NHS England

Evidence review: Percutaneous left atrial catheter ablation for the treatment of paroxysmal atrial fibrillation

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Prepared by: Solutions for Public Health (SPH) on behalf of NHS England Specialised Commissioning

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1 Introduction

Introduction

- Atrial fibrillation (AF) is the uncoordinated electrical activity within the walls of the atria (filling chambers of the heart). This can cause the ventricles (pumping chambers of the heart) to beat irregularly and sometimes beat very rapidly (Skelly et al 2015).

- While AF can occur in isolation, it may also be associated with other arrhythmias such as atrial flutter or atrial tachycardia. AF is classified into:
    - Paroxysmal AF (starts and stops spontaneously, in most cases within 48 hours)
    - Persistent AF (starts spontaneously but lasts longer than seven days including episodes that are terminated by cardioversion)
    - Permanent AF (long-standing AF in which restoring and/or maintaining sinus rhythm has failed and/or rhythm control is no longer the treatment strategy).

- Long-standing persistent AF is usually defined as AF that persists for over one year. Long-standing persistent and permanent AF is more commonly seen in older patients with structural heart disease (Skelly et al 2015).

- People with AF may be asymptomatic (no symptoms at all) or symptomatic (palpitations, dizziness, shortness of breath, chest pain, reduced exercise capacity, fatigue and significantly impaired quality of life). AF increases the risk of embolic stroke and people may require anticoagulation to mitigate this (Skelly et al 2015).

Existing guidance from the National Institute of Health and Care Excellence (NICE)

- There is no relevant NICE Technology Appraisal Guidance (with statutory requirement for NHS organisations to make funding available) specifically for the use of percutaneous left atrial catheter ablation for the treatment of persistent AF.

- NICE published Clinical Guideline (CG) 180 Atrial Fibrillation: Management in June 2014. NICE Interventional procedures guidance (IPG) 427 (Percutaneous balloon cryoablation for pulmonary vein isolation in atrial fibrillation) and IPG 563 (Percutaneous endoscopic laser balloon pulmonary vein isolation for atrial fibrillation in adults) were published in May 2012 and July 2016 respectively.

- NICE CG 180 (Atrial Fibrillation: Management) makes the following recommendations regarding left atrial ablation and a pace and ablate strategy (NICE 2014):

    "Left atrial ablation

    - *If drug treatment has failed to control symptoms of atrial fibrillation or is unsuitable:*
        - *offer left atrial catheter ablation to people with paroxysmal atrial fibrillation*
        - *consider left atrial catheter or surgical ablation for people with persistent atrial fibrillation*
        - *discuss the risks and benefits with the person.*
    - *Consider left atrial surgical ablation at the same time as other cardiothoracic surgery for people with symptomatic atrial fibrillation."*

    "Pace and ablate strategy

    - *Consider pacing and atrioventricular node ablation for people with permanent atrial fibrillation with symptoms or left ventricular dysfunction thought to be caused by high ventricular rates.*

- *When considering pacing and atrioventricular node ablation, reassess symptoms and the consequent need for ablation after pacing has been carried out and drug treatment further optimised.*

- *Consider left atrial catheter ablation before pacing and atrioventricular node ablation for people with paroxysmal atrial fibrillation or heart failure caused by non-permanent (paroxysmal or persistent) atrial fibrillation."*

- NICE IPG 427 makes the following recommendations regarding percutaneous balloon cryoablation for pulmonary vein isolation in AF (NICE 2012):

  "1.1 Current evidence on the efficacy and safety of percutaneous balloon cryoablation for pulmonary vein isolation in atrial fibrillation is adequate to support the use of this procedure provided that normal arrangements are in place for clinical governance, consent and audit.

  1.2 Patient selection and treatment should only be carried out by interventional cardiologists with expertise in electrophysiology and complex ablation procedures.

  1.3 This procedure should be carried out only in units with arrangements for emergency cardiac surgical support in case of complications.

  1.4 Clinicians should enter details about all patients undergoing percutaneous balloon cryoablation for pulmonary vein isolation in atrial fibrillation onto the UK Central Cardiac Audit Database.

  1.5 NICE encourages clinicians to enter patients into research studies with the particular aims of guiding selection of patients and of defining the place of percutaneous balloon cryoablation in relation to other procedures for treating atrial fibrillation. Further research should define patient selection criteria clearly and should document adverse events and long-term control of atrial fibrillation."

- NICE IPG 563 makes the following recommendations regarding percutaneous endoscopic laser balloon pulmonary vein isolation for AF (NICE 2016):

  "*1.1 Current evidence on the safety of percutaneous endoscopic laser balloon pulmonary vein isolation for atrial fibrillation shows there are serious but well-recognised complications. Evidence on efficacy is adequate in quantity and quality to support the use of this procedure provided that standard arrangements are in place for clinical governance, consent and audit.*

  1.2 Clinicians should ensure that patients fully understand the potential complications, the uncertainty about the success of the procedure in the short term and the risk of recurrent atrial fibrillation. In addition, the use of NICE's information for the public is recommended.

  1.3 Patient selection and treatment should be carried out only by interventional cardiologists with expertise in electrophysiology and experience of doing complex ablation procedures.

  1.4 This procedure should be done only in units with arrangements for emergency cardiac surgical support.

  1.5 Clinicians should enter details about all patients having percutaneous endoscopic laser balloon pulmonary vein isolation for atrial fibrillation onto the UK Central Cardiac Audit Database and review local clinical outcomes."

The indication and epidemiology

- Atrial fibrillation is the most common cardiac arrhythmia. It is estimated that 1.4 million

people in England have AF. This is equal to 2.5% of the population and 3% in persons over 20 years old (Adderley et al 2019).

- The condition is uncommon in those younger than 40 years old and is extremely rare in children without congenital heart disease. The incidence and prevalence of AF are increasing due to the aging population, higher prevalence of known AF risk factors in older people and better screening strategies for arrhythmia detection in the primary care setting (PHE 2017).
- AF prevalence is higher in men than in women, 2.9% versus 2.0%. AF prevalence increases with age; 2.8% of the total estimated AF in the population is likely to occur in people aged under 45, 16.6% in people aged 45-65 and 80.5% in people aged over 65 (PHE 2017).
- Obesity increases the risk of developing AF. Furthermore, obesity increases the likelihood that AF will progress from paroxysmal to permanent AF. Additional factors associated with an increased risk of AF include smoking, hypertension, hyperthyroidism, obstructive sleep apnoea, diabetes, myocardial infarction, heart failure, and cardiac surgery (Skelly et al 2015).
- AF is associated with significant mortality, morbidity, and health care costs. Patients with AF have a twofold greater risk of death than do those without this disease. AF is associated with an increased risk of stroke; this affects nearly 7% of AF patients with heart failure each year. Furthermore, ischaemic stroke that occurs in the setting of AF tends to be either fatal or of moderate to high severity in most patients. AF can also cause several cardiac conditions, including myocardial ischaemia or infarction, exacerbation of heart failure, and cardiomyopathy (Skelly et al 2015).

Standard treatment and pathway of care

- Treatment of AF involves rate control, rhythm control, prevention of thromboembolic events, and treating the underlying disease (e.g. hypertension) if applicable (Skelly et al 2015).
- The mainstay of treatment for AF has been through pharmacological methods. These drugs, known as anti-arrhythmic drugs either slow the heart rate (rate control) or maintain a normal heart rhythm (rhythm control). Whilst these drugs can be used successfully, they are not always tolerated or effective (NICE 2012, Skelly et al 2015).
- Non-pharmacological methods include electric cardioversion (use of an electric stimulus to reset the heart rhythm to normal), catheter and surgical ablation to create lesions to stop the abnormal electrical impulses that cause AF (NICE 2012).

