 studies, 2803 patients)	n/N NR 12.7%	n/N NR 15.5%	OR 0.81 (0.55, 1.18) P=0.26	NR
		Cryoablation vs. RFA[17] (5 RCTs, 1306 patients)	n/N NR 10.2%	n/N NR 9.0%	OR 1.11 (0.73, 1.69) P=0.61	NR
AHRQ 2015[18] *Low*	Paroxysmal AF (12 months)	Cryoablation vs. RFA Second-line (1 RCT)	6/25 (24.0%)	0/25 (0%)	RR 0.22 (0.07, 0.37) P=0.01	NA
	Mixed AF (12 months)	Cryoablation vs. RFA Second-line (1 RCT)	9/30 (30.0%)	4/30 (13.3%)	RR 2.25 (0.78, 6.51) P=0.12	NA
	Mixed AF (mean 14 months)	Cryoablation vs. RFA Second-line (1 non-RCT)	17/124 (13.7%)	12/53 (22.6%)	NR	NA

Abbreviations: AF, atrial fibrillation; CI, confidence interval; HF, heart failure; MT, medical therapy; NA, not applicable; NR, not reported; OR, odds ratio; RFA, radiofrequency ablation; RCT, randomised control trial.
a Risk of bias assessed using the AMSTAR 2. See **Appendix E** for further details.

Cardiac hospitalisation/re-admission

All reviews shown in the table below reported that hospitalisation was more frequent in patients who received medical therapy compared with cardiac ablation. However, studies did not provide detail regarding reasons for hospitalisation and the extent to which hospitalisation for re-ablation procedures or crossover from medical therapy to ablation were included.

Table 12 Results from selected systematic reviews – Cardiac hospitalisation/re-admission

Study ID *Risk of bias*[a]	Population (follow up)	Analysis subgroup (no. studies)	Intervention n/N (%)	Comparator n/N (%)	Risk estimate (95% CI)	Heterogeneity P-value; I^2
Cardiac ablation vs. medical therapy						
Khan 2018 *Low*	Any AF (mean 19 months, range 6-60 months)	CA vs. MT with HF (3 RCTs)	96/314 (30.6%)	151/318 (47.5%)	RD -0.17 (-0.24, -0.10) P<0.001	NR
					RR 0.63 (0.46, 0.87) P=0.01	P=NR; I^2=43%
		CA vs. MT without HF (4 RCTs)	30/312 (9.6%)	100/317 (31.5%)	RD -0.28 (-0.55, -0.01) P=0.04	NR
					RR 0.32 (0.23, 0.45) P=0.001	P=NR; I^2=0%
Chen 2018 *Low*	Persistent AF (6-24 months)	CA vs. AAD (2 RCTs)	34/200 (17.0%)	61/149 (40.9%)	RR 0.54 (0.39, 0.74) P=0.0002	P=0.57; I^2=0%
AHRQ 2015 *Low*	Paroxysmal AF (12-24 months)	RFA vs. MT First-line (2 RCTs)	3/178 (1.7%)	21/183 (11.5%)	NR	NR

[17] After 3-month blanking period.
[18] Data are for repeat ablation for recurrent AF. Data are also reported for repeat ablation for any arrhythmia.

Study ID *Risk of bias*[a]	Population (follow up)	Analysis subgroup (no. studies)	Intervention n/N (%)	Comparator n/N (%)	Risk estimate (95% CI)	Heterogeneity P-value; I^2
	Persistent AF (12 months)	RFA vs. MT Second-line (2 RCTs)	2/98 (2.0%)	3/48 (6.3%)	NR	NR

Abbreviations: AF, atrial fibrillation; CA, cardiac ablation; CI, confidence interval; HF, heart failure; MT, medical therapy; NR, not reported; RD, risk difference; RFA, radiofrequency ablation; RCT, randomised control trial; RR, risk ratio.
a Risk of bias assessed using the AMSTAR 2. See **Appendix E** for further details.

Periprocedural and safety outcomes

Cardoso 2016 demonstrated an overall significantly lower incidence of pericardial effusions/tamponade with cryoablation compared with RF ablation. The authors postulated that this difference may be due to:

- more homogeneous, diffuse pressure applied by cryoablation technology, which may cause less tissue damage as compared to focal point-by-point pressure with RF ablation catheters;
- abbreviated procedural times with cryoablation, as prolonged duration has been recognised as a risk factor for the development of effusions in AF cardiac ablations;
- the need for single transseptal puncture with cryoablation in contrast to double transseptal puncture with irrigated RF.

Although the use of contact force-sensing RF ablation may mitigate pericardial effusions/tamponade by warning the operator when contact force is too high, there are insufficient data in *Cardoso 2016* to determine whether the incidence of pericardial effusions with contact force-sensing catheters has diminished so as to be comparable with cryoablation.

Table 13 Results from selected systematic reviews – Periprocedural and safety outcomes

Study ID *Risk of bias*[a]	Population (follow up)	Analysis subgroup (no. studies)	Intervention n/N (%)	Comparator n/N (%)	Risk estimate (95% CI)	Heterogeneity P-value; I^2
Cardiac ablation vs. medical therapy						
Pulmonary vein stenosis						
Khan 2018 *Low*	Any AF (mean 19 months, range 6-60 months)	CA vs. MT (6 RCTs)	7/574 (1.2%)	0/535 (0%)	RR 3.02 (0.83, 10.93) P=0.09	NR
AHRQ 2015[19] *Low*	Paroxysmal AF (12-24 months)	RFA vs. MT First-line (3 RCTs)	3/315 (1.0%)	NA	NA	NR
	Paroxysmal AF (1-12 months)	RFA vs. MT Second-line (2 RCTs)	1/229 (0.4%)	NA	NA	NR
	Mixed AF (12 months)	Cryoablation vs. MT (1 RCT)	7/228 (3.1%)	NA	NA	NR
	Persistent AF (6-12 months)	RFA vs. MT Second-line (2 RCTs)	1/137 (0.73%)	NA	NA	NR
	Paroxysmal AF (12 months)	RFA vs. MT (1 non-RCT)	0/85 (0%)	NA	NA	NA
	Persistent AF (1 month)	RFA vs. MT (1 non-RCT)	0/158 (0%)	NA	NA	NA
	Mixed AF (12 months)	RFA vs. MT (1 RCT)	0/137 (0%)	NA	NA	NA

[19] Not reported for the medical group as the outcome is assumed to be related to ablation.

Study ID *Risk of bias*[a]	Population (follow up)	Analysis subgroup (no. studies)	Intervention n/N (%)	Comparator n/N (%)	Risk estimate (95% CI)	Heterogeneity P-value; I^2
Pericardial complications						
Khan 2018 *Low*	Any AF (mean 19 months, range 6-60 months)	CA vs. MT (12 RCTs)	23/991 (2.3%)	1/899 (0.1%)	RR 3.71 (1.58, 8.73) P<0.001	I^2=0%
Pericardial effusion[19]						
AHRQ 2015 *Low*	Paroxysmal AF (24 months)	RFA vs. MT First line (1 RCT)	1/194 (0.5%)	NA	NA	NA
	Paroxysmal AF (periprocedural to 1 month)	RFA vs. MT Second-line (2 RCTs)	2/325 (0.6%)	NA	NA	NA
	Persistent AF (periprocedural)	RFA vs. MT (1 RCT)	1/116 (0.9%)	NA	NA	NA
	Mixed AF (periprocedural)	RFA vs. MT (1 RCT)	0/137 (0%)	NA	NA	NA
	Persistent AF (1 month)	RFA vs. MT Second-line (1 non-RCT)	3/158 (1.9%)	NA	NA	NA
Cardiac tamponade[19]						
AHRQ 2015 *Low*	Paroxysmal AF (24 months)	RFA vs. MT First-line (2 RCTs)	7/283 (2.5%)	NA	NA	NR
	Paroxysmal AF (1-12 months)	RFA vs. MT Second-line (2 RCTs)	2/229 (0.9%)	NA	NA	
	Persistent AF (periprocedural)	RFA vs. MT (3 RCTs)	4/73 (5.48%)	NA	NA	NR
	Mixed AF (12 months)	Cryoablation vs. MT (1 RCT)	2/228 (0.9%)	NA	NA	NR
	Paroxysmal AF (12 months)	RFA vs. MT Second-line (1 non-RCT)	0/85 (0%)	NA	NA	NA
	Persistent AF (1 month)	RFA vs. MT Second-line (1 non-RCT)	0/158 (0%)	NA	NA	NA
Major bleeding						
Khan 2018 *Low*	Any AF (mean 19 months, range 6-60 months)	CA vs. MT (7 RCTs)	15/405 (3.7%)	1/406 (0.2%)	RR 3.98 (1.31, 12.16) P=0.02	I^2=0%
AHRQ 2015[20] *Low*	Paroxysmal AF (1 month)	RFA vs. MT First-line (1 RCT)	2/32 (6.3%)	1/35 (1.9%)	NR	NA
	Mixed AF (1 month)	RFA vs. MT Second-line (1 RCT)	2/35 (5.7%)	2/35 (5.7%)	NR	NA
	Persistent AF (1 month)	RFA vs. MT Second-line (1 non-RCT)	2/153 (1.3%)	2/259 (0.8%)	NR	NA
	Mixed AF (12 months)	Cryoballoon vs. MT (1 RCT)	2/163 (1.2%)	2/82 (2.4%)	NR	NA

[20] Outcome refers to bleeding (major)/haemorrhage/transfusion.

Study ID *Risk of bias*[a]	Population (follow up)	Analysis subgroup (no. studies)	Intervention n/N (%)	Comparator n/N (%)	Risk estimate (95% CI)	Heterogeneity P-value; I^2
RF ablation vs. cryoablation						
Pulmonary vein stenosis						
AHRQ 2015 *Low*	Paroxysmal AF (periprocedural)	Cryoablation vs. RFA (2 non-RCTs)	0/1041 (0%)	0/3130 (0%)	NR	NR
	Mixed AF (periprocedural)	Cryoablation vs. RFA (1 non-RCT)	0/62 (0%)	0/62 (0%)	NR	NR
Pericardial effusion						
Cardoso 2016 *Low*	Any AF (12-40 months)	Cryoablation vs. RFA (3 RCTs, 10 non RCTs)	25/3113 (0.8%)	84/4004 (2.1%)	OR 0.44 (0.28, 0.69) P=0.0004	P=0.96; I^2=0%
	Any AF (12-40 months)	Cryoablation vs. RFA (RCTs only)	n/N NR (0.5%)	n/N NR (1.5%)	OR 0.37 (0.11, 1.26) P=0.11	NR
	Paroxysmal AF (12-40 months)	Cryoablation vs. RFA (11 studies, 5821 patients)	n/N NR (0.8%)	n/N NR (2.1%)	OR 0.45 (0.28, 0.75) P<0.01	NR
AHRQ 2015 *Low*	Paroxysmal AF (periprocedural)	Cryoablation vs. RFA (2 non-RCTs)	14/182 (7.7%)	38/347 (11.0%)	NR	NR
	Mixed AF (periprocedural)	Cryoablation vs. RFA (2 non-RCTs)	1/152 (0.7%)	3/115 (2.6%)	NR	NR
Pericardial tamponade						
Cardoso 2016 *Low*	Any AF (12-40 months)	Cryoablation vs. RFA (2 RCTS, 6 non-RCTs)	7/1922 (0.4%)	44/3198 (1.4%)	OR 0.31 (0.15, 0.64) P=0.002	P=1.00; I^2=0%
	Paroxysmal AF (12-40 months)	Cryoablation vs. RFA (7 studies, 5020 patients)	n/N NR (0.3%)	n/N NR (1.3%)	OR 0.30 (0.14, 0.65) P<0.01	NR
AHRQ 2015 *Low*	Paroxysmal AF (periprocedural)	Cryoablation vs. RFA (3 non-RCTs)	9/1087 (0.8%)	42/3217 (1.3%)	NR	NR
Major vascular complications						
Cardoso 2016 *Low*	Any AF (12-40 months)	Cryoablation vs. RFA (7 studies)	n/N NR (1.1%)	n/N NR (1.3%)	OR 0.79 (0.38, 1.62) P=0.52	NR
Major bleeding						
AHRQ 2015 *Low*	Paroxysmal AF (periprocedural)	Cryoablation vs. RFA (3 non-RCTs)	5/905 (0.6%)	30/2879 (1.1%)	NR	NR

Abbreviations: AF, atrial fibrillation; CA, cardiac ablation; CI, confidence interval; MT, medical therapy; NA, not applicable; NR, not reported; OR, odds ratio; RFA, radiofrequency ablation; RCT, randomised control trial; RR, risk ratio.
a Risk of bias assessed using the AMSTAR 2. See **Appendix E** for further details.