The intervention

- Percutaneous left atrial catheter ablation is an intervention to treat AF that was first described in 1994 (Haïssaguerre et al 1994). Ablation is a minimally invasive procedure that can be done under general anaesthesia or sedation (NICE 2012).
- Catheters and electrodes are introduced through the skin in the groin into the femoral vein and moved towards the heart under fluoroscopic (X-ray) guidance. The catheters enter the right atrium before passing into the left atrium via a trans-septal puncture. Certain areas of the left atrium are then targeted with heat or cold resulting in localised irreversible damage to the heart muscle causing disruption to the erratic signals thus preventing AF.

Rationale for use

- In catheter ablation, energy is sent through an electrode at the tip of a catheter into specific areas of the heart to destroy (ablate) or electrically isolate small areas of tissue where abnormal electrical signals that trigger abnormal heart beats originate. The goal of catheter ablation for treatment of AF is to ablate or isolate triggers that mostly originate in the pulmonary veins (Skelly et al 2015).

2 Summary of results

- One Health Technology Appraisal (HTA), one systematic review (SR) and three randomised controlled trials (RCTs) fulfilling the PICO criteria for clinical effectiveness and safety were identified for inclusion.
- One Health Technology Appraisal (HTA) (Skelly et al 2015) and three more recently published randomised controlled trials (RCTs) (Marrouche et al 2018, Nielsen et al 2017, and Bertaglia et al 2017) were found assessing the effectiveness of catheter ablation compared with medical treatment.
- One systematic review (SR) (Phan et al 2016) and one more recently published RCT (Jan et al 2018) were found comparing catheter ablation with surgical ablation.
- One UK based study of the cost effectiveness of catheter ablation in comparison to medical therapy (Reynold et al 2014) was found. No studies eligible for inclusion were found investigating the cost effectiveness of catheter ablation versus surgical ablation.

2.1 Catheter ablation (CA) versus medical therapy (MT) (rhythm and/or rate control) in the treatment of paroxysmal AF

- **All-cause mortality:** Skelly et al (2015) reported no difference in all-cause mortality between the intervention groups within 30 days based on pooled results from three RCTs (n=570) [CA 0% to 0.7% versus medical therapy 0%]; however, no test of statistical significance was reported. There was also no difference between the two study arms at up to 12 months [three RCTs (n=333) CA 0% to 1% versus MT 0% to 3.6%)] and at 24 months [two RCTs (n=408) CA 1.4% versus MT 2.8%] p value not reported for both.
- **Freedom from arrhythmia recurrence:** The HTA by Skelly et al (2015) reported a statistically significant difference in favour of CA for freedom from arrhythmia recurrence at 12 months based on pooled results from four RCTs [CA n=226/286 (79%) versus MT n=64/245 (26.1%); risk ratio (RR) 3.06 (95% CI 2.35 to 3.90); p<0.05]. They also report results for 24 to 48 months based on three RCTs [CA n=226/311 (72.6%) versus MT n=178/308 (57.8%); RR 1.24 (95% CI 1.11 to 1.47) in favour of CA; p<0.05]. Freedom from any AF was also reported by Nielsen et al (2017) after a five-year follow-up [CA n=126/146 (86%) versus MT n=105/148 (71%); RR=0.82 (95% CI 0.73 to 0.93) in favour of CA, p=0.001] and symptomatic AF; [CA n=137/146 (94%) versus MT n=126/148 (85%); RR 0.91 (95% CI 0.84 to 0.98); p=0.015].
- **Freedom for AF burden:** Neilson et al (2017) (n=294) reported a significantly lower AF burden in the CA group compared with medical therapy (anti-arrhythmic drugs) at five-year follow-up. 85% and 95% percentiles[1] for the CA group were 0% and 56% respectively versus 7% and 97% respectively for the antiarrhythmic drugs (AADs) group; p=0.003.

[1] The 95th percentile implies that 95% of the time, the burden is below this amount: so, the remaining 5% of the time, the burden is above that amount and 85th percentile implies that 85% of the time, the burden is below this amount: so, the remaining 15% of the time, the burden is above that amount.

Corresponding percentiles for symptomatic AF were also significantly lower for CA: 0%, 7% (CA) versus 0%, 11% (AADs); p=0.02.

- **Maintenance of sinus rhythm:** Bertaglia et al (2017) (n=92) did not find any difference in the maintenance of sinus rhythm after a 12-year follow-up between patients who had undergone CA and those on AADs [n=22/42 (51.2%) versus n=22/50 (44%) respectively; p=0.402].

- **Improvement in LVEF (patients with HF):** Marrouche et al (2018) reported on the median LVEF changes in paroxysmal AF (PAF) patients with HF (LVEF of 35% or less). At 60 months median LVEF increases were: CA (n=14) 7% [interquartile range (IQR) 5% to 16%) versus MT (n=11) 8% (IQR -1% to 23%]; however, the difference was not statistically significant (p=0.81).

- **Cardiac hospitalisation or re-admission:** Skelly et al (2015) reported that, at 12 to 24 months following CA, patients had fewer cardiac hospitalisations or re-admissions than those on MT based on results from two RCTs. One RCT (n=67) reported at 12 months CA 9.4% versus MT 54.3% and the other (n=294) at 24 months CA 0% versus MT 1.4%. However, results were not pooled and no tests of statistical significance were reported.

- **Reablation rates:** Skelly et al (2015) reported that based on data from three RCTs (n=184), the frequency of reablation following RFA ranged from 0% to 43% within 12 months of CA. The results were not pooled. They report that over follow-up periods of longer than 12 months to 48 months, frequency of reablation varied across four trials including 619 patients, this ranged from 12.5% to 49.2% with a pooled risk of 24.2% (95% CI 12.6 to 41.5).

- **Composite of death or hospitalisation for worsening heart failure:** Marrouche et al (2018) (n=118[2]) reported that, at a median follow up of 37.6 months, composite of death or hospitalisation for worsening heart failure (HF) was numerically but not statistically significantly in favour of CA [CA n=17/54 (31.5%) versus MT n=34/64 (53.1%); hazard ratio (HR) 0.60 (95% CI 0.34 to 1.08)], no p value was reported.

- **Quality of life:** Nielsen et al (2017) (n=294) reported no difference in quality of life scores after a five-year follow-up between the CA and MT study groups; SF-36[3] physical component scores were: CA 51 (interquartile range (IQR) 44 to 56) versus MT 52 (IQR 46 to 55), p=0.88; SF-36 mental component scores were CA 54 (IQR 47 to 57) versus MT 54 (IQR 49 to 56), p=0.94; there was no difference between groups in each of the eight scales from the SF-36 questionnaire (p>0.15 for all); no further details were provided. For the Arrhythmia-Specific questionnaire in Tachycardia and Arrhythmia (ASTA) score[4,] no difference was observed between groups in the ASTA index (mean 0.56± SD 0.71 (CA) vs 0.61±SD 0.63 (MT), p=0.18).

- Skelly et al (2015) reported no statistical differences between treatment groups for the SF-36 MCS scores at 12 months based on two RCTs (n=406); this held true whether the analysis was done using the difference in mean scores at follow-up 2.26 (95% CI -2.12 to 7.40) or using the difference in change from baseline scores 1.88 (95% CI -0.47 to 4.50). For PCS, catheter ablation was favoured over medical therapy when the pooled estimate was calculated using differences in mean follow-up scores (overall effect 2.85; 95% CI 0.93 to 4.82), however when the analysis was based on the change from baseline the

[2] Patients with paroxysmal AF

[3] The SF-36 questionnaire is a 36-item, patient-reported survey of patient health, it consists of eight scaled scores, which are the weighted sums of the questions in their section.