Potential moderator variables

Impact of patient age

There were no systematic reviews identified that focus on the effect of age on the effectiveness and safety of cardiac ablation versus medical therapy, or RF ablation versus cryoablation.

Barra 2018 includes primary studies with a mean age ranging from 49 to 76 years. A meta-regression was performed on age individually to assess its impact on the effectiveness of cardiac ablation over medical therapy. It was found that cardiac ablation has a larger benefit in the reduction of mortality and stroke for studies with a higher mean patient age: intercept = 4.69; slope = -0.09; P<0.001 (see **Appendix G**).

In contrast, all other relevant reviews reported that age had no significant effect on the outcomes of interest (*Buiatti 2017*; *Chen 2017*; *Chen 2017a*; *Hakalahti 2015*; *Zheng 2015*; *Xu 2014*). However, given the narrow age range of participants within the included primary studies (for example, the mean age across primary studies in *Buiatti 2017* ranged from 58 to 63 years), the lack of observed effect is unsurprising.

The *AHRQ 2015* HTA concluded that there were no studies that provide evidence as to how age modifies the effects of the interventions. However, the authors noted two poor quality observational studies that provide data specifically in populations over the age of 65 years. One found no statistical difference between cardiac ablation and medical therapy for mortality, myocardial infarction or major bleeding. The other study found a lower risk of mortality in the RF ablation group compared with medical therapy.

Impact of comorbidities

Barra 2018 performed individual assessments of potential moderator variables through meta-regression. In studies with a higher prevalence of diabetes mellitus, coronary artery and cerebrovascular disease, the benefit of cardiac ablation was less pronounced. In an RCT subgroup analysis measuring mortality, the pooled benefit of cardiac ablation was mostly attributed to two studies (AAATAC and CASTLE-AF trial). Both trials only enrolled patients with heart failure and left ventricular systolic dysfunction.

AHRQ 2015 identified no studies that report whether the presence of heart failure modified treatment effect; however, they identified three small fair-quality RCTs (total N=143) that evaluated the comparative efficacy and safety of RF ablation versus medical therapy in patients with heart failure and persistent AF. Due to inconsistency in these RCTs, and the lack of evidence comparing patients with heart failure to those without, the authors were unable to evaluate the impact of heart failure on the effectiveness of the interventions.

AHRQ 2015 identified one RCT in patients with diabetes that suggests a benefit of cardiac ablation over medical therapy; however, no studies evaluated the comparative benefit of the interventions in patients with and without diabetes.

First- versus second-generation devices

Cardoso 2016 assessed the impact of first- and second-generation catheter technology. Freedom of atrial tachyarrhythmia (AT) during follow up (termed 'success rate') for cryoballoon and RF ablations overall were 69.1% and 63.1% respectively. Success rates for second-generation cryoballoon and contact-force sensing RF ablations were higher: 78.1% (888/1137) and 78.2% (269/344) respectively. When only including studies using first-generation technology, the success rates for cryoballoon and RF ablations were lower, at 57.9% (601/1037) and 58.1% (1550/2667) respectively.

First- versus second-line therapy

The *AHRQ 2015* HTA explored the impact of patients being treated with cardiac ablation as first-line therapy (three RCTs) versus second-line therapy (i.e. failed previous medical therapy; eight RCTs). Overall, although data were insufficient to test for an interaction, results suggested that RF ablation was favored in terms of short-term freedom from recurrence regardless of whether patients were treated with first- versus second-line therapy.

Chen 2018 found that for patients with persistent AF, there was a significant benefit of cardiac ablation compared with medical therapy in terms of maintaining sinus rhythm irrespective of whether AADs were used after the ablation procedure; that is, the efficacy of cardiac ablation with or without medical therapy is superior to that of medical therapy alone. Based on these findings, the authors suggest that cardiac ablation may be considered as a first-line treatment for patients with persistent AF.

Operator experience

AHRQ 2015 was the only selected systematic review that sought to assess the impact of operator experience. No relevant primary studies were identified.

2.4 LIMITATIONS

2.4.1 Limitations of the review process

A limitation of this review is that the findings rely on the assessment and analysis of the evidence undertaken by other authors. The *AHRQ 2015* HTA noted that every attempt was made to assure that variables and outcomes were assessed and abstracted accurately; however, wide variability across studies (in the quality of reporting of study methods, in how outcomes were defined, and in which patients were included) has the potential for introducing inaccuracies.

Furthermore, although there was considerable overlap in the individual (primary) studies included in the selected reviews, the risk of bias (quality) of the primary studies was rated differently across the published reviews. For example, *AHRQ 2015* considered all but one RCT to be of insufficient, low or moderate quality, whereas the other systematic reviews considered the same RCTs to be low risk of bias.

Importantly, due to the pragmatic approach taken in this Rapid Review to identify and select evidence for inclusion, it is possible that some studies may have been omitted, and the nuances (in the technologies, ablation procedures and patient populations) are not explored in detail. Comparative evaluation of ablation techniques and approaches was beyond the scope of this review, as was an evaluation of mapping modalities and strategies.

2.4.2 Limitations of the evidence base

Published reviews were limited by the heterogeneity of the primary studies (particularly observational studies) in terms of study participants, comparative medical therapy, procedural techniques, outcome definitions, and follow-up durations. Other factors that are not well reported can also contribute to variability in results, such as operators' skills, adjunctive antiarrhythmic therapy, arrhythmia tracking methods, definitions of failure outcomes, and use of anticoagulation therapy.

Important limitations of the evidence base include the sample size of the available trials, limited data available on key clinical outcomes particularly at follow up times >12 months, and the substantial crossover from medical therapy to cardiac ablation in most trials, which may hinder drawing definitive conclusions regarding the full benefits and harms of cardiac ablation compared with medical therapy.

Study sizes were likely insufficient to effectively determine risk of several key clinical outcomes (e.g. mortality and stroke) and rare complications (e.g. pulmonary vein stenosis) for either group, or to detect statistical differences between treatment groups. Of note, more recent trials with larger sample sizes have focused on hard outcome assessment in patients with AF.[21]

Most studies focused on the intermediate outcome related to arrhythmia recurrence (or freedom from recurrence), which was variably defined across studies with variations in the type of arrhythmia (i.e. AF, AF or atrial flutter, or any atrial arrhythmia), whether study reports were limited to symptomatic or asymptomatic AF or not, and whether characteristics related to duration were considered. In addition, studies that specified a blanking period reported a range from one to three months.

Follow up duration in the studies typically ranged from 6 to 24 months, which may be too short to assess intermediate outcomes (including freedom from recurrence of arrythmia) and long-term outcomes such as all-cause mortality.

[21] The Catheter Ablation Versus Standard Conventional Treatment in Patients With Left Ventricular Dysfunction and Atrial Fibrillation (CASTLE-AF) trial reported in 2017. The Catheter Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) trial has not yet reported in a full text publication.

2.5 SUMMARY OF FINDINGS

2.5.1 Is there sufficient clinical evidence to demonstrate the superiority of cardiac ablation over treatment with anti-arrhythmic medication?

The key findings relating to the assessment of cardiac ablation compared with medical therapy are summarised in Table 14, taken from the best available evidence. Please note that as this is a rapid review, the strength of evidence is based on informal judgement rather than formal assessment.

There is low strength evidence that cardiac ablation is associated with lower risk of all-cause mortality compared with medical therapy; however, the benefit appears to be mainly driven by trials performed in patients with LV dysfunction and heart failure. No firm conclusions can be drawn regarding the effect of cardiac ablation on all-cause mortality in patients with paroxysmal or persistent AF (there is no statistical difference between treatments in these populations).

There is low strength evidence that cardiac ablation reduces the risk of stroke in patients with AF; however, this benefit was only seen in observational studies and is attributed to the inclusion of patients with heart failure. No differences between groups were seen for the outcome of stroke in RCTs, but cerebrovascular events were uncommon and the studies may have been insufficiently powered. Definitive conclusions cannot be drawn for the effect of cardiac ablation on risk of stroke in patients with paroxysmal or persistent AF.

Cardiac ablation is superior to medical therapy in improving freedom from recurrence of any atrial arrhythmia in patients with paroxysmal AF in the long-term (follow up to 48 months) and in patients with persistent AF in the short-term (follow up to 24 months). The strength of evidence for this outcome is moderate. However, repeat ablation was common, occurring in up to 54% of patients at 12 months (insufficient evidence due to large variability between studies). Re-hospitalisation for cardiac causes was significantly more common in the medical treatment group than in the ablation group.

Pulmonary vein stenosis developed in 0% to 3% of RF ablation patients as reported by RCTs, with no clear difference in this risk in paroxysmal versus persistent AF patients. Pulmonary vein stenosis was reported in 0 to 7.1 percent of patients across comparative observational studies, though definitive conclusions could not be made due to study limitations.

Pericardial effusion risk ranged from 0.5% to 4.5% as reported by RCTs and were less than 2% in observational studies.

Cardiac tamponade risk ranged from 0% to 9.5% following RF ablation. These overall ranges are from controlled studies conducted in tertiary referral centers with procedures performed by experienced personnel and may not reflect broader clinical practice outside of such centers. Although risk was higher in RCTs of persistent AF patients, small sample sizes may preclude accurate determination of risk.

There is low strength evidence that cardiac ablation significantly increases the risk of major bleeding compared with medical therapy; however, events are uncommon and no firm conclusions can be drawn regarding this risk in paroxysmal versus persistent AF patients.

Data for the comparison of cryoballoon ablation versus medical therapy or RF ablation was limited and therefore no definitive conclusions can be made.

In summary, there is moderate evidence that RF ablation is superior to medical therapy for enhancing patient freedom from recurrence of atrial arrhythmias in both the short and long term regardless of AF type, but re-ablation is common. Cardiac ablation has a beneficial impact on all-cause mortality in patients with AF; however, this benefit appears to be largely driven by the inclusion of patients with heart failure. Evidence from observational studies suggests that cardiac ablation may decrease risk of stroke compared with medical therapy, but this benefit is not seen in RCTs, which are likely underpowered for this outcome.

Evidence comparing cryoballoon ablation with medical therapy is insufficient to draw firm conclusions regarding efficacy or safety.

Table 14 Key findings and strength of evidence: cardiac ablation (CA) vs. medical therapy (MT)

Outcome	Population	No. of studies *[source]*[a]	Strength of evidence[b]	Conclusion
All-cause mortality	Any AF	10 RCT (NR) FU 6-53 months *[Barra 2018]*	Low	**Favours CA** 4.2% for CA vs. 8.9% for MT; P=0.001. Similar results when 8 OBS are included in analysis. Benefit is attributed to inclusion of HF patients.
	Paroxysmal AF	2 RCT (N=408) FU to 24 months *[AHRQ 2015]*	Low	**No difference** 0.97% for RFA vs. 2.0% for MT; P=NS. Similar results for RFA with FU to 12 months.
	Persistent AF	3 RCT (N=559) FU 6-24 months *[Chen 2018]*	Low	**No difference** 2.7% for CA vs. 8.1% for MT; P=0.05.
Stroke	Any AF	7 RCT, 10 OBS (NR) FU 6-53 months *[Barra 2018]*	Low	**Favours CA** 2.3% for CA vs. 5.5% for MT; P<0.001. No significant difference when OBS are excluded. Benefit is attributed to inclusion of HF patients.
	Paroxysmal AF	2 RCT (N=194) FU 12-24 months *[AHRQ 2015]*	Insufficient	**No difference** 0% for RFA vs. 0% for MT; P=NS. Definitive conclusions are not possible.
	Persistent AF	1 RCT (N=146) FU 12 months *[AHRQ 2015]*	Insufficient	**No difference** 0% for RFA vs. 0% for MT; P=NS. Definitive conclusions are not possible.
Arrythmia recurrence	Any AF	11 RCT (N=1481) FU mean 19 months *[Khan 2018]*	Moderate	**Favours CA** 27.0% for CA vs. 63.8% for MT; P<0.001. Similar results for 6 RCTs of HF patients.
Freedom from arrythmia recurrence	Paroxysmal AF	3 RCT (N=619) FU 24-48 months *[AHRQ 2015]*	Moderate	**Favours CA** 72.6% for RFA vs. 57.8% for MT; P<0.05. Similar results for 4 RCTs with FU to 12 months.
	Persistent AF	3 RCT (N=559) FU 6-24 months *[Chen 2018]*	Moderate	**Favours CA** 61.2% for CA vs. 30.3% for MT; P<0.00001. Similar results for patients without AADs after CA.
Repeat ablation	Any AF	8 RCT (N=430) FU 6-12 months *[AHRQ 2015]*	Insufficient	Ranges from 0 – 53% after RFA. Definitive conclusions are not possible.
	Paroxysmal AF	4 RCT (N=337) FU 12-48 months *[AHRQ 2015]*	Insufficient	Ranges from 12.5 – 49.2% after RFA. Definitive conclusions are not possible.
	Persistent AF	5 RCT (N=246) FU 6-12 months *[AHRQ 2015]*	Insufficient	Ranges from 8.1 – 53.8% after RFA. Definitive conclusions are not possible.
Cardiac hospitalisation/ re-admission	Any AF	4 RCT (N=629) FU mean 19 months *[Khan 2018]*	Low	**Favours CA** 9.6% for CA vs. 31.5% for MT; P=0.001. Similar results (P=0.01) for 3 RCTs of HF patients.
	Paroxysmal AF	2 RCT (N=361) FU 12-24 months *[AHRQ 2015]*	Insufficient	**Favours CA** 17.0% for CA vs. 40.9% for MT; P=NR. Definitive conclusions are not possible.
	Persistent AF	2 RCT (N=349) FU 6-24 months *[Chen 2018]*	Insufficient	**Favours CA** 1.7% for RFA vs. 11.5% for MT; P=0.0002. Definitive conclusions are not possible.
Pulmonary vein stenosis	Any AF	6 RCT (N=1109) FU mean 19 months *[Khan 2018]*	Low	**No difference** 1.2% for RFA vs. 0% for MT; P=0.09. Events are uncommon.

Outcome	Population	No. of studies *[source]*[a]	Strength of evidence[b]	Conclusion
	Paroxysmal AF	5 RCT (N=544) FU 1-24 months *[AHRQ 2015]*	Insufficient	0.7% for RFA. Definitive conclusions are not possible. Events are uncommon.
	Persistent AF	2 RCT, 1 OBS (N=295) FU 1-12 months *[AHRQ 2015]*	Insufficient	0.3% for RFA. Definitive conclusions are not possible. Events are uncommon.
Pericardial effusion	Any AF	5 RCT, 1 OBS (N=930) FU 1 month *[AHRQ 2015]*	Insufficient	0.8% for RFA. Definitive conclusions are not possible. Events are uncommon.
	Paroxysmal AF	3 RCT (N=519) FU 1 month *[AHRQ 2015]*	Insufficient	0.6% for RFA. Definitive conclusions are not possible. Events are uncommon.
	Persistent AF	1 RCT, 1 OBS (N=274) FU 1 month *[AHRQ 2015]*	Insufficient	1.5% for RFA. Definitive conclusions are not possible. Events are uncommon.
Cardiac tamponade	Any AF	8 RCT, 2 OBS (N=1056) FU 1-24 months *[AHRQ 2015]*	Insufficient	1.4% for CA. Definitive conclusions are not possible. Events are uncommon.
	Paroxysmal AF	4 RCT, 1 OBS (N=597) FU 1-24 months *[AHRQ 2015]*	Insufficient	1.5% for RFA. Definitive conclusions are not possible. Events are uncommon.
	Persistent AF	3 RCT, 1 OBS (N=231) FU 1 months *[AHRQ 2015]*	Insufficient	1.7% for RFA. Definitive conclusions are not possible. Events are uncommon.
Major bleeding	Any AF	7 RCT (N=811) FU mean 19 months *[Khan 2018]*	Low	**Favours MT** 3.7% for CA vs. 0.2% for MT; P=0.02
	Paroxysmal AF	1 RCT (N=67) FU 1 month *[AHRQ 2015]*	Insufficient	6.3% for RFA vs. 1.9% for MT; P=NR. Definitive conclusions are not possible. Events are uncommon.
	Persistent AF	1 OBS (N=412) FU 1 month *[AHRQ 2015]*	Insufficient	1.3% for RFA vs. 0.8% for MT; P=NR. Definitive conclusions are not possible. Events are uncommon.

Abbreviations: AAD, antiarrhythmic drug; AF, atrial fibrillation; CA, cardiac ablation; CBA, cryoballoon ablation; FU, follow up; HF, heart failure; MT, medical therapy; NR, not reported; NS, not statistically significant; OBS, observational study; RCT, randomised controlled trial; RFA, radiofrequency ablation.

a Refers to the published review that provides the best evidence.

b Strength of evidence has been judged informally by the authors of the Rapid Review.

Of note, initial results from a landmark RCT conducted in 10 countries were recently reported in a conference presentation but are yet to be formally published.[22] The *Catheter ABlation vs ANtiarrhythmic Drug Therapy in Atrial Fibrillation* (CABANA) trial randomised 2,204 patients with AF (all types) to cardiac ablation or medical therapy (rate or rhythm control and anti-coagulation). Clinicians could use their preferred ablation catheter and procedural approach. Follow up was five years. Based on intention-to-treat (ITT) analyses, there was no significant difference between the two arms in the primary endpoint of the trial (the composite of all-cause mortality, disabling stroke, serious bleeding, or cardiac arrest), which occurred in 9.2% of patients in the drug group and 8% of patients in the ablation group (hazard ratio [HR] 0.86; 95% CI 0.65, 1.15; P=0.30). There were also no significant differences in the individual components of the primary endpoint. One secondary outcome, the rate of death or cardiovascular hospitalisation, was significantly reduced from 58.1% to 51.7% (HR 0.83; 95% CI 0.74, 0.93; P=0.001). As expected, ablation was

[22] Available at Cabana trial Accessed 11 October 2018.

also associated with a significant reduction in recurrence of AF (HR 0.53; 95% CI 0.46, 0.61; P<0.0001). No safety concerns emerged in the trial.

The CABANA trial is only single-blinded (not to intervention received) and high crossover rates were noted, which can confound assessment of the various endpoints. Based on recent experiences from important sham-controlled trials (e.g. the SIMPLICITY trial of renal denervation for uncontrolled hypertension), these findings have prompted calls for a sham-controlled trial to assess the true efficacy of cardiac ablation in modulating cardiovascular outcomes among patients with AF.

2.5.2 Is there sufficient clinical evidence to demonstrate the superiority of one cardiac ablation technique over another?

The key findings relating to the assessment of RF ablation compared with cryoablation are summarised in Table 15, taken from the best available evidence. Please note that as this is a rapid review, the strength of evidence is based on informal judgement rather than formal assessment.

The best evidence for the comparative efficacy/effectiveness and safety of RF ablation (specifically irrigated RF ablation) compared with cryoballoon ablation is from *Cardoso 2016*, which included 22 studies (5 randomised and 17 non-randomised) and over 8,500 patients. The main findings were:

- there was no significant difference between groups with regards to freedom from AT in a follow up of at least 12 months;
- post-procedural phrenic nerve palsy was significantly more common in the cryoballoon group, although the overwhelming majority resolved within 1 year (data not shown in this report);
- the incidence of pericardial effusion and cardiac tamponade was higher with RF ablations; and
- non-AF AT during follow-up were less frequent in the cryoballoon group.

Cardoso 2016 found that the success rate of ablation procedures in terms of freedom from AT was much lower in studies restricted to first-generation cryoablation (7 studies, 601/1,037 patients, 57.9%) and non-contact force sensing RF ablation (8 studies, 1,550/2,667 patients, 58.1%). Although increased operator experience may also have contributed to improved results, advances in both cryoablation technology (second-generation cryoablation, 78.1% freedom from AT) and RF ablations (contact force-sensing RF, 78.2% freedom from AT) have been associated with increased procedural success rates.

Table 15 Key findings and strength of evidence: RF ablation vs. cryoablation

Outcome	Population	No. of studies *[source]*[a]	Strength of evidence[b]	Conclusion
All-cause mortality	Any AF	0 studies	-	-
	Paroxysmal AF	1 OBS (N=396) FU mean 23 months *[AHRQ 2015]*	Insufficient	**No difference** 1.2% for CBA vs. 0% for RFA. Definitive conclusions are not possible.
	Persistent AF	0 studies	-	-
Stroke	Any AF	NR (N= 4058) FU ≥12 months *[Cardoso 2016]*	Low	**No difference** 0.2% for CBA vs. 0.3% for RFA; P=0.63.
	Paroxysmal AF	0 studies	-	-
	Persistent AF	0 studies	-	-
Arrythmia recurrence	Any AF	5 RCT (N=1306) FU 12-40 months *[Cardoso 2016]*	Moderate	**No difference** 62.4% for CBA vs. 61.1% for RFA; P=0.99. Similar results when 14 OBS are included in analysis.
	Paroxysmal AF	NR (N=6055) FU 12-40 months *[Cardoso 2016]*	Moderate	**No difference** 66.3% for CBA vs. 62.1% for RFA; P=0.28.

Outcome	Population	No. of studies *[source]*[a]	Strength of evidence[b]	Conclusion
	Persistent AF	0 studies	-	-
Repeat ablation	Any AF	5 RCT (N=1306) FU 12-40 months *[Cardoso 2016]*	Moderate	**No difference** 10.2% for CBA vs. 9.0% for RFA; P=0.61. Similar results when OBS are included in analysis.
	Paroxysmal AF	1 RCT (N=50) FU 12 months *[AHRQ 2015]*	Insufficient	**Favours RFA** 24.0% for CBA vs. 0% for RFA; P=0.01. Definitive conclusions are not possible.
	Persistent AF	0 studies	-	-
Cardiac hospitalisation/ re-admission	Any AF	0 studies	-	-
	Paroxysmal AF	0 studies	-	-
	Persistent AF	0 studies	-	-
Pericardial effusion	Any AF	3 RCT, 10 OBS (N=7117) *[Cardoso 2016]*	Low	**Favours CBA** 0.8% for CBA vs. 2.1% for RFA; P<0.001. No significant difference when OBS are excluded from analysis.
	Paroxysmal AF	11 studies (N=5821) *[Cardoso 2016]*	Low	**Favours CBA** 0.8% for CBA vs. 2.1% for RFA; P<0.01.
	Persistent AF	0 studies	-	-
Pericardial tamponade	Any AF	2 RCT, 6 OBS (N=5120) *[Cardoso 2016]*	Low	**Favours CBA** 0.4% for CBA vs. 1.4% for RFA; P=0.002.
	Paroxysmal AF	7 studies (N=5020) *[Cardoso 2016]*	Low	**Favours CBA** 0.3% for CBA vs. 1.3% for RFA; P<0.01.
	Persistent AF	0 studies	-	-
Pulmonary vein stenosis	Any AF	3 OBS (N=4295) *[AHRQ 2015]*	Low	**No difference** 0% for CBA vs. 0% for RFA.
	Paroxysmal AF	2 OBS (N=4171) *[AHRQ 2015]*	Low	**No difference** 0% for CBA vs. 0% for RFA.
	Persistent AF	0 studies	-	-
Major vascular complications	Any AF	7 studies (NR) *[Cardoso 2016]*	Low	**No difference** 1.1% for CBA vs. 1.3% for RFA; P=0.52.
	Paroxysmal AF	0 studies	-	-
	Persistent AF	0 studies	-	-

Abbreviations: AF, atrial fibrillation; CBA, cryoballoon ablation; FU, follow up; NR, not reported; OBS, observational study; RCT, randomised controlled trial; RF, radiofrequency; RFA, radiofrequency ablation.
a Refers to the published review that provides the best evidence.
b Strength of evidence has been judged informally by the authors of the Rapid Review.

2.5.3 What are the gaps?

The gaps identified below should be considered in light of the pragmatic approach used to identify and select evidence in this Rapid Review. It is possible that the gaps reflect a limitation of the methodology and reliance on published secondary evidence, rather than representing a true research gap.

There are limited data on the impact of RF ablation compared with medical therapy on final clinical outcomes such as risk of mortality and stroke, particularly in the long term.

Data were sparse for the comparison of cryoballoon ablation versus medical therapy for all efficacy outcomes, and were also limited for the comparison of cryoballoon ablation with RF ablation for risk of mortality and stroke.

Comparative data on rare harms were limited by study sample sizes and/or study quality particularly in those with persistent AF. This was true for the comparisons of RF ablation versus medical therapy as well as for the comparisons of cryoballoon ablation with medical therapy or RF ablation.