[4] The ASTA questionnaire scores eight symptoms of arrhythmia

effect was no longer statistically significant (overall effect 2.88; 95% CI 0.18 to 5.25). No p values were reported.

- The authors also reported no difference in both quality of life measures at 24 months for mean MCS scores [one RCT (n=294), CA: 51.1 ± SD 9.2 versus MT 50.9 ± SD 8.0] and mean PCS scores [one RCT (n=294), CA: 50.0 ± SD 8.8 versus MT 47.9 ± SD 8.9] and 48 months for mean MCS scores [one RCT (n=198) RFA: 52.9 ± SD 9 versus MT 51.9 ± SD 9] and mean PCS scores [one RCT (n=198) RFA: 52.3 ± SD 9 versus MT 52.6 ± SD 8]. No other details were reported.

2.2 Catheter ablation (CA) versus surgical ablation (SA) in the treatment of paroxysmal AF

- **Freedom from AF or any arrhythmia:** The RCT by Jan et al (2018) reported on the incidence of AF or any arrhythmia at mean follow-up of 30.5 months; [SA n=8/24 (33.4%) versus CA n=17/26 (65.4%); odds ratio (OR) 3.78 (95% CI 1.17 to 12.19); p=0.048]. This is in line with results from the SR by Phan et al (2016) which reported that surgical ablation is better at preventing AF (or any arrhythmia) than CA at up to 12 months follow-up; [SA (n=133) 82% versus CA (n=136) 62.5%; RR 1.35 (95% CI 1.01 to 1.79); p=0.04].

- **Re-intervention rates:** Jan et al (2018) (n=50) reported re-intervention rates at mean follow-up of 30.5 months in SA versus CA as n=4/24 (16.7%) versus n=9/26 (34.6%) respectively; however, no tests of statistical significance were reported.

Safety

2.3 Catheter ablation versus medical therapy (rhythm and/or rate control) in the treatment of paroxysmal AF

- **Stroke occurrence:** Skelly et al (2015) reported no difference in stroke occurrence within 30 days based on pooled results from three RCTs (n=481) [CA 0% to 0.7% versus medical therapy 0%; no test of statistical significance reported] and beyond 30 days based on two RCTs [CA n=0/98 (0%) versus MT n=0/96 (0%), p=NS]. No transient ischaemic attacks (TIAs) were reported at 12 or 48 months; however, one RCT (n=294) reported 0.7% in both the CA (1/146) and MT (1/148) groups. No p values were reported.

- **Major bleeding:** Skelly et al (2015) reported on major bleeding at one month from one RCT (n=67) although no tests of statistical significance was reported; [2/32 (6.3%) CA versus 1/35 (1.9%) MT].

- **Other complications:** Skelly et al (2015) reported on other complications attributable to CA such as cardiac tamponade within 24 months (n=512) [pooled risk from four RCTs of 1.7% (95% CI 0.8 to 3.6)], pericardial effusion within 48 months (n=519) [pooled risk from three RCTs 0.6% (95% CI 0.2 to 1.8)], pulmonary vein stenosis at 12 months [pooled risk based on two studies (n=122) was 1.6% (95% CI 0.4 to 6.3) and pooled risk based on two studies (n=283) with 24-month follow-up was 0.7% (95% CI 0.2 to 2.8). Other ablation-related harms reported in the HTA included perforation at the trans-septal puncture (one RCT n=194, 0.5%), perimyocarditis (two RCTs n=333, 0% to 1.7%) and haematoma at catheter insertion site (2 RCTs n=276, 1.6% to 2.2%).The authors also reported drug intolerance requiring discontinuation based on one RCT (n=99) in 23.2% of patients in the MT arm and 0% in the CA arm.

2.4 Catheter ablation versus surgical ablation (SA) in the treatment of paroxysmal AF

- **Peri-procedural complication rates:** The RCT by Jan et al (2018) (n=50) reported peri-procedural complication rates of CA n=3/24 (12.5%) CA versus SA n=0/26 (0%) but no

test of statistical significance was reported.

Cost effectiveness

2.5 Catheter ablation versus medical therapy (rhythm and/or rate control)

- Reynolds et al (2014) reported an ICER of £21,957 per QALY gained, with the use of cryoballoon ablation versus antiarrhythmic drugs (AADs). The authors concluded that, beyond a threshold of £22,000 per QALY gained, ablation becomes the more cost effective intervention, with probabilities of 86% and 97.2% of being cost effective at thresholds of £30,000 and £40,000 per QALY gained, respectively.

Conclusion

- One Health Technology Appraisal (HTA), one systematic review (SR) and three randomised controlled trials (RCTs) fulfilling the PICO criteria for clinical effectiveness and safety were identified for inclusion.
- There was moderate quality evidence for the effectiveness of CA compared with medical therapy, in patients with paroxysmal AF, and very limited data compared with surgical ablation. Compared with medical therapy, CA appeared to improve AF freedom, which could be sustained at five years. However, there were no benefits in terms of all-cause mortality (beyond 30 days), quality of life or LVEF (in PAF patients with HF). These results should be interpreted with caution because of the limitations of the data included in the HTA by Skelly et al (2015). There was substantial heterogeneity across included studies, which were mostly small, and a formal assessment of publication bias was not conducted. There was wide variability across studies and only one trial was considered to be good quality. Other important limitations of the evidence base include unclear randomisation concealment and lack of assessor blinding. These factors make it difficult to draw firm conclusions from the results of this review. Results from the RCT by Marrouche et al (2018) were based on a small number of patients with PAF in the study (n=118). In addition, physicians were not blinded in any of the studies although the assessors were mostly blinded. The long-term follow-up studies also involved significant loss of patients to follow up and crossover from medical therapy to ablation.
- Surgical ablation appears to be more effective at maintaining AF freedom and reducing recurrent of any form of atrial arrhythmias included symptomatic AF. However, peri-procedural complication rates appear higher with surgical ablation. These results should be interpreted with caution because they are based on limited data from one indirect comparison and two very small direct comparison studies included in one of the systematic reviews identified.
- There was moderate quality evidence for the cost effectiveness of cryoballoon ablation compared with medical therapy, with a UK NHS perspective. Cryoballoon ablation was cost effective beyond a threshold of £22,000 per QALY gained. This result should be treated with caution because the RCT data used for the efficacy assessment in the calculation may have exaggerated the benefit of cryoballoon ablation. The study was also funded by the equipment manufacturer.
- The published data on the effectiveness, safety and cost effectiveness of CA in paroxysmal AF, especially long-term data are fraught with limitations which make any conclusive interpretation difficult. No conclusions regarding which patients may benefit most, or regarding which patients may not benefit from CA, are possible with current evidence. Further long-term studies are required to establish whether preservation of sinus rhythm by CA or AADs therapy in AF has any impact on long-term outcome measured as survival and freedom from stroke and heart failure.

3 Methodology

- The methodology to undertake this review is specified by NHS England in their 'Guidance on conducting evidence reviews for Specialised Commissioning Products' (2016).
- A description of the relevant Population, Intervention, Comparison and Outcomes (PICO) to be included in this review was prepared by NHS England's Policy Working Group for the topic (see section 9 for PICO).
- The PICO was used to search for relevant publications in the following sources Embase, MEDLINE, Cochrane Library, TRIP and NICE Evidence (see section 10 for search strategy).
- The search dates for publications were between 1 January 2005 and 8 March 2019.
- The titles and abstracts of the results from the literature searches were assessed using the criteria from the PICO. Full text versions of papers which appeared potentially useful were obtained and reviewed to determine whether they were appropriate for inclusion. Papers which matched the PICO were selected for inclusion in this review.
- Using established hierarchy of evidence criteria[5], the best quality and most reliable studies which matched the PICO were selected for inclusion in this review. As randomised evidence was available, non-randomised studies were excluded.
- Studies were excluded if they did not report outcomes separately for patients with paroxysmal AF.
- Studies were excluded if they were already included in systematic reviews. Systematic reviews were excluded if more recent systematic reviews included the same primary studies.
- Evidence from all papers included was extracted and recorded in evidence summary tables, critically appraised and their quality assessed using National Service Framework for Long-term Conditions (NSF-LTC) evidence assessment framework (see section 7 below).
- The body of evidence for individual outcomes identified in the papers was graded and recorded in grade of evidence tables (see section 8 below).

4 Results

One Health Technology Appraisal (HTA), one systematic review (SR) and three randomised controlled trials (RCTs) fulfilling the PICO criteria for clinical effectiveness and safety were identified for inclusion.

One Health Technology Appraisal (HTA) (Skelly et al 2015) and three more recently published randomised controlled trials (RCTs) (Marrouche et al 2018, Nielsen et al 2017 and Bertaglia et al 2017) were found assessing the effectiveness of catheter ablation compared with medical treatment.

One systematic review (SR) (Phan et al 2016) and one more recently published RCT (Jan et al 2018) were found comparing catheter ablation with surgical ablation.

One UK based study of the cost effectiveness of catheter ablation in comparison to medical therapy (Reynold et al 2014) was found. No studies eligible for inclusion were found investigating the cost effectiveness of catheter ablation versus surgical ablation.

[5] https://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/

In patients with paroxysmal AF, what is the clinical effectiveness (including duration of benefit) of percutaneous left atrial catheter ablation compared with medical management, AV node ablation plus pacemaker or surgical ablation?

The clinical effectiveness outcomes reported in the HTA, SR and RCTs include freedom from arrhythmias, AF burden, maintenance of sinus rhythm, improvement in LVEF, hospitalisation, stroke occurrence, major bleeding, re-intervention rates, composite of death or hospitalisation for worsening HF, all-cause mortality and quality of life.

4.1 Catheter ablation versus medical therapy (rhythm or rate control) in the treatment of paroxysmal AF (one HTA and 3 RCTs)

All-cause mortality (<30 days)
Pooled results from three RCTs included in Skelly et al (2015) (n=570) reported no 30-day mortalities in either group. CA 0% to 0.7% versus medical therapy 0%. No test of statistical significance was reported.

All-cause mortality (>30 days)
Based on data from RCTs included in Skelly et al (2015), CA does not appear to affect all-cause mortality in patients with paroxysmal AF at up to 12 months [three RCTs (n=333) CA 0% to 1% versus MT 0% to 3.6%)] and at 24 months [two RCTs (n=408) CA 1.4% versus MT 2.8%] p value not reported for both.

Freedom from arrhythmia recurrence
Pooled results from four RCTs in the HTA by Skelly et al (2015) reported a significant difference in freedom of recurrence of AF between paroxysmal AF (PAF) patients treated with CA versus medical therapy. At 12 months, n=226/286 (79%) of CA patients versus n=64/245 (26.1%) of MT patients were free from AF; RR 3.06 (95% CI 2.35 to 3.90) favours CA, p<0.05. There was also a significant difference at 24 to 48 months in the pooled results from 3 RCTs: n=226/311 (72.6%) of CA patients versus n=178/308 (57.8%) in the MT group; RR 1.24 (95% CI 1.11 to 1.47) in favour of CA; p<0.05.

Nielsen et al (2018) reported the results of long-term follow-up of an RCT comparing CA versus medical therapy. At five years, Nielsen et al (2018) reported a significantly higher rate of AF freedom after CA compared with anti-arrhythmia drug therapy; n=126/146 (86%) RFA versus n=105/148 (71%) AADs; RR=0.82 (95% CI 0.73 to 0.93); p=0.001. Freedom from symptomatic AF was also significantly better in the CA group. CA versus AADs at 5-year follow-up: n=137/146 (94%) versus n=126/148 (85%); RR 0.91 (95% CI 0.84 to 0.98); p=0.015.

Freedom from AF burden
Neilson et al (2018) reported a significantly lower AF burden in the CA group compared with medical therapy. Burden of any AF at five years was significantly lower in the RFA than in the AADs group. 85% and 95% percentiles[6] for the RFA group were 0% and 56% respectively versus 7% and 97% respectively for the AADs group; p=0.003. Corresponding percentiles for symptomatic AF were also significantly lower for RFA: 0%, 7% (RFA) versus 0%, 11% (AADs); p=0.02.

Maintenance of sinus rhythm
Bertaglia et al (2017) reported no significant difference in the long-term maintenance of sinus

[6] The 95th percentile implies that 95% of the time, the burden is below this amount: so, the remaining 5% of the time, the burden is above that amount and 85th percentile implies that 85% of the time, the burden is below this amount: so, the remaining 15% of the time, the burden is above that amount.

rhythm between PAF patients treated with CA versus AADs. At 12 years: CA n=22/42 (51.2%) versus AADs n= 22/50 (44%); p=0.402.

Improvement in LVEF (HF patients)
Marrouche et al (2018) reported on the median LVEF changes in PAF patients with HF (LVEF of 35% or less). At 60 months median LVEF increases were: CA (n=14) 7% (5% to 16%) versus MT (n=11) 8% (-1% to 23%); however, the difference was not statistically significant (p=0.81).

Cardiac hospitalisation/readmission
Skelly et al (2015) reported that at 12 to 24 months following CA, patients had fewer cardiac hospitalisations or re-admissions than those on MT based on results from two RCTs. One RCT (n=67) reported at 12 months CA 9.4% versus MT 54.3% and the other (n=294) at 24 months CA 0% versus MT 1.4%. However, results were not pooled and no tests of statistical significance were reported.

Reablation rates
Reablation rates varied across studies both within 12 months and longer than 12 months. Skelly et al (2015) reported that the frequency of reablation following RFA ranged from 0% to 43% within 12 months of CA based on data from three RCTs (n=184). These results were not pooled. The authors report that over follow-up periods ranging from longer than 12 months to 48 months, frequency of reablation based on four trials including 619 patients ranged from 12.5% to 49.2% with a pooled risk of 24.2% (95% CI 12.6 to 41.5).

Composite of death or hospitalisation for worsening HF
At a median follow-up of 37.6 months, Marrouche et al (2018) reported no significant difference in the composite of death or hospitalisation for worsening HF in PAF patients with HF (LVEF of 35% or less). CA n=17/54 (31.5%) versus MT n=34/64 (53.1%); HR 0.60 (95% CI 0.34 to 1.08), p value was not reported.

Quality of life
Nielsen et al (2017) reported that quality of life (QoL) scores at five years did not differ between patients receiving CA (using RFA) or MT (using AADs). SF-36 physical component scores were 51 (IQR 44 to 56) in the CA group versus 52 (IQR 46 to 55) for MT; p=0.88. Mental component scores were 54 (IQR 47 to 57) for CA versus 54 (IQR 49 to 56) in the MT group; p=0.94. No differences were observed between the groups at five years comparing each of the eight scales from the SF-36 QoL questionnaire (p>0.15 for all). For the Arrhythmia-Specific questionnaire in Tachycardia and Arrhythmia (ASTA) score, no difference was observed between groups in the ASTA index (mean 0.56±SD 0.71 (RFA) vs 0.61±SD 0.63 (AADs), p=0.18).

Skelly et al (2015) reported no statistical differences between treatment groups for the SF-36 MCS at 12 months based on two RCTs (n=406); this held true whether the analysis was done using the difference in mean scores at follow-up 2.26 (95% CI -2.12 to 7.40) or using the difference in change from baseline scores 1.88 (95% CI -0.47 to 4.50). For PCS, RFA was favoured over medical therapy when the pooled estimate was calculated using differences in mean follow-up scores (overall effect 2.85; 95% CI 0.93 to 4.82), however when the analysis was based on the change from baseline the effect was no longer statistically meaningful (overall effect 2.88; 95% CI 0.18 to 5.25). No p values were reported.