Available RCTs did not have sufficient power to evaluate differential efficacy or harm of cardiac ablation (RF ablation or cryoballoon ablation) verses medical therapy or for comparison of cryoballoon ablation with RF ablation for specific patient subgroups or provider settings. Based on the evidence available, no firm conclusions can be drawn regarding which patients may benefit most, or which patients may not benefit from cardiac ablation.

Limited data are available on the use of RF ablation as the first treatment of choice (first-line therapy) versus a second-line therapy following failure of antiarrhythmic medications. No data for cryoablation were available to evaluate its use as first versus second-line therapy.

2.5.4 Are the clinical outcomes different in different age groups?

No systematic reviews were identified that focus on the effect of age on clinical outcomes for cardiac ablation. The *AHRQ 2015* HTA concluded that there were no studies that provide evidence as to how age modifies the effects of the interventions. However, the authors noted two poor quality observational studies that provide data specifically in populations over the age of 65 years. One found no statistical difference in mortality risk between cardiac ablation and medical therapy, whereas the other found a lower mortality risk in the ablation group.

One systematic review (*Barra 2018*) performed a meta-regression to assess the individual impact of moderator variables on the effectiveness of cardiac ablation. The analysis showed that for studies with a higher mean patient age, cardiac ablation had a more pronounced benefit in the reduction of all-cause mortality and stroke (see **Appendix G**). In contrast, all other systematic reviews that analysed potential sources of heterogeneity by meta-regression found that age was not a contributory confounder. Given that many of these reviews included studies with participants in a narrow age range, it is unlikely that a significant effect would be found.

3 References

Barra, S, Baran, J, Narayanan, K, Boveda, S, Fynn, S, Heck, P, Grace, A, Agarwal, S, Primo, J, Marijon, E, Providência, R. (2018). Association of catheter ablation for atrial fibrillation with mortality and stroke: A systematic review and meta-analysis. International Journal of Cardiology. 266(1):136-142.

Buiatti, A, Von Olshausen, G, Barthel, P, Schneider, S, Luik, A, Kaess, B, Laugwitz, K, Hoppmann, P. (2017). Cryoballoon vs. radiofrequency ablation for paroxysmal atrial fibrillation: an updated meta-analysis of randomized and observational studies. Europace. 19(3):378-384.

Cardoso, R, Mendirichaga, R, Fernandes, G, Healy, C, Lambrakos, L, Viles-Gonzalez, J, Goldberger, J, Mitrani, R. (2016). Cryoballoon versus radiofrequency catheter ablation in atrial fibrillation: a meta-analysis. Journal of Cardiovascular Electrophysiology. 27(10):1151-1159.

Chatterjee, N, Upadhyay, G, Ellenbogen, K, McAlister, F, Choudhry, N, Singh, J. (2012). Atrioventricular nodal ablation in atrial fibrillation: a meta-analysis and systematic review. Circulation: Arrhythmia and electrophysiology. 5(1):68-76.

Chen, C, Gao, X, Duan, X, Chen, B, Liu, X, Xu, Y. (2017). Comparison of catheter ablation for paroxysmal atrial fibrillation between cryoballoon and radiofrequency: a meta-analysis. Journal of Interventional Cardiac Electrophysiology. 48(3):1-16.

Chen, C, Zhou, X, Zhu, M, Chen, S, Chen, J, Cai, H, Dai, J, Xu, X, Mao, W. (2018). Catheter ablation versus medical therapy for patients with persistent atrial fibrillation: a systematic review and meta-analysis of evidence from randomized controlled trials. Journal of Interventional Cardiac Electrophysiology. 52(1):9

Chen, H, Wen, J, Wu, S, Liu, J. (2012). Catheter ablation for paroxysmal and persistent atrial fibrillation. Cochrane Database of Systematic Reviews.4(4): CD007101.

Chen, Y, Lu, Z, Xiang, Y, Hou, J, Wang, Q, Lin, H, Li, Y. (2017). Cryoablation vs. radiofrequency ablation for treatment of paroxysmal atrial fibrillation:

Cheng, X, Hu, Q, Zhou, C, Liu, L, Chen, T, Liu, Z, Tang, X. (2015). The long-term efficacy of cryoballoon vs irrigated radiofrequency ablation for the treatment of atrial fibrillation: a meta-analysis. International Journal of Cardiology. 181(C):297-302.

Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, Gillum RF, Kim YH, McAnulty JH, Zheng ZJ, Forouzanfar MH, Naghavi M, Mensah GA, Ezzati M, Murray CJ (2014) Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. Circulation. 129: 837-847.

Garg, J, Chaudhary, R, Palaniswamy, C, Shah, N, Krishnamoorthy, P, Bozorgnia, B, Natale, A. (2016). Cryoballoon versus radiofrequency ablation for atrial fibrillation: a meta-analysis of 16 clinical trials. Journal of Atrial Fibrillation. 9(3):1429-14

Hakalahti, A, Biancari, F, Nielsen, J, Raatikainen, M. (2015). Radiofrequency ablation vs. antiarrhythmic drug therapy as first line treatment of symptomatic atrial fibrillation: systematic review and meta-analysis. Europace. 17(3):370-378.

Hashimoto, R, Raich, A, Junge, M, Skelly, A. (2013). Catheter ablation procedures for supraventricular tachyarrhythmia (SVTA) including atrial flutter and atrial fibrillation. Washington State Health Care Authority Health Technology Assessments.

Jiang, J, Li, J, Zhong, G, Jiang, J. (2017). Efficacy and safety of the second-generation cryoballoons versus radiofrequency ablation for the treatment of paroxysmal atrial fibrillation: a systematic review and meta-

analysis. Journal of Interventional Cardiac Electrophysiology. 48(1):1-11. a systematic review and meta-analysis. Europace Electrophysiology. 19(5):784-794.

Kabunga, P, Phan, K, Ha, H, Sy, R. (2016). Meta-analysis of contemporary atrial fibrillation ablation strategies: irrigated radiofrequency versus duty-cycled phased radiofrequency versus cryoballoon ablation. JACC: Clinical Electrophysiology. 2(3):377-39038.

Khan, A, Khan, S, Sheikh, M, Khuder, S, Grubb, B, Moukarbel, G. Catheter ablation and antiarrhythmic drug therapy as first- or second-line therapy in the management of atrial fibrillation: systematic review and meta-analysis. Circulation. Arrhythmia and electrophysiology. 7(5):853-860.

Khan, S, Rahman, H, Talluri, S, Kaluski, E. (2018). The clinical benefits and mortality reduction associated with catheter ablation in subjects with atrial fibrillation: a systematic review and meta-analysis. JACC: Clinical electrophysiology. 4(5):626-635.

Liu, X, Chen, C, Gao, X, Xu, Y. (2016). Safety and efficacy of different catheter ablations for atrial fibrillation: a systematic review and meta-analysis. Pacing and Clinical Electrophysiology. 39(8):883-899.

Ma, H, Sun, D, Luan, H, Feng, W, Zhou, Y, Wu, J, He, C, Sun, C. (2017). Efficacy and safety of cryoballoon ablation versus radiofrequency catheter ablation in atrial fibrillation: an updated meta-analysis. Postepy w Kardiologii Interwencyjnej. 13(3):240-249.

Nyong, J, Amit, G, Adler, A, Owolabi, O, Perel, P, Prieto-Merino, D, Lambiase, P, Casas, J, Morillo, C. (2016). Efficacy and safety of ablation for people with non-paroxysmal atrial fibrillation. Cochrane Database of Systematic Reviews. 1(11): CD012088.

Parkash, R, Tang, A, Sapp, J, Wells, G. Approach to catheter ablation techniqur of paroxysmal and persistent atrial fibrillation: a meta-analysis of the randomised controlled trials. Electrophysiology. 22(1):729-738.

Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA (2017). AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 358:j4008.

Shi, L, Heng, R, Liu, S, Leng, F. Effect of catheter ablation versus antiarrhythmic drugs on atrial fibrillation: A meta-analysis of randomized controlled trials. Experimental and Therapeutic Medicine. 10(2):816-822.

Skelly, A, Hashimoto, R, Al-Khatib, S, Sanders-Schmidler, G, Fu, R, Brodt, E, McDonagh, M. (2015). Catheter Ablation for Treatment of Atrial Fibrillation. Technology Assessment. AHRQ Publication. Rockville, MD: Agency for Healthcare Research and Quality.

Van Brabandt, H, Neyt, M, Devos, C. (2012) Catheter ablation of atrial fibrillation. KCR report. Brussels. Belgian Health Care Knowledge Centre.

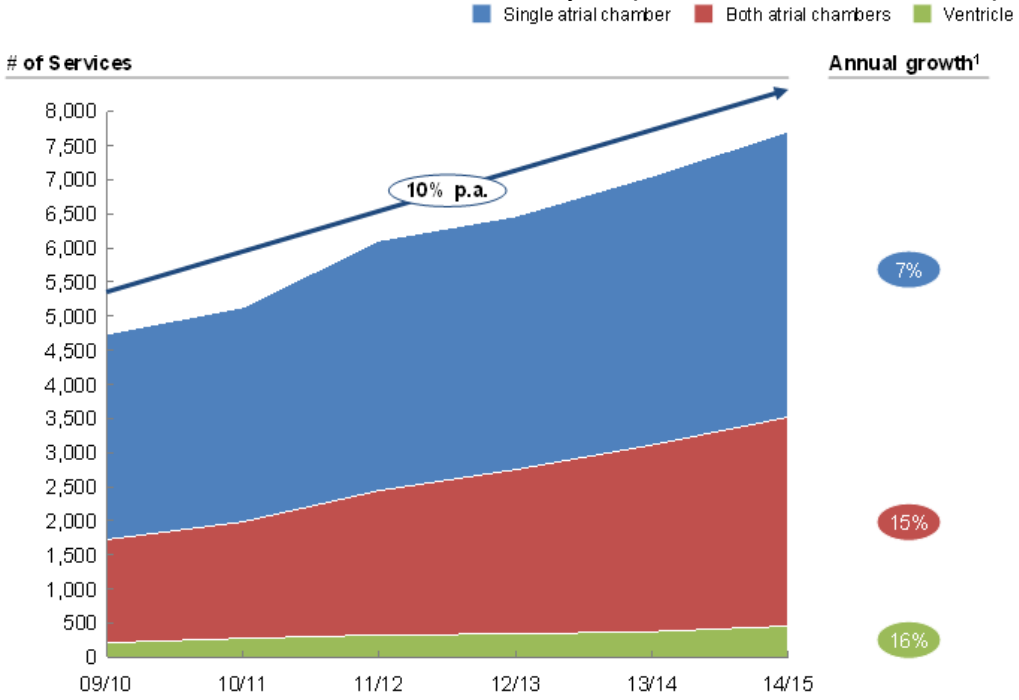
Wynn, G, Das, M, Bonnett, L, Panikker, S, Wong, T, Gupta, D. (2014). Efficacy of catheter ablation for persistent atrial fibrillation: a systematic review and meta-analysis of evidence from randomized and nonrandomized controlled trials. Circulation. Arrhythmia and Electrophysiology. 7(5):841-852.

Xu, J, Huang, Y, Cai, H, Qi, Y, Jia, N, Shen, W, Lin, J, Peng, F, Niu, W. (2014). Is cryoballoon ablation preferable to radiofrequency ablation for treatment of atrial fibrillation by pulmonary vein isolation? A meta-analysis. PloS One. 9(2):e90323.

Zheng, Y, Chen, Z, Ye, L, Wang, L. (2015). Long-term stroke rates after catheter ablation or antiarrhythmic drug therapy for atrial fibrillation: a meta-analysis of randomized trials. Journal of Geriatric Cardiology. 12(5):507-514.

Appendix A MBS INFORMATION

Figure 1 Growth of cardiac ablation services over five years (MBS items 38287, 38290, 38293)



Source: Medicare Benefits Schedule Review Taskforce. Report from the Cardiac Services Clinical Committee, 2017. Data is by date of service. Unpublished data from 2009-15 using claims processed between 1 July 2014 – 30 April 2016 (Department of Health). Single atrial chamber – Item 38287; both atrial chambers – Item 38290; ventricle – Item 38293.

[1] Compound annual growth over 5 years.