The authors also reported no difference in both QoL measures at 24 months, MCS scores [one RCT (n=294) CA: 51.1 ± SD 9.2 versus MT 50.9 ± SD 8.0] and PCS scores [one RCT (n=294) CA: 50.0 ± SD 8.8 versus MT 47.9 ± SD 8.9] and 48 months for MCS scores [one RCT (n=198) CA: 52.9 ± SD 9 versus MT 51.9 ± SD 9] and PCS scores [one RCT (n=198) CA: 52.3 ± SD 9

versus MT 52.6 ± SD 8]. No other details were reported.

4.2 Catheter ablation versus surgical ablation in the treatment of paroxysmal AF

Freedom from AF or any arrhythmias

Jan et al (2018) reported a significant reduction in recurrence of AF/atrial tachycardia (AT)/atrial flutter (AFL) with SA [convergent epicardial and endocardial ablation procedure (CVP)] compared with CA. At a mean follow-up of 30.5 months, recurrence was observed in n=8/24 (33.4%) of SA versus n=17/26 (65.4%) of CA patients. OR 3.78 (95% CI 1.17 to 12.19), p=0.048.

Pooled results from four RCTs included in the systematic review by Phan et al (2016) (n=269) showed that, for the PAF group, there was a higher prevalence of freedom from AF at 12 months in the SA (n=133) cohort versus CA (n=136) cohort (82.0% versus 62.5%; RR, 1.35 (95% CI 1.01, 1.79); I^2 = 54%; p=0.04.

Re-intervention rates

In the RCT by Jan et al (2018), through the entire follow-up period (30.5±6.9 months), n=9/26 (34.6%) CA patients and n=4/24 (16.7%) SA patients required re-intervention. No tests of statistical significance were reported.

In patients with paroxysmal AF, what is the safety of percutaneous left atrial catheter ablation compared with medical management[7]?

4.3 Catheter ablation versus medical therapy (rhythm and /or rate control) in the treatment of paroxysmal AF (one HTA)

Stroke occurrence (<30 days)

Pooled results from three RCTs included in Skelly et al (2015) (n=481) reported no strokes within 30 days of procedure in either group. CA 0% to 0.7% versus medical therapy 0%. No test of statistical significance was reported.

Stroke occurrence (>30 days)

In two fair quality RCTs included in the HTA by Skelly et al (2015), no strokes were observed in either group past the 30-day peri-procedural time and at 12 to 24 months follow-up. CA n=0/98 (0%) versus MT n=0/96 (0%); p=NS. No transient ischaemic attacks (TIAs) were reported at 12 or 48 months however, one RCT (n=294) reported 0.7% in both the CA (1/146) and MT (1/148) groups. No p values were reported.

Major bleeding

One RCT included in the HTA by Skelly et al (2015), reported on the rates of major bleeding or haemorrhage, including those requiring transfusion that occurred with 30 days of the CA procedure. There was no difference in the risk of 30-day major bleeding, haemorrhage, or transfusion between treatment groups. Major bleeding occurred in n=2/32 (6.3%) of CA patients versus n=1/35 (1.9%) in the MT group. No tests of statistical significance were reported.

Other complications

Skelly et al (2015) reported on other complications attributable to CA such as cardiac tamponade within 24 months (n=512) [pooled risk from four RCTs of 1.7% (95% CI 0.8 to 3.6)], pericardial effusion within 48 months (n=519) [pooled risk from three RCTs 0.6% (95% CI 0.2 to 1.8)], pulmonary vein stenosis at 12 months [pooled risk based on two studies (n=122) was 1.6% (95% CI 0.4 to 6.3) and pooled risk based on two studies (n=283) with 24-month follow-up was 0.7% (95% CI 0.2 to 2.8). Other ablation-related harms reported in the HTA included perforation at the

[7] Surgical ablation and "pace and ablate" are very separate procedures that have different sets of complications and are incomparable to left atrial catheter ablation. Therefore, it will be very unlikely to identify any relevant research.

trans-septal puncture (one RCT n=194, 0.5%), perimyocarditis (two RCTs n=333, 0% to 1.7%) and haematoma at catheter insertion site (2 RCTs n=276, 1.6% to 2.2%). There were no reports of atrio-oesophageal fistula, diaphragmatic paralysis, heart block and pneumothorax.

The authors also reported drug intolerance requiring discontinuation based on one RCT (n=99) in 23.2% of patients in the MT arm and 0% in the CA arm.

4.4 Catheter ablation versus surgical ablation in the treatment of paroxysmal AF

Per-procedural complication rates
Jan et al (2018) reported a trend of major peri-procedural complication rates higher in SA treated patients 3/24 (12.5%) versus 0/26 (0%) in patient who underwent CA. No tests of statistical significance reported.

In patients with paroxysmal AF, what is the cost effectiveness of percutaneous left atrial catheter ablation compared with medical management, AV node ablation plus pacemaker or surgical ablation?

Cost effectiveness (ICER)
In a cost effectiveness analysis from a UK NHS perspective, Reynolds et al (2014) reported an ICER of £21,957 per QALY gained, with the use of cryoballoon ablation versus AADs. The authors concluded that, beyond a threshold of £22, 000 per QALY gained, ablation becomes the more cost effective intervention, with probabilities of 86% and 97.2% of being cost effective at thresholds of £30,000 and £40,000 per QALY gained, respectively.

From the evidence selected, are there any subgroups that may benefit from percutaneous left atrial catheter ablation more than the wider population of interest (such as heart failure)?
The evidence selected did not include any suitable sub-group analysis or other comparison that can help identify sub-groups of patients who would gain greater benefit from percutaneous left atrial catheter ablation more than the wider population of interest.

From the evidence selected, are there any subgroups of patients that would not benefit from percutaneous left atrial catheter ablation?
The evidence selected did not include any suitable sub-group analysis or other comparison that can help identify sub-groups of patients who would not benefit from percutaneous left atrial catheter ablation. However, the RCT by Marrouche et al (2018) assessed whether CA lowers morbidity and mortality compared with MT in patients with coexisting AF and medically managed HF. The results of this study are reported in section 4.

From the evidence selected, is there a maximum number of clinically effective procedures undertaken per patient that can be performed safely in paroxysmal AF?
The evidence selected did not include any suitable analysis which can help elicit whether there is a maximum number of clinically effective procedures undertaken per patient that can be performed safely in paroxysmal AF.

5 Discussion

The HTA by Skelly et al (2015) represents moderate quality evidence for the effectiveness of CA compared with medical therapy (rhythm and/or rate control) in the management of patients with paroxysmal AF. Pooled data from four RCTs showed that, compared with medical therapy, CA significantly improved freedom from AF at 12 months. Cardiac hospitalisation and readmission were also significantly reduced in CA compared with medical therapy. However, all-cause mortality and stroke occurrence (including TIAs) beyond 30 days were not significantly different between the treatment groups. There was also no difference between CA and medical therapy in terms of major bleeding, stroke or all-cause mortality within 30 days. Longer term follow-up data by Nielsen et al (2017) showed that freedom from all AF, symptomatic AF and AF burden remained improved in the CA arm versus medical therapy at five years. However, there was no difference between the groups in terms of quality of life; this is in line with the findings reported in the HTA carried out by Skelly et al (2015). A longer-term follow-up study by Bertaglia et al (2017) showed no significant difference between CA and medical therapy in maintenance of sinus rhythm at 12 years. A moderate quality RCT by Marrouche et al (2018) reported no significant difference in LVEF improvements between CA and medical therapy in PAF patients with HF (ejection fraction <35%). Marrouche et al (2018) also reported no significant difference in rates of composite of death or hospitalisation for worsening HF. Reablation was quite common after CA and varied across studies ranging from 0% to 43%. The evidence suggests that CA is associated with complications such as cardiac tamponade, pericardial effusion and pulmonary vein stenosis.