Appendix B LITERATURE SEARCH STRATEGY

Table App 1 Databases and search strings

Database	Search date	Search string	Records screened
Epistemonikos epistemonikos	26 Sept 2018	(atrial arrhythmi* OR atrial fibrillat*) AND ((catheter AND (ablation OR isolation)) OR (cardiac AND ablation) OR cryoablation) *Filters:* Publication year – 2012 to 2018 Publication type – Systematic Review	240
HTA Database – University of York Centre for Reviews and Dissemination University of York	26 Sept 2018	(atrial arrhythmi* OR atrial fibrillat*) AND (cardiac ablation OR catheter ablation OR catheter isolation OR cryoablation) *Filters:* Publication year – 2012 to 2018	11
NHS Evidence NICE	26 Sept 2018	cardiac ablation OR catheter ablation OR catheter isolation OR cryoablation *Filters:* Health Technology Assessments	59

Abbreviations: HTA, Health Technology Assessment; NHS, National Health Service.

Appendix C EVIDENCE MATRICES

The tables below list the primary studies (in reverse chronological order) included within the systematic reviews and HTAs that met the inclusion/exclusion criteria for the Rapid Review.

C.1 Cardiac ablation versus medical therapy

Table App 2 Studies included in eligible systematic reviews and HTAs of cardiac ablation vs. medical therapy

Item	Khan 2018	Barra 2018	Chen 2018	Nyong 2016	Skelly 2015	Wynn 2014	Zheng 2015	Hakalahti 2015	Shi 2015	Khan 2014	Hashimoto 2013	Chatterjee 2012	Van Brabandt 2012	Parkash 2012	Chen 2012
Study design	SR	SR	SR	SR Cochrane	HTA AHRQ	SR	SR	SR	SR	SR	HTA WSHCA	SR	HTA KCE	SR	SR Cochrane
Search date	Feb 2018	Aug 2017	Oct 2017	Apr 2016	Nov 2014	Oct 2013	Dec 2014	Aug 2014	May 2014	Mar 2014	Sep 2012	Jun 2011	2011	Jul 2010	Aug 2009
Population	AF[23]	AF	Persistent AF	Persistent AF	Non-paroxysmal & paroxysmal AF	Persistent AF	AF	Symptomatic AF	AF	AF	Non-paroxysmal & paroxysmal AF	AF with right ventricular pacing	AF	Paroxysmal & persistent AF	Paroxysmal & persistent AF
Intervention	CA	CA	CA	RFCA	RFCA & CBA	CA	CA	First line RFCA	CA	RFCA	CA	RFCA	CA	RFCA	CA
Comparator	Medical therapy	Medical therapy	Medical rhythm & rate control	AAD	Medical therapy	Medical therapy	AAD	AAD	AAD	AAD	Medical therapy[24]	Medical therapy	Medical therapy	AAD & rate control therapy[24]	Medical therapy
Included studies	*RCT*	*RCT & non-RCT*	*RCT*	*RCT*	*RCT & non-RCT*	*RCT & non-RCT*	*RCT*	*RCT*	*RCT*	*RCT*	*RCT & non-RCT*	*RCT & non-RCT*	*RCT*	*RCT*	*RCT*
RCTS															
CAMERA-MRI 2017	✓	✓	✓												
CASTLE AF 2017	✓	✓													
AATAC (Di biase) 2016	✓	✓	✓												
RAAFT2 (Morillo) 2016	✓							✓							
CAMTAF 2014	✓	✓	✓		✓										
Hummel 2014		✓	✓			✓	✓								
SARA (Mont) 2014	✓	✓	✓	✓	✓	✓	✓			✓					

[23] Although not analysed separately, the type of AF (paroxysmal or non-paroxysmal) has been recorded and evidence has been presented in support of keeping the population together; *'Current published reports note variable efficacy of CA for different types of AF. This heterogeneity in success rates probably reflects operators' skills, procedural techniques, adjunctive antiarrhythmic therapy, arrhythmia tracking methods, and definitions of failure outcomes. Similarly, former meta-analyses advocating CA for persistent AF alone used as their basis studies comprising >80% of patients with persistent AF (17,18,20,50). Conversely, our report included 44% of patients with paroxysmal AF and 56% with persistent AF.'*

[24] Review included many different comparators. The studies shown in the table refer to the comparison with medical therapy only.

Item		Khan 2018	Barra 2018	Chen 2018	Nyong 2016	Skelly 2015	Wynn 2014	Zheng 2015	Hakalahti 2015	Shi 2015	Khan 2014	Hashimoto 2013	Chatterjee 2012	Van Brabandt 2012	Parkash 2012	Chen 2012
RAAFT2 (Morillo)	2014		✓			✓		✓		✓	✓					
Blandino	2013									✓						
Jones	2013	✓	✓	✓		✓										
STOP AF (Packer)	2013		✓			✓		✓								
MANTRA-PAF (Nielsen)	2012	✓	✓			✓		✓	✓	✓	✓					
Brignole	2011												✓			
MacDonald	2011		✓	✓		✓						✓		✓		
Pappone	2011		✓			✓		✓		✓		✓				
McDonald	2010	✓														
Reynolds	2010											✓				
Wilber	2010	✓	✓			✓		✓		✓	✓	✓		✓	✓	
Disenhofer	2009															✓
Forleo	2009	✓	✓		✓	✓		✓		✓	✓			✓	✓	✓
Oral	2009															✓
Pontoppidan	2009															✓
Rajappan	2009															✓
Dixit	2008															✓
A4 study (Jais)	2008	✓	✓			✓		✓		✓	✓			✓	✓	✓
Khan	2008														✓	
Wang	2008															✓
Arentz	2007															✓
Marrouche	2007															✓
Verma	2007															✓
Zhang	2007															✓
APAF (Pappone)	2006	✓				✓					✓	✓		✓	✓	✓
Calo	2006															✓
Liu	2006															✓
Liu02	2006															✓
Nilsson	2006															✓
Oral	2006	✓	✓			✓	✓	✓		✓	✓	✓		✓	✓	✓
Sheikh	2006															✓
Stabile	2006	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓		✓	✓	✓
Victor	2006												✓			
Willems	2006															✓
Brignole	2005												✓			
Doshi	2005												✓			
Fassini	2005															✓
Hocini	2005															✓

Item		Khan 2018	Barra 2018	Chen 2018	Nyong 2016	Skelly 2015	Wynn 2014	Zheng 2015	Hakalahti 2015	Shi 2015	Khan 2014	Hashimoto 2013	Chatterjee 2012	Van Brabandt 2012	Parkash 2012	Chen 2012
Karch	2005															✓
RAAFT-1 (Wazni)	2005	✓	✓			✓		✓	✓	✓	✓			✓	✓	✓
Haissaguerre	2004															✓
Katritsis	2004															✓
Oral	2004															✓
Pappone	2004															✓
Krittayaphong	2003	✓	✓					✓		✓	✓			✓	✓	✓
Oral	2003															✓
Wazni	2003											✓				✓
Weerasooryia	2003												✓			
Brignole	2002												✓			
Brignole	1998												✓			
Lee	1998												✓			
Brignole	1997												✓			
Brignole	1994												✓			
Menozzi	1994												✓			
Morady	1993												✓			
Observational																
Saliba	2017		✓													
Friberg	2016		✓													
Noseworthy	2015		✓													
Chang	2014		✓													
Blandino	2013		✓			✓										
Lin	2013		✓													
Sang	2013					✓										
Reynolds	2012		✓			✓										
Yu	2012					✓										
Bunch	2011		✓													
Hunter	2011		✓													
Choi	2010		✓													
Lan	2009					✓	✓									
Poci	2009												✓			
Sonne	2009					✓	✓						✓			
Rozillo	2008					✓	✓									
Tan	2008												✓			
Tops	2008												✓			
Occhetta	2007												✓			
Hsieh	2005												✓			
Petrac	2005												✓			
Szili-Torok	2005												✓			
Ozcan	2003												✓			

Item		Khan 2018	Barra 2018	Chen 2018	Nyong 2016	Skelly 2015	Wynn 2014	Zheng 2015	Hakalahti 2015	Shi 2015	Khan 2014	Hashimoto 2013	Chatterjee 2012	Van Brabandt 2012	Parkash 2012	Chen 2012
Pappone	2003		✓													
Takahashi	2003						✓						✓			
Nowinski	2002												✓			
Ozcan	2002												✓			
Yeung-lai Wah	2002												✓			
Ozcan	2001												✓			
Ueng	2001												✓			
Abe	2000												✓			
Gasparini	2000												✓			
Marshall	1999												✓			
Natale	1999												✓			
Proclemer	1999												✓			
Kay	1998												✓			
Manolis	1998												✓			
Twidale	1998												✓			
Buys	1997												✓			
Conti	1997												✓			
Darpo	1997												✓			
Geelen	1997												✓			
Fitzpatrick	1996												✓			
Piot	1996												✓			
Edner	1995												✓			
Jensen	1995												✓			
Souza	1992												✓			

Abbreviations: AAD, antiarrhythmic drug; AF, atrial fibrillation; AHRQ, Agency for Healthcare Research and Quality; CA, cardiac ablation; CBA, cryoballoon ablation; HTA, health technology assessment; SR, systematic review; RCT, randomised control trial; RFCA, radiofrequency cardiac ablation; WSHCA, Washington State Health Care Authority

C.2 Radiofrequency ablation versus cryoablation

Table App 3 Studies included in eligible systematic reviews and HTAs of RF ablation vs. cryoablation

Item		Ma 2017	Chen 2017	Chen 2017a	Jiang 2017	Buiatti 2017	Garg 2016	Cardoso 2016	Liu 2016	Kabunga 2016	Skelly 2015	Cheng 2015	Xu 2014	Hashimoto 2013
Study design		SR	SR	SR	SR	SR	SR	SR	SR	SR	HTA (AHRQ)	SR	SR	HTA (WSHCA)
Search date		Dec 2016	Sep 2016	Jul 2016	May 2016	Apr 2016	Apr 2016	Apr 2016	Apr 2016	Dec 2014	Nov 2014	Oct 2014	Sep 2013	Sep 2012
Population		AF	Paroxysmal AF	Paroxysmal AF	Paroxysmal AF	Paroxysmal AF	Paroxysmal AF	AF	AF	AF	Non-parox. & parox. AF	AF	AF	AF
Intervention		CBA	CBA	CBA	CBA2	CBA	CBA	CBA	CBA	CBA	CBA	CBA	CBA	CBA
Comparator		RFA	RFA	RFA	RFA	RFA	RFA	RFA	RFA	RFA[25]	RFA	RFA	RFA	RFA
Included studies		*RCT & non RCT*	*RCT & non RCT*	*RCT & non RCT*	*RCT & non RCT*	*RCT & non RCT*	*RCT & non RCT*	*RCT & non RCT*	*RCT & non RCT*	*RCT & non RCT*	*RCT & non RCT*	*RCT & non RCT*	*RCT & non RCT*	*RCT*
RCTs														
Kuck	2016	✓	✓	✓		✓	✓	✓	✓					
Gunawardene	2016	✓												
Luik	2015	✓	✓	✓		✓	✓	✓	✓					
Hunter	2015	✓	✓	✓			✓	✓						
Koch	2014								✓					
Perez-Castellano	2014	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓		
Malmborg	2013	✓							✓					
Nagy	2013								✓					
Pokushalov	2013		✓						✓			✓		
Schmidt	2013		✓				✓		✓	✓			✓	
Herrera Sikoldy	2012	✓	✓					✓	✓	✓	✓	✓	✓	
Koch	2012		✓											
Bittner	2011	✓												
TSA	2005		✓						✓					
Observational														
Antolic	2016		✓											
Aryana	2016		✓		✓									
Attanasio	2016		✓											
Kardos	2016		✓	✓										
Khoueiry	2016	✓	✓	✓		✓	✓	✓						
Kojodjojo	2016	✓					✓	✓						
Nagy	2016				✓									
Oh	2016	✓												
Providencia	2016		✓	✓										
Straube	2016	✓	✓	✓		✓	✓	✓						
Schmidt	2016		✓	✓			✓	✓						
Aryana	2015	✓	✓					✓	✓					
Ciconte	2015							✓	✓					

[25] Studies for phase duty cycle radiofrequency ablation have not been extracted as they are considered out of scope.