Jan et al (2018) reported a significant reduction in recurrence of AF and other atrial arrhythmias with surgical ablation compared with CA. Surgical ablation patients also tended to require refer re-interventions. The systematic review by Phan et al (2016) also reported a higher prevalence of freedom from AF with surgical ablation compared with CA. There was tendency towards a higher rate in major peri-procedural complications associated with SA treated patients but the statistical significance of this was not reported.

Reynolds et al (2014) reported an ICER of £21,957 per QALY gained, with the use of cryoballoon ablation versus AADs. They concluded that, beyond a threshold of £22, 000 per QALY gained, ablation becomes the more cost effective intervention.

These results should be interpreted with caution because of the limitations in these studies. Results from meta-analyses were or limited reliability due to the heterogeneity in the interventions, patient groups and outcome definition across the included studies. Most of the included studies were of limited size and with no clear concealment of allocation. There are no large RCTs investigating CA versus medical therapy or surgical ablation specifically in paroxysmal AF patients. The available data have therefore been synthesized from those RCTs that reported outcomes on paroxysmal AF patients separately. However, we do not know whether the paroxysmal AF patients in these studies were balanced enough in baseline characteristics as to make a conclusive inference on the results. The available comparative data versus surgical ablation is even more limited to an indirect comparison and two very small direct comparison studies. The single cost effectiveness study could also have exaggerated the comparative efficacy of the ablation over medication therapy which could have increased the cost effectiveness.

6 Conclusion

We found moderate quality evidence for the effectiveness of CA compared with medical therapy, in patients with paroxysmal AF, and very limited data compared with surgical ablation.

Compared with medical therapy, CA appeared to improve AF freedom, which could be sustained at five years. However, there are no benefits in terms of all-cause mortality, quality of life or LVEF (the latter in PAF patients with HF). There were no differences in short term (within 30 days) mortality, stroke and major bleeding.

The quality of evidence supporting the comparative effectiveness of CA versus surgical ablation was low. Surgical ablation appears to be more effective at maintaining AF freedom and reducing recurrent of any form of atrial arrhythmias included symptomatic AF. However, peri-procedural complication rates appear higher with surgical ablation.

We found moderate quality evidence for the cost effectiveness of cryoballoon ablation compared with medical therapy, from a UK NHS perspective. Cryoballoon ablation was cost effective beyond a threshold of £22,000 per QALY gained. However, the result may have been exaggerated by the high recurrence rate used for assessment of cost in the AADs group.

The published data on the effectiveness, safety and cost effectiveness of CA in paroxysmal AF, especially long-term data are fraught with limitations which make interpretation difficult. No conclusions regarding which patients may benefit most or regarding which patients may not benefit from catheter ablation are possible with current evidence. Further long-term studies are required to establish whether preservation of sinus rhythm by CA or AADs therapy in AF has any impact on long-term outcome measured as survival and freedom from stroke and heart failure.

7 Evidence Summary Table

For abbreviations see list after each table

a) Use of catheter ablation vs. medical therapy to treat paroxysmal AF									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Marrouche et al 2018 CASTLE-AF 33 sites in Europe, Australia and the United States	P1-multicentre RCT	Patients with HF; history of symptomatic PAF (n=118) or persistent AF (n=245); absence of response, unacceptable side effects, or unwilling to take AADs and NYHA class II, III, IV HF and a LVEF 35% or less Total n=363 Mean follow-up for all included patients: ablation group 37.6±20.4 months (median, 38.7 months; IQR, 22.3 to 60.0); medical therapy group 37.4±17.7 months (median, 37.0 months; IQR, 24.4 to 55.9)	CA (n=179 of which n=54 (30.2%) with PAF); to achieve isolation of all pulmonary veins and restore sinus rhythm. Additional ablation lesions were made at the operators' discretion **Versus** Medical therapy (n=184; =of which n=64 (34.8%) with PAF); rate or rhythm control, to achieve ventricular rate of 60 to 80 beats per minute at rest and 90 to 115 beats per minute during moderate exercise	Primary Clinical effectiveness	Composite of death or hospitalisation for worsening HF in PAF patients	At a median follow up of 37.6 months CA 17/54 (31.5%) vs. MT 34/64 (53.1%); HR 0.60 (95% CI 0.34 to 1.08), p value not reported	7	Direct	Both groups were well matched for baseline characteristics including the proportion of patients with persistent AF vs paroxysmal AF. However, it is not clear whether the paroxysmal AF subset of patients in each group were equally well matched. In addition, just over 30% of the patients had paroxysmal AF. All patients were accounted for at the end of the study, albeit there were more than twice as many patients lost to follow up in the CA group 23/179 (12.8%) versus 10/184 (5.4%). The authors did not comment on reasons for this. One of the limitations of this trial is the lack of blinding regarding randomisation and treatment. It would have been quite difficult to perform a truly blinded trial with a sham ablation procedure, but the lack of blinding could have led to bias in such decisions as to whether to admit a patient for worsening heart failure. All the patients had an implantable cardioverter–defibrillator (ICD) device or a cardiac resynchronization therapy defibrillator (CRT-D) with automatic daily remote monitoring capabilities, which may have affected overall mortality in the two groups. A greater number of patients in the ablation group (28 patients 15.6%) than in the medical therapy group (18 patients 9.8%) crossed over to the other treatment group, but the results of per-protocol and as treated analyses were similar to those of the primary analysis. Finally, although medical therapy (for both AF and HF) was managed systematically, we cannot exclude the possibility that a different or more aggressive approach to medical management might have influenced the
				Secondary Clinical effectiveness	Improvement in LVEF (median percentage improvement) in PAF patients	At 12 months: CA (n=41) 8% [IQR 0 to 10] vs MT (n=54) 3% [IQR -3 to 9]; p=0.2 At 36 months: CA (n=24) 4% (IQR -1.5 to 11) vs MT (n=34) 0.5% (IQR -7 to 9); p=0.30 At 60 months: CA (n=14) 7% (IQR 5 to 16) vs MT (n=11) 8% (IQR -1 to 23); p=0.81			

a) Use of catheter ablation vs. medical therapy to treat paroxysmal AF									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
									trial results. Furthermore, side effects and unwillingness to take antiarrhythmic drugs were listed as recruitment criteria, and it was not clear whether this could have affected the outcome in the medical therapy arm. For example, no attempt to assess compliance with medical therapy was reported.
Nielsen et al 2017 10 centres in Scandinavia and Germany	P1-Multicentre RCT 5-year follow-up	Patients ≤ 70 years of age with PAF, candidates for AADs with ≥2 episodes of symptomatic PAF within preceding 6 months Exclusion criteria included: previous treatment with class IC or class III AADs, previous ablation for AF, or left atrial diameter >50 mm, left ventricular ejection fraction <40%, moderate to severe mitral valve disease, and severe heart failure 245 (83%) of the 294 patients	RFA (n=146) vs. AADs (n=148 At 5-year follow-up RFA (n=125) vs. AADs (n=120)	Primary Clinical effectiveness	Freedom from AF	**RFA vs. AADs at 5-year FU** n=126/146 (86%) vs. n=105/148 (71%) RR=0.82; 95% CI 0.73 to 0.93; p=0.001	7	Direct	Although the Holter[8] analysis was blinded, treatments in this trial could not be blinded, and this could have introduced some bias to the results. The significant loss to follow-up (49 patients, 16.6%) is a major limitation, and bias caused by that loss cannot be excluded. However, the majority of patients lost to follow-up were included in the analysis making bias less likely. The authors report data from one 7-day Holter recording obtained 5 years after the start of the study. No data regarding the occurrence or burden of AF from 2- to 5-year follow-up were available. It is likely that more AF would have been detected had more intense monitoring been employed. It is also a limitation that we have no data from the period between the 2- and 5-year follow-ups, and thus may have missed complications with AADs. Per protocol, only AF episodes >1 min were taken into account, not >30 s as recommended today. Comparisons between groups may have been different using more intensive monitoring or another cut-off for AF episode length. Freedom
				Primary Clinical effectiveness	Freedom from symptomatic AF	**RFA vs. AADs at 5-year FU** n=137/146 (94%) vs. n=126/148 (85%) RR 0.91; 95% CI 0.84 to 0.98; p=0.015			
				Primary Clinical effectiveness	Any AF burden[9]	85% and 95% percentiles[10] : RFA 0%, 56% vs. AADs 7%, 97%, p=0.003			
				Primary Clinical effectiveness	Symptomatic AF burden	85% and 95% percentiles: RFA 0%, 7% vs. AADs 0%, 11% p=0.002			

[8] A Holter monitor is a battery-operated portable device that measures and records your heart's activity (ECG) continuously for 24 to 48 hours or longer depending on the type of monitoring used.

[9] AF burden was defined as the percentage of time in AF according to Holter readings; AF episodes longer than 1 minute

[10] The 95th percentile implies that 95% of the time, the burden is below this amount: so, the remaining 5% of the time, the burden is above that amount and 85th percentile implies that 85% of the time, the burden is below this amount: so, the remaining 15% of the time, the burden is above that amount.

a) Use of catheter ablation vs. medical therapy to treat paroxysmal AF									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		initially randomised were analysed at 5 years		Primary Clinical effectiveness	QoL; SF-36 physical component score	**RFA vs. AADs at 5-year FU** 51 (IQR 44 to 56) vs. 52 (IQR 46 to 55) p=0.88			from AF cannot be confirmed without more intense monitoring. Data on stroke, heart failure or hospitalisations after the 2-year follow-up were not reported. Cardioversions after 2 years were not reported, so we cannot exclude the possibility that the different use of cardioversions in the two groups affected the results in this non-blinded study. It also cannot be excluded that clinical events such as complications with the CA procedures occurred beyond the 2-year follow-up. In contrast to the immediate complications occurring with CA, the complication risk with AADs persists during the treatment period.
				Primary Clinical effectiveness	QoL; SF-36 mental component score	**RFA vs. AADs at 5-year FU** 54 (IQR 47 to 57) vs. 54 (IQR 49 to 56) p=0.94			
				Primary Clinical effectiveness	QoL; SF-36 (8 scales)	**RFA vs. AADs at 5-year FU** p>0.15 for all scales, no further details reported			
				Primary Clinical effectiveness	QoL; ASTA score (8 scales)	**RFA vs. AADs at 5-year FU** No difference between groups in the ASTA index (mean 0.56±0.71 (RFA) vs 0.61±0.63 (AADs), p=0.18).			
Bertaglia et al 2017 Prospective, multi-centre, randomized, controlled study Italy	P1 – RCT 12-year FU of CACAF study. n=97/137 alive & analysed	Patients with PAF (n= 92/137) & persistent AF intolerant of AADs or ≥2 AADs had failed	CA + AADs (n=42) vs. AADs alone (n=50)	Primary Clinical effectiveness	Maintenance of sinus rhythm in PAF patients	**CA vs. AADs at 12-year FU** n=22/42 (51.2%) vs. n=22/50 (44%) p=0.402	6	Direct	The study groups appeared to be well balanced in terms of clinical and echocardiographic characteristics. The study has several potential limitations. This 12-year analysis was not planned at the outset of the CACAF Study and may therefore suffer from hidden biases and other unidentified confounders. The number of patients lost to follow-up was low but not insignificant, and the number of patients randomised to AADs who underwent CA after failure of AADs could have increased sinus

a) Use of catheter ablation vs. medical therapy to treat paroxysmal AF									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
									rhythm persistence in this population. Sinus rhythm maintenance was mainly based on the last ECG. Without routine ambulatory monitors and ECGs, long-term arrhythmia recurrence rates and sinus rhythm rates could be overestimated because of the inability to detect subclinical arrhythmias. Although over 60% of patients had a structural heart disease, most of them had well-preserved systolic function. The data cannot, therefore, be extrapolated to patients with more severe heart disease and impaired systolic function. Study entry criteria included intolerance of AADs. There was no report on compliance with AADs. AADs are commonly associated with side effects and compliance could have affected the outcome. Although amiodarone was the preferred AADs, the final decision was left to the physician who was not reported to be blinded to the treatment. The physician's belief about the residual risk in each patient could have biased their choice of AADs.
Skelly et al 2015 USA 13 RCTs 6 RCTs included paroxysmal patients only (of which 3 RCTs studied CA as first line treatment and 3 RCTs studied	S1- HTA	Patients with any AF (persistent or paroxysmal AF) [total n=968, (range 70 to 294) patients with PAF] Patients who had no prior treatment with AADs (n=475); patients with prior but unsuccessful treatment with	Radiofrequency catheter ablation (n=503) vs. medical therapy (n=465)	Primary Clinical effectiveness	Freedom from recurrence of any arrhythmia	**CA vs. MT** **At ≤12 months (4 RCTs) n=531** n=226/286 (79%) vs. n=64/245 (26.1%) RR 3.06 (95% CI 2.35 to 3.90) favours CA No significant heterogeneity (I^2 = 2.2%; p=0.381) **At 24 to 48 months (3 RCTs) n=619**	8	Direct	Thirteen RCTs compared CA (RFA) with medical therapy. There was 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. Only one trial was considered by the HTA authors to be good quality; the remaining trials were all considered fair quality. Four RCTs did not report information on random sequence generation. One RCT did not perform an intention-to-treat analysis. Discrepancies in baseline characteristics as well as unclear

a) Use of catheter ablation vs. medical therapy to treat paroxysmal AF									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
CA as second line treatment) and 2 RCTs included patients with both persistent or paroxysmal AF[11]		AADs (n=464)				n=226/311 (72.6%) vs. n=178/308 (57.8%) RR 1.24 (95% CI 1.11 to 1.47) favours CA p<0.05 No significant heterogeneity (I^2 =0.0%, p=0.388)			randomisation methods were observed. There was substantial crossover (37.0% to 87.9%) from medical therapy to CA in six trials, crossover figures were not reported separately for PAF. The high frequency of crossover from medical therapy to ablation in most included studies may hinder drawing definitive conclusions regarding the full benefits and harms of CA compared with medical therapy. Considerably smaller number of patients crossed over from ablation to medical therapy (0% to 9.4%) in seven RCTs, crossover figures was not reported separately for PAF. Other important limitations of the evidence base include the sample size of the available trials, limited data available on primary clinical outcomes particularly at follow-up times >12 months, and unclear allocation concealment (only one documented concealed allocation) and lack of assessor blinding for primary outcomes. These factors make it difficult to draw strong conclusions regarding the effects and benefits of CA. Study sizes were likely insufficient to effectively determine risk of the primary clinical outcomes (e.g. mortality) for either group or to detect statistical differences between treatment groups. Discrepancies in baseline characteristics as well as unclear randomisation methods were observed in some of the studies Most studies focused on freedom from recurrence. This was variably defined and adjudicated across studies; there was heterogeneity across studies regarding whether recurrence included any atrial arrhythmia or AF only, whether symptomatic and asymptomatic recurrences were included, and whether
				Primary Clinical effectiveness	Reablation	**At ≤12 months** 3 RCTs (n=184): Rates varied widely (0% to 43.3%) These results are not pooled. **At >12 to 48 months**, 4 RCTs (n=619): 24.2% (95%CI 12.6 to 41.5%)			
				Primary Clinical effectiveness	Cardiac hospitalisation/re-admission	**At 12 months (1 RCT n=67)** CA 9.4% vs. MT 54.3% **At 24 months (1 RCT n=294)** CA 0% vs. MT 1.4%			
				Primary Safety	Stroke occurrence/transient ischaemic attack	**Stroke** **CA vs. MT** **≤ 30 days (3 RCTs, n=481)** 0% to 0.7% vs. 0% No p value reported **≥ 30 days (2 RCTs)** **At ≤12 months** (1			