Item		Ma 2017	Chen 2017	Chen 2017a	Jiang 2017	Buiatti 2017	Garg 2016	Cardoso 2016	Liu 2016	Kabunga 2016	Skelly 2015	Cheng 2015	Xu 2014	Hashimoto 2013
Julia	2015		✓	✓				✓						
Miyazaki	2015		✓		✓									
Straube	2015		✓						✓[26]					
Squara	2015	✓	✓	✓	✓		✓	✓						
Wasserlauf	2015	✓	✓	✓	✓	✓	✓	✓	✓					
Deville	2014		✓											
Mugnai	2014	✓	✓	✓			✓	✓	✓	✓	✓	✓		
Schmidt	2014	✓	✓			✓	✓	✓	✓	✓	✓			
Jourda	2014	✓	✓	✓	✓	✓	✓	✓	✓					
Julia	2014								✓					
Knecht	2014	✓	✓	✓		✓	✓	✓	✓			✓		
Akerstrom	2014		✓					✓	✓					
Amin	2014							✓						
Dulac	2014				✓			✓						
Betts	2013												✓	
Herm	2013		✓										✓	
Maagh	2013											✓		
Mandell	2013								✓	✓	✓	✓		
Wissner	2013								✓					
Kojodjojo	2012										✓		✓	
Mokrani	2012							✓						
Schmidt	2012								✓				✓	
Gaita	2011		✓				✓		✓				✓	
Herrera Sikoldy	2011								✓					
Neumann	2011		✓						✓	✓				
Chierchia	2010		✓						✓	✓	✓		✓	
Defaye	2010		✓						✓					
Hofmann	2010													
Kojodjojo	2010								✓	✓		✓		
Kuhne	2010	✓	✓	✓		✓			✓	✓		✓	✓	
Sorgente	2010								✓	✓		✓	✓	
Linhart	2009		✓						✓			✓	✓	
Sauren	2009								✓	✓			✓	

Abbreviations: AF, atrial fibrillation; CBA, cryoballoon ablation; CBA2, second-generation cryoballoon ablation; RCT, randomised control trial; RFA, radiofrequency ablation; SR, systematic review.

[26] Incorrectly classified as an RCT in Liu 2016.

Appendix D EVIDENCE SELECTION

The tables below list the citation details and authors' conclusions from systematic reviews and HTAs that met the inclusion/exclusion criteria for the Rapid Review, together with the reason for selection or non-selection for further assessment.

D.1 Cardiac ablation versus medical therapy

Table App 4 Systematic reviews and HTAs that met the inclusion/exclusion criteria: cardiac ablation vs. medical therapy

Study ID *[Country of authors]*	Citation	Author conclusions	Selected for assessment
Khan 2018 *[USA]*	Khan, S, Rahman, H, Talluri, S, Kaluski, E. (2018). The clinical benefits and mortality reduction associated with catheter ablation in subjects with atrial fibrillation: a systematic review and meta-analysis. JACC: Clinical electrophysiology. 4(5):626-635.	Although CA reduced the risk of cardiac hospitalisation and recurrent atrial arrhythmia both in subjects with HF and in subjects without HF, the reduction in all-cause mortality was limited to subjects with HF only. However, given the low statistical power and limited follow-up duration, a possible benefit cannot be excluded completely.	**Yes.** Recent and comprehensive. No minimum follow up requirement but discussion of the impact of follow up.
Barra 2018 *[UK and France]*	Barra, S, Baran, J, Narayanan, K, Boveda, S, Fynn, S, Heck, P, Grace, A, Agarwal, S, Primo, J, Marijon, E, Providência, R. (2018). Association of catheter ablation for atrial fibrillation with mortality and stroke: A systematic review and meta-analysis. International Journal of Cardiology. 266(1):136-142.	Ablation of AF associates with a survival benefit compared with medical treatment alone, although evidence is restricted to the setting of HF LV systolic dysfunction. Reduction in stroke risk was confined to observational studies alone.	**Yes.** Recent and comprehensive. Includes RCTs and non RCTs, with a subgroup analysis of RCTs only. Assesses the impact of moderator variables including age. Minimum requirement of 6 months' follow up.
Chen 2018 *[China]*	Chen, C, Zhou, X, Zhu, M, Chen, S, Chen, J, Cai, H, Dai, J, Xu, X, Mao, W. (2018). Catheter ablation versus medical therapy for patients with persistent atrial fibrillation: a systematic review and meta-analysis of evidence from randomized controlled trials. Journal of Interventional Cardiac Electrophysiology. 52(1):9-18.	CA appeared to achieve significantly greater freedom from atrial arrhythmia in addition to reducing cardioversion and hospitalisation in persistent AF patients compared with medical rhythm control. CA also seemed to improve LVEF and QoL in persistent AF patients with HF compared with medical rate control. Overall, CA appeared to be superior to medical therapy in persistent AF patients with the increasing efficacy of modern protocols. CA might be considered as a first-line therapy for some persistent AF patients especially for those with HF.	**Yes.** Most recent analysis that specifically focuses on patients with persistent AF (which is where evidence is lacking).
Nyong 2016 Cochrane Review *[Canada]*	Nyong, J, Amit, G, Adler, A, Owolabi, O, Perel, P, Prieto-Merino, D, Lambiase, P, Casas, J, Morillo, C. (2016). Efficacy and safety of ablation for people with non-paroxysmal atrial fibrillation. Cochrane Database of Systematic Reviews. 1(11): CD012088.	In people with non-paroxysmal AF, evidence suggests a superiority of RFCA to AADs in achieving freedom from atrial arrhythmias, reducing the need for cardioversion, and reducing cardiac-related hospitalisations. There was uncertainty surrounding the effect of RFCA with significant bradycardia (or need for a pacemaker), periprocedural complications, and other safety outcomes. Evidence should be interpreted with caution, as event rates were low and quality of evidence ranged from moderate to very low.	**No.** Only includes studies of persistent AF patients. Other SRs are more recent and comprehensive.
Hakalahti 2015 *[Finland]*	Hakalahti, A, Biancari, F, Nielsen, J, Raatikainen, M. (2015). Radiofrequency ablation vs. antiarrhythmic drug therapy as first line treatment of symptomatic atrial fibrillation: systematic review and meta-analysis. Europace. 17(3):370-378.	RFCA seems to be more effective than medical therapy as first-line treatment of paroxysmal AF in relatively young and otherwise healthy patients, but may also cause more severe adverse effects. These findings support the use of RFCA as first-line therapy in selected patients, who understand the benefits and risks of the procedure.	**No.** Only includes studies with patients that have failed first-line medical therapy, but similar conclusions are drawn in a more recent, comprehensive SR.

Study ID *[Country of authors]*	Citation	Author conclusions	Selected for assessment
Shi 2015 *[China]*	Shi, L, Heng, R, Liu, S, Leng, F. Effect of catheter ablation versus antiarrhythmic drugs on atrial fibrillation: A meta-analysis of randomized controlled trials. Experimental and Therapeutic Medicine. 10(2):816-822.	CA was demonstrated to markedly reduce AF recurrence and improve QoL when compared with AAD therapy. However, the incidence rates of all‐cause mortality and stroke/TIA were comparable between CA and AAD therapy.	**No.** Other SRs are more recent and comprehensive.
Skelly 2015 **AHRQ** *[USA]*	Skelly, A, Hashimoto, R, Al-Khatib, S, Sanders-Schmidler, G, Fu, R, Brodt, E, McDonagh, M. (2015). Catheter Ablation for Treatment of Atrial Fibrillation. Technology Assessment. AHRQ Publication. Rockville, MD: Agency for Healthcare Research and Quality.	In the general population, there was moderate evidence that RFCA is superior to medical therapy for enhancing patient freedom from recurrence of atrial arrhythmias in both the short and long term regardless of AF type, but re-ablation was common. RFCA does not appear to impact all-cause mortality in the short or long term in those with paroxysmal AF (low strength of evidence); however, there was insufficient evidence to draw conclusions regarding other primary clinical outcomes in the short or long term. Firm conclusions regarding HRQoL were not possible given heterogeneity across studies for instruments employed, measurement timing, and clinical characteristics. For harms, no differences between RFCA and medical therapy in 30-day mortality, stroke, or 3-month risk of AF were seen, with low strength of evidence.	**Yes.** Includes all types of AF patients and results are separated by type. In contrast to other identified SRs, most of our additional considerations are examined.
Zheng 2015 *[China]*	Zheng, Y, Chen, Z, Ye, L, Wang, L. (2015). Long-term stroke rates after catheter ablation or antiarrhythmic drug therapy for atrial fibrillation: a meta-analysis of randomized trials. Journal of Geriatric Cardiology. 12(5):507-514.	This meta-analysis RCTs showed similar rates of ischemic stroke or TIA and death in AF patients undergoing CA compared to drug therapy.	**No.** Other SRs are more recent and comprehensive.
Khan 2014 *[USA]*	Khan, A, Khan, S, Sheikh, M, Khuder, S, Grubb, B, Moukarbel, G. Catheter ablation and antiarrhythmic drug therapy as first- or second-line therapy in the management of atrial fibrillation: systematic review and meta-analysis. Circulation. Arrhythmia and electrophysiology. 7(5):853-860.	CA seems to be superior to AAD therapy in drug naïve, resistant, and intolerant patients with AF. However, it should be performed in carefully selected patients after weighing the risks and benefits of the procedure.	**No.** Other SRs are more recent and comprehensive.
Wynn 2014 *[UK]*	Wynn, G, Das, M, Bonnett, L, Panikker, S, Wong, T, Gupta, D. (2014). Efficacy of catheter ablation for persistent atrial fibrillation: a systematic review and meta-analysis of evidence from randomized and nonrandomized controlled trials. Circulation. Arrhythmia and Electrophysiology. 7(5):841-852.	For patients with persistent AF, CA achieves significantly greater freedom from recurrent AF compared with medical therapy. The most efficacious strategy is likely to combine isolation of the pulmonary veins with limited linear ablation within the left atrium.	**No.** Only includes studies of persistent AF patients. Other SRs are more recent and comprehensive.
Hashimoto 2013 **WSHCA** *[USA]*	Hashimoto, R, Raich, A, Junge, M, Skelly, A. (2013). Catheter ablation procedures for supraventricular tachyarrhythmia (SVTA) including atrial flutter and atrial fibrillation. Washington State Health Care Authority Health Technology Assessments.	There is moderate quality evidence that RF PVI results in significantly more freedom from recurrence compared with AADs in both the short- and long-term. There is low quality evidence that cryo-PVI results in significantly more freedom from recurrence in the short-term. There is low quality evidence that suggests that there is no difference between PVI (RF or cryo) and AADs in the 12-month rates of mortality, stroke, and congestive HF not attributed to any treatment given. There is low quality evidence that there is no difference in rates of mortality, thromboembolic events, pericardial effusion, cardiac tamponade or pulmonary vein stenosis following PVI (RF or cryo) compared with AADs.	**No.** Other SRs are more recent and comprehensive.

Study ID *[Country of authors]*	Citation	Author conclusions	Selected for assessment
Chatterjee 2012 *[USA]*	Chatterjee, N, Upadhyay, G, Ellenbogen, K, McAlister, F, Choudhry, N, Singh, J. (2012). Atrioventricular nodal ablation in atrial fibrillation: a meta-analysis and systematic review. Circulation: Arrhythmia and electrophysiology. 5(1):68-76.	In the management of refractory AF, atrioventricular nodal ablation is associated with improvement in symptoms and quality of life, with a low incidence of procedure morbidity. In patients with reduced systolic function, atrioventricular nodal ablation demonstrates small but significantly improved echocardiographic outcomes relative to medical therapy alone.	**No.** Other SRs are more recent and comprehensive.
Chen 2012 Cochrane Review *[China]*	Chen, H, Wen, J, Wu, S, Liu, J. (2012). Catheter ablation for paroxysmal and persistent atrial fibrillation. Cochrane Database of Systematic Reviews.4(4): CD007101.	There is limited evidence to suggest that CA may be a better treatment option compared to medical therapies in the management of persistent AF. This review was also unable to recommend the best CA method.	**No.** Other SRs are more recent and comprehensive.
Parkash 2012 *[Canada]*	Parkash, R, Tang, A, Sapp, J, Wells, G. Approach to catheter ablation techniqur of paroxysmal and persistent atrial fibrillation: a meta-analysis of the randomised controlled trials. Electrophysiology. 22(1):729-738.	Despite significant methodological limitations, it appears that additional ablations beyond PVI are necessary for persistent AF but not proven for paroxysmal AF. The optimal technique for persistent AF, however, deserves a further study, in the setting of a large, RCT.	**No.** Other SRs are more recent and comprehensive.
Van Brabandt 2012 KCE *[Belgium]*	Van Brabandt, H, Neyt, M, Devos, C. (2012) Catheter ablation of atrial fibrillation. KCE report. Brussels. Belgian Health Care Knowledge Centre.	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, CA 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. CA 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 CA 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 CA for AF.	**No** Other SRs are more recent and comprehensive.

Abbreviations: AAD, antiarrhythmic drug; AF, atrial fibrillation; AHRQ, Agency for Healthcare Research and Quality; CA, cardiac ablation; HF, heart failure; HRQoL, health-related quality of life; HTA, health technology assessment; LV, and left ventricular; LVEF, left ventricular ejection fraction; PVI, pulmonary vein isolation; QoL, quality of life; RCT, randomised controlled trial; RF, radiofrequency; RFCA, radiofrequency cardiac ablation; SR, systematic review; TIA, transient ischaemic attack; UK, United Kingdom; USA, United States of America; WSHCA, Washington State Health Care Authority.
Note: SRs/HTAs selected for inclusion in the Rapid Review are shaded in the table above.

D.2 Radiofrequency ablation versus cryoablation

Table App 5 Systematic reviews and HTAs that met the inclusion/exclusion criteria: RF ablation vs. cryoablation

Study ID *[Country of authors]*	Citation	Author conclusions	Selected for assessment
Buiatti 2017 *[Germany]*	Buiatti, A, Von Olshausen, G, Barthel, P, Schneider, S, Luik, A, Kaess, B, Laugwitz, K, Hoppmann, P. (2017). Cryoballoon vs. radiofrequency ablation for paroxysmal atrial fibrillation: an updated meta-analysis of randomized and observational studies. Europace. 19(3):378-384.	In patients with paroxysmal AF, ablation therapy with CB is associated with efficacy and safety comparable to that of RF. Second-generation CB catheters seem to reduce procedure duration; however, the fluoroscopy time remains comparable. Further studies are warranted to disclose the impact of second-generation CBA catheters compared with RF for ablation of paroxysmal AF.	**No.** Only includes studies of paroxysmal AF patients. Other SRs with the same search date include all AF patients. Minimum requirement of only 6 months' follow up.
Chen 2017 *[China]*	Chen, C, Gao, X, Duan, X, Chen, B, Liu, X, Xu, Y. (2017). Comparison of catheter ablation for paroxysmal atrial fibrillation between cryoballoon and radiofrequency: a meta-analysis. Journal of Interventional Cardiac Electrophysiology. 48(3):1-16.	Available overall and subgroup data suggested that both first-generation CBA and second-generation CBA were more beneficial than RF ablation, and the main advantages were reflected in comparing them with non-contact force RF. However, contact force RF and second-generation CBA showed similar clinical benefits.	**No.** Only includes studies of paroxysmal AF patients. No minimum follow up requirement. All study types are meta-analysed together, with no subgroup analysis based on study design or quality.
Chen 2017a *[China]*	Chen, Y, Lu, Z, Xiang, Y, Hou, J, Wang, Q, Lin, H, Li, Y. (2017). Cryoablation vs. radiofrequency ablation for treatment of paroxysmal atrial fibrillation: a systematic review and meta-analysis. Europace Electrophysiology. 19(5):784-794.	Compared with RF ablation, cryoablation present a comparable long-term AF/atrial tachycardial-free survival and procedure-related adverse events. Meanwhile, cryoablation markedly shorten the procedure time, nonetheless, with negligible impact on the fluoroscopy time.	**No.** Only includes studies of paroxysmal AF patients. Other SRs with the same search date include all AF patients.
Jiang 2017 *[China]*	Jiang, J, Li, J, Zhong, G, Jiang, J. (2017). Efficacy and safety of the second-generation cryoballoons versus radiofrequency ablation for the treatment of paroxysmal atrial fibrillation: a systematic review and meta-analysis. Journal of Interventional Cardiac Electrophysiology. 48(1):1-11.	Second-generation CBA tended to be more effective in comparison to non-contact force sensing catheter and at least non-inferior to contact force sensing catheter, with shorter procedure time and similar safety endpoint.	**No.** Only includes studies of paroxysmal AF patients. No RCTs included. Other SRs also report subgroup analysis of first- and second-generation technology. Minimum requirement of only 3 months' follow up.
Ma 2017 *[China]*	Ma, H, Sun, D, Luan, H, Feng, W, Zhou, Y, Wu, J, He, C, Sun, C. (2017). Efficacy and safety of cryoballoon ablation versus radiofrequency catheter ablation in atrial fibrillation: an updated meta-analysis. Postepy w Kardiologii Interwencyjnej. 13(3):240-249.	For AF, CBA was as effective as RFCA. However, CBA had a shorter procedure time and a non-significantly shorter fluoroscopy time, a significantly high risk of PNP and a low incidence of pericardial effusions/cardiac tamponade compared with RFCA.	**No.** All study types are meta-analysed together, with no subgroup analysis based on study design or quality. Minimum requirement of only 6 months' follow up. High risk of bias (see Table App 6).
Cardoso 2016 *[USA]*	Cardoso, R, Mendirichaga, R, Fernandes, G, Healy, C, Lambrakos, L, Viles-Gonzalez, J, Goldberger, J, Mitrani, R. (2016). Cryoballoon versus radiofrequency catheter ablation in atrial fibrillation: a meta-analysis. Journal of Cardiovascular Electrophysiology. 27(10):1151-1159.	There was comparable freedom from AT between CB and RF in patients with AF undergoing PVI. Additionally, freedom from AT was similar between second-generation CB and contact force sensing RF. However, CB was associated with a lower incidence of pericardial effusions or tamponade, albeit with a higher rate of transient PNP.	**Yes.** Contains most recent RCTs and includes all types of AF patients. Includes RCTs and non RCTs, with a subgroup analysis of RCTs only. Minimum requirement of 12-months' follow up.

Study ID *[Country of authors]*	Citation	Author conclusions	Selected for assessment
Garg 2016 *[USA]*	Garg, J, Chaudhary, R, Palaniswamy, C, Shah, N, Krishnamoorthy, P, Bozorgnia, B, Natale, A. (2016). Cryoballoon versus radiofrequency ablation for atrial fibrillation: a meta-analysis of 16 clinical trials. Journal of Atrial Fibrillation. 9(3):1429-1438.	CBA was non-inferior to RFA for CA of paroxysmal AF. RFA was associated with a higher groin complications and pericardial effusion/ cardiac tamponade, whereas CBA was associated with higher rates of transient and persistent phrenic nerve injury. Based on these data, there is insufficient evidence to suggest superiority of one ablation strategy over the other for PVI.	**No.** Only includes paroxysmal AF patients. Other SRs with the same search date that include all AF patients. No minimum follow up requirement.
Kabunga 2016 *[Australia]*	Kabunga, P, Phan, K, Ha, H, Sy, R. (2016). Meta-analysis of contemporary atrial fibrillation ablation strategies: irrigated radiofrequency versus duty-cycled phased radiofrequency versus cryoballoon ablation. JACC: Clinical Electrophysiology. 2(3):377-390.	Although preliminary meta-analysis of pooled data suggested the highest efficacy with phased duty-cycled RF, this was not replicated when analysis was limited to randomised data. Therefore, there was insufficient evidence to suggest that one ablation modality is more efficacious than another. However, there was a consistent reduction in procedural duration associated with phased duty-cycled RF in all analyses.	**No.** Other SRs are more recent and comprehensive. No minimum follow up requirement. All RCTs had <100 patients (awaiting KUCK 2016, which was included in more recent SRs). First-generation cryoballoon only.
Liu 2016 *[China]*	Liu, X, Chen, C, Gao, X, Xu, Y. (2016). Safety and efficacy of different catheter ablations for atrial fibrillation: a systematic review and meta-analysis. Pacing and Clinical Electrophysiology. 39(8):883-899.	CBA was associated with greater freedom from AF, shorter procedural time, and lower rate of major complications compared with RFCA. Especially, [second-generation] CBA was more advantageous. However, multiparty catheter seems promising for RF ablation.	**No.** All study types are meta-analysed together, with no subgroup analysis based on study design or quality. Discrepancies noted in study design classification. Minimum requirement of only 3 months' follow up.
Cheng 2015 *[China]*	Cheng, X, Hu, Q, Zhou, C, Liu, L, Chen, T, Liu, Z, Tang, X. (2015). The long-term efficacy of cryoballoon vs irrigated radiofrequency ablation for the treatment of atrial fibrillation: a meta-analysis. International Journal of Cardiology. 181(C):297-302.	CBA was as effective as RFCA for the treatment of AF during long-term follow-up with comparable procedural features. CBA appears to be related to a shorter fluoroscopy time than RFCA, but it is associated with a significantly higher risk of transient PNP.	**No.** Other SRs are more recent and comprehensive. Minimum requirement of only 3 months' follow up.
Skelly 2015 AHRQ *[USA]*	Skelly, A, Hashimoto, R, Al-Khatib, S, Sanders-Schmidler, G, Fu, R, Brodt, E, McDonagh, M. (2015). Catheter Ablation for Treatment of Atrial Fibrillation. Technology Assessment. AHRQ Publication. Rockville, MD: Agency for Healthcare Research and Quality.	Evidence comparing cryoballoon ablation with RFA was insufficient to draw conclusions.	**Yes.** HTA selected to address the comparison of CA vs. medical therapy. Analyses were stratified by type of AF and length of follow up (>12 months vs. ≤12 months).
Xu 2014 *[China]*	Xu, J, Huang, Y, Cai, H, Qi, Y, Jia, N, Shen, W, Lin, J, Peng, F, Niu, W. (2014). Is cryoballoon ablation preferable to radiofrequency ablation for treatment of atrial fibrillation by pulmonary vein isolation? A meta-analysis. PloS One. 9(2):e90323.	Our findings demonstrate greater improvement in fluoroscopic time and total procedure duration for AF patients referred for CBA than those for RFCA. However, success rate of PVI, the percentages of recurrent AF and major complications were comparable between the two procedures.	**No.** Other SRs are more recent and comprehensive. No minimum follow up requirement.
Hashimoto 2013 WSHCA *[USA]*	Hashimoto, R, Raich, A, Junge, M, Skelly, A. (2013). Catheter ablation procedures for supraventricular tachyarrhythmia (SVTA) including atrial flutter and atrial fibrillation. Washington State Health Care Authority Health Technology Assessments.	No RCTs were identified that compared RF ablation to cryoablation in patients with atrial fibrillation.	**No.** Other SRs are more recent and comprehensive. Minimum requirement of only 6 months' follow up.

Abbreviations: AF, atrial fibrillation; AHRQ, Agency for Healthcare Research and Quality; AT, atrial tachyarrhythmia; CA, cardiac ablation; CB, cryoballoon; CBA, cryoballoon ablation; HTA, health technology assessment; PNP, phrenic nerve palsy; PVI, pulmonary vein isolation; RCT, randomised controlled trial; RF, radiofrequency; RFCA, radiofrequency cardiac ablation; SR, systematic review; USA, United States of America; WSHCA, Washington State Health Care Authority.

Note: SRs/HTAs selected for inclusion in the Rapid Review are shaded in the table above.

Appendix E RISK OF BIAS ASSESSMENT

Table App 6 Risk of bias assessment of selected systematic reviews and HTAs using AMSTAR 2

Questions		*Barra 2018*	*Chen 2018*	*Khan 2018*	*Ma 2017*	*Cardoso 2016*	*Skelly 2015 AHRQ HTA*
1.	Did the research questions and inclusion criteria for the review include the components of PICO? *Yes/No*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*
2.	Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? *Yes/Partial Yes/No*	*Yes*	*Yes*	*Yes*	*Partial yes*	*Yes*	*Yes*
3.	Did the review authors explain their selection of the study designs for inclusion in the review? *Yes/No*	*No*	*No*	*No*	*No*	*No*	*Yes*
4.	Did the review authors use a comprehensive literature search strategy? *Yes/Partial Yes/No*	*Yes*	*Partial yes*	*Yes*	*Partial yes*	*Yes*	*Yes*
5.	Did the review authors perform study selection in duplicate? *Yes/No*	*Yes*	*Unclear*	*Yes*	*Yes*	*Yes*	*Yes*
6.	Did the review authors perform data extraction in duplicate? *Yes/No*	*Yes*	*Yes*	*Yes*	*Unclear*	*Yes*	*Yes*
7.	Did the review authors provide a list of excluded studies and justify the exclusions? *Yes/Partial Yes/No*	*No*	*No*	*No*	*No*	*No*	*Yes*
8.	Did the review authors describe the included studies in adequate detail? *Yes/Partial Yes/No*	*Partial yes*	*Yes*	*Yes*	*No*[27]	*Yes*	*Yes*
9.	Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? *Yes/Partial Yes/No*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*
10.	Did the review authors report on the sources of funding for the studies included in the review? *Yes/No*	*No*	*No*	*No*	*No*	*No*	*Yes*
11.	If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results? *Yes/No/No meta-analysis conducted*	*Yes*	*Yes*	*Yes*	*No*[28]	*Yes*	*Yes*
12.	If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis? *Yes/No/No meta-analysis conducted*	*Yes*	*Yes*	*Yes*	*No*	*Yes*	*Yes*
13.	Did the review authors account for RoB in primary studies when interpreting/discussing the results of the review? *Yes/No*	*Yes*	*Yes*	*Yes*	*No*	*Yes*	*Yes*
14.	Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? *Yes/No*	*Yes*	*Yes*	*Yes*	*No*	*Yes*	*Yes*
15.	If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? *Yes/No/No meta-analysis conducted*	*Yes*	*Yes*	*Yes*	*No*	*Yes*	*No*[29]
16.	Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review? *Yes/No*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*
Overall assessment		***Low***	***Low***	***Low***	***High***	***Low***	***Low***

Refer to Shea et al 2017 for AMSTAR 2 details.

[27] Research designs not stated.
[28] RCTs and observational studies have been combined and no adjustments have been made.
[29] Formal assessment of publication bias was not conducted as there were fewer than 10 studies available for outcomes based on AF type, and research indicates that such methods can be misleading with smaller numbers of studies

Appendix F REVIEWS OF CARDIAC ABLATION IN SPECIFIC MEDICAL SUBPOPULATIONS

The table below lists the citation details for systematic reviews of cardiac ablation in specific medical subpopulations. These reviews may provide evidence for appropriate target populations for cardiac ablation but are considered out-of-scope for the Rapid Review.

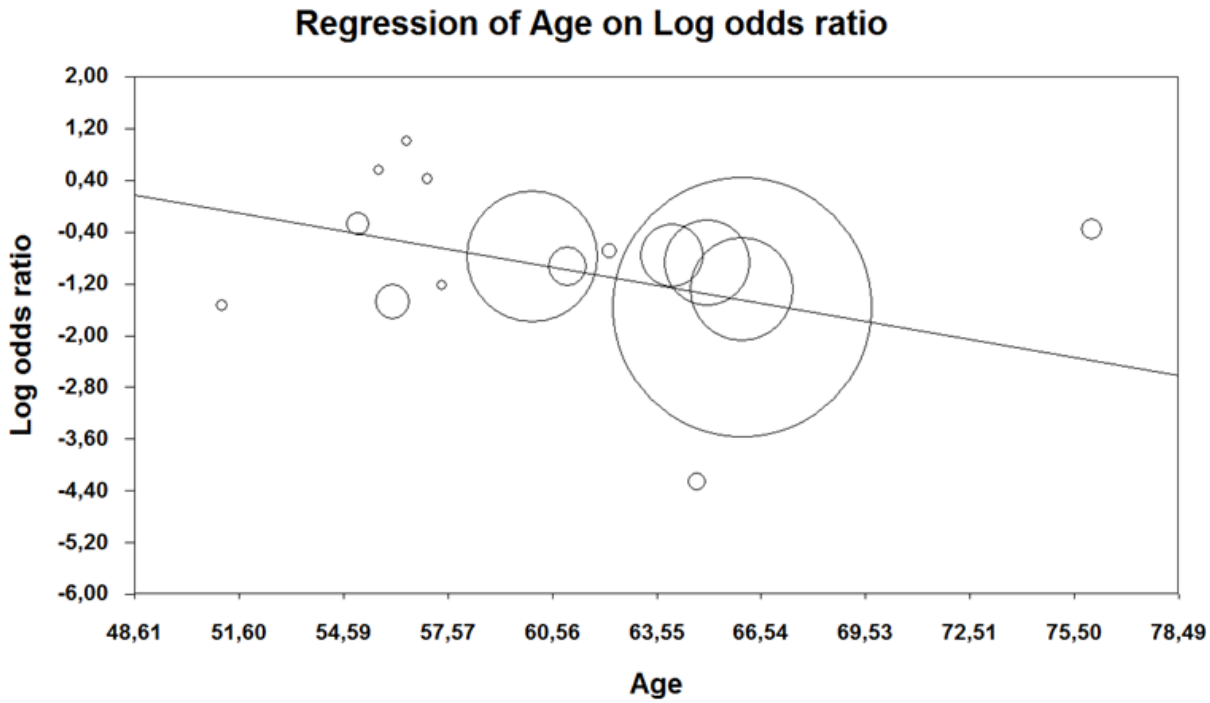
Table App 7 Systematic reviews of cardiac ablation in specific medical subpopulations

Study ID	Citation	Selected for assessment
Diabetes mellitus		
Anselmino 2015	Anselmino, M, Matta, M, D'Ascenzo, F, Pappone, C, Santinelli, V, Bunch, T, Neumann, T, Schilling, R, Hunter, R, Noelker, G, Fiala, M, Frontera, A, Thomas, G, Katritsis, D, Jais, P, Weerasooriya, R, Kalman, J, Gaita, F. (2015). Catheter ablation of atrial fibrillation in patients with diabetes mellitus: a systematic review and meta-analysis. Europace. 17(10):1518-1525.	**No.** Out-of-scope
Obstructive sleep apnoea		
Li 2014	Li, L, Wang, Z, Li, J, Ge, X, Guo, L, Wang, Y, Guo, W, Jiang, C, Ma, C. (2014). Efficacy of catheter ablation of atrial fibrillation in patients with obstructive sleep apnoea with and without continuous positive airway pressure treatment: a meta-analysis of observational studies. Europace. 16(9):1309-1314.	**No.** Out-of-scope
Heart failure		
Ahn 2018	Ahn, J, Kim, H, Choe, J, Park, J, Lee, H, Oh, J, Choi, J, Lee, H, Cha, K, Hong, T, Kim, Y. (2018). Treatment strategies for atrial fibrillation with left ventricular systolic dysfunction - meta-analysis. Circulation Journal. 82(7):1770-1777.	**No.** Out-of-scope
Briceño 2018	Briceño, D, Markman, T, Lupercio, F, Romero, J, Liang, J, Villablanca, P, Birati, E, Garcia, F, Di Biase, L, Natale, A, Marchlinski, F, Santangeli, P. (2018). Catheter ablation versus conventional treatment of atrial fibrillation in patients with heart failure with reduced ejection fraction: a systematic review and meta-analysis of randomized controlled trials. Journal of Interventional Cardiac Electrophysiology. 53(1):19-29.	**No.** Out-of-scope
Elgendy 2018	Elgendy, A, Mahmoud, A, Khan, M, Sheikh, M, Mojadidi, M, Omer, M, Elgendy, I, Bavry, A, Ellenbogen, K, Miles, W, McKillop, M. (2018). Meta-Analysis Comparing Catheter-Guided Ablation Versus Conventional Medical Therapy for Patients With Atrial Fibrillation and Heart Failure With Reduced Ejection Fraction. The American Journal of Cardiology. 122(5):806-813.	**No.** Out-of-scope
Kheiri 2018	Kheiri, B, Osman, M, Abdalla, A, Haykal, T, Ahmed, S, Bachuwa, G, Hassan, M, Bhatt, D. (2018). Catheter ablation of atrial fibrillation with heart failure: An updated meta-analysis of randomized trials. International Journal of Cardiology. 269(1):170-173.	**No.** Out-of-scope
Ma 2018	Ma, Y, Bai, F, Qin, F, Li, Y, Tu, T, Sun, C, Zhou, S, Liu, Q. (2018). Catheter ablation for treatment of patients with atrial fibrillation and heart failure: a meta-analysis of randomized controlled trials. BMC. 18(10):165.	**No.** Out-of-scope
Smer 2018	Smer, A, Salih, M, Darrat, Y, Saadi, A, Guddeti, R, Mahfood Haddad, T, Kabach, A, Ayan, M, Saurav, A, Abuissa, H, Elayi, C. (2018). Meta-analysis of Randomized Controlled Trials on Atrial Fibrillation Ablation in Patients with Heart Failure with Reduced Ejection Fraction. Clinical Cardiology. 1002/clc.23068.	**No.** Out-of-scope
Providencia 2016	Providencia, R, Elliott, P, Patel, K, McCready, J, Babu, G, Srinivasan, N, Bronis, K, Papageorgiou, N, Chow, A, Rowland, E, Lowe, M, Segal, O, Lambiase, P. (2016). Catheter ablation for atrial fibrillation in hypertrophic cardiomyopathy: a systematic review and meta-analysis. Heart. 102(19):1533-1543.	**No.** Out-of-scope
Zhang 2016	Zhang, B, Shen, D, Feng, S, Zhen, Y, Zhang, G. (2016). Efficacy and safety of catheter ablation vs. rate control of atrial fibrillation in systolic left ventricular dysfunction: A meta-analysis and systematic review. Herz. 41(4):342-350.	**No.** Out-of-scope
Zhao 2016	Zhao, D, Shen, Y, Zhang, Q, Lin, G, Lu, Y, Chen, B, Shi, L, Huang, J, Lu, H. (2016). Outcomes of catheter ablation of atrial fibrillation in patients with hypertrophic cardiomyopathy: a systematic review and meta-analysis. Europace. 18(4):508-520.	**No.** Out-of-scope

Study ID	Citation	Selected for assessment
Zhu 2016	Zhu, M, Zhou, X, Cai, H, Wang, Z, Xu, H, Chen, S, Chen, J, Xu, X, Xu, H, Mao, W. (2016). Catheter ablation versus medical rate control for persistent atrial fibrillation in patients with heart failure: A PRISMA-compliant systematic review and meta-analysis of randomized controlled trials. Medicine. 95(30):e4377.	**No.** Out-of-scope
Al Halabi 2015	Al Halabi, S, Qintar, M, Hussein, A, Alraies, M, Alraies, M, Jones, D, Wong, T, MacDonald, M, Petrie, M, Cantillon, D, Tarakji, K, Kanj, M, Bhargava, M, Varma, N, Baranowski, B, Wilkoff, B, Wazni, O, Callahan, T, Saliba, W, Chung, M. (2015). Catheter Ablation for Atrial Fibrillation in Heart Failure Patients: A Meta-Analysis of Randomized Controlled Trials. JACC: Clinical Electrophysiology. 1(3):200-209.	**No.** Out-of-scope
Ganesan 2015	Ganesan, A, Nandal, S, Lüker, J, Pathak, R, Mahajan, R, Twomey, D, Lau, D, Sanders, P. (2015). Catheter Ablation of Atrial Fibrillation in Patients with Concomitant Left Ventricular Impairment: a Systematic Review of Efficacy and Effect on Ejection Fraction. Heart, Lung & Circulation. 24(3):270-280.	**No.** Out-of-scope
Ha 2015	Ha, H, Wang, N, Wong, S, Phan, S, Liao, J, Kumar, N, Qian, P, Yan, T, Phan, K. (2015). Catheter ablation for atrial fibrillation in hypertrophic cardiomyopathy patients: a systematic review. Journal of Interventional Cardiac Electrophysiology. 44(2):161-170.	**No.** Out-of-scope
Anselmino 2014	Anselmino, M, Matta, M, D'Ascenzo, F, Bunch, T, Schilling, R, Hunter, R, Pappone, C, Neumann, T, Noelker, G, Fiala, M, Bertaglia, E, Frontera, A, Duncan, E, Nalliah, C, Jais, P, Weerasooriya, R, Kalman, J, Gaita, F. (2014). Catheter ablation of atrial fibrillation in patients with left ventricular systolic dysfunction: a systematic review and meta-analysis. Circulation: Arrhythmia and Electrophysiology. 7(6):1011-1018.	**No.** Out-of-scope
Kanmanthareddy 2014	Kanmanthareddy, A, Buddam, A, Reddy, M, Koripalli, S, Vallakati, A, Sridhar, A, Bommana, S, Atkins, D, Lakkireddy, D. (2014). Catheter ablation of atrial fibrillation improves left ventricular function in patients with left ventricular dysfunction. Journal of Cardiac Failure. 20(8):S91-S92.	**No.** Out-of-scope

Appendix G EFFECT OF INCREASING AGE

Figure 2 Regression analysis of increasing patient age on all-cause mortality



Source: Barra et al 2018, Supplementary Figure b. Benefit of cardiac ablation for the primary endpoint with increasing patient age (with increasing age, Log OR decreases = OR decreases = larger benefit).