[11] Results for the studies with mixed populations are not included here

a) Use of catheter ablation vs. medical therapy to treat paroxysmal AF									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						RCT, n=67) **At 24 months** (1 RCT, n=127) no strokes reported **TIA** **At 12 months** (1 RCT, n=67) no TIAs (0%) reported; **At 24 months** (1 RCT, n=294) 1/146 (0.7%) vs. 1/148 (0.7%) No p value reported **At 48 months** (1 RCT, n=198) no TIAs (0%) reported;			characteristics related to duration were considered. In addition, blanking periods ranged from 1 to 3 months across 11 RCTs (one RCT did not report on the length of the blanking period), figures were not reported separately for PAF. This variability in study protocols likely introduces variation in the cross-study calculations of the proportion of those free from AF after the blanking period. The majority of trials received funding from manufacturers. Conflicts of interest were mainly in the form of grants or consulting fees from biomedical companies and were disclosed by eight trials, and one did not report whether any conflicts existed among its authors. There was substantial heterogeneity across included studies with regard to techniques and approaches that precluded comparative evaluation of studies. Formal assessment of publication bias was not conducted by the HTA authors as there were fewer than 10 studies available for outcomes based on AF type. Stratification by AF type was felt to be clinically important and stratification to assess data at follow-up at >12 months was important to answering key questions. This resulted in fewer studies available for pooling within follow-up strata. Profile likelihood methods were used to provide more conservative estimates and confidence intervals given the small number of studies. This, combined with sparse data for many outcomes, may have limited the ability to explore statistical heterogeneity and precluded ability for further subgroup analyses.
				Primary Safety	Major bleeding	**CA vs. MT** **At 1 month (1 RCTs) n=67** n=2/32 (6.3%) vs. n=1/35 (1.9%) No tests of statistical significance reported			
				Primary Safety	Cardiac tamponade	**At ≤24 months**: 4 RCTs (n=512), 1.7% of CA patients (95%CI 0.8 to 3.6%)			
				Primary Safety	Pericardial effusion	**At ≤48 months:** 3 RCTs (n=519), pooled estimate 0.6% of CA patients			

a) Use of catheter ablation vs. medical therapy to treat paroxysmal AF									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						(95% CI 0.2 to 1.8)			
				Primary Safety	Pulmonary vein stenosis	**At 12 months:** 2 RCTs (n=122), 1.6% of CA patients (95% CI 0.4% to 6.3%) **At 24 months:** 2 RCTs (n=283), 0.7% of CA patients (95% CI 0.2% to 2.8%)			
				Primary Safety	Other ablation-related complications	Perimyocarditis: 2 RCT (n=194, n=139) 0% to 0.5% of CA patients Perforation at transseptal puncture: 1 RCT (n=194) 0.5% of CA patients Haematoma at catheter insertion site: (2 RCTs n=276) 1.6% to 2.2% of CA patients Other complications measured, each with 0% occurrence: Atrio-oesophageal fistula Diaphragmatic paralysis Heart block Pneumothorax Drug-related			

a) Use of catheter ablation vs. medical therapy to treat paroxysmal AF									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						adverse events: most frequent was 'drug intolerance requiring discontinuation' reported in 23.2% (n=23/99) of MT patients vs 0% (n= 0/99) CA			
				Primary Safety	All-cause mortality (MI numbers are included as all MIs were fatal)	**CA vs. MT** **≤ 30 days (3 RCTs, n=570)** 0% to 0.7% vs. 0% No p value reported **At ≤ 12 months (3 RCTs**, n=333) CA 0% to 1% vs MT 0% to 3.6% **At 24 months (2 RCTs, n=408)** CA 1.4% versus MT 2.8% p=not reported			

a) Use of catheter ablation vs. medical therapy to treat paroxysmal AF									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
				Primary Clinical effectiveness	QoL; SF-36 MCS scores	**At ≤12 Months (2 RCTs) n=406** Difference in change from baseline scores 1.88 (95% CI -0.47 to 4.50) Difference in mean scores at follow-up 2.26 (95% CI -2.12 to 7.40) **No difference for both** **At 24 months (1 RCT) n=294** RFA: 51.1 ± SD 9.2 vs. MT 50.9 ± SD 8.0 **At 48 months (1 RCT) n=198** RFA: 52.9 ± SD 9 vs. MT 51.9 ± SD 9 **No difference for both** **No other details were reported**			

a) Use of catheter ablation vs. medical therapy to treat paroxysmal AF									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
				Primary Clinical effectiveness Primary Cost effectiveness	QoL; SF-36 PCS scores	**At ≤12 Months (2 RCTs) n=406** Difference in change from baseline scores 2.88 (95% CI -0.18 to 5.25) **No difference** Difference in mean scores at follow-up 2.85 (95% CI 0.93 to 4.82) **Favours RFA** **At 24 months (1 RCT) n=294** RFA: 50.0 ± SD 8.8 vs. MT: 47.9 ± SD 8.9 **At 48 months (1 RCT) n=198** RFA: 52.3 ± SD 9 vs. MT: 52.6 ±SD 8 **No difference for both** **No other details were reported**			

a) Use of catheter ablation vs. medical therapy to treat paroxysmal AF									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
					Cost	**Cryoballoon ablation vs. AADs** £21,162 vs. £17,627			
Reynolds et al 2014 UK	S2- cost effectiveness analysis	Patients with paroxysmal AF unsuccessfully treated with ≥1 AAD Total n=245; CA (n=163); medical therapy (n =82)	Cryoballoon ablation (n=163) vs. AADs (n=82)	Primary Cost effectiveness	QALY	**Cryoballoon ablation vs. AADs** 3.565 vs. 3.404	7	Direct	The authors developed a Markov model to assess the cost effectiveness of cryoablation compared with AADs in patients with PAF. They took a UK NHS perspective and costs were based on 2011 prices. QALYs were discounted at 3.5% per year, in line with guidance from the National Institute for Health and Clinical Excellence. A 5-year horizon was used in the base-case analysis to reflect uncertainty in long-term outcomes in this population. Quality of life data were collected in STOP-AF via the SF-36, which was administered at baseline and at the 12-month follow-up visit of the STOP-AF study. One-way sensitivity analyses showed that the model result was the most sensitive to the time horizon used, the costs of follow-up care in patients with recurrent AF, and the total cost of the ablation procedure. The study however had a number of limitations, which may have affected the results. Firstly, the efficacy assessment was based on STOP-AF study (n=163) comparing cryoablation with AADs. In this study at 12 months, treatment success was 69.9% of CA patients compared with 7.3% of AADs patients (ARR, 62.6% [p < 0.001]). This effect size is considerably greater than that those observed in other CA vs. AADs studies, mostly due to a higher recurrence rate in
					ICER	Based on a 5-year time horizon & with both costs and QALYs discounted at 3.5% per year. £21 957 per QALY gained.			

a) Use of catheter ablation vs. medical therapy to treat paroxysmal AF									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
									the AADs group. The results of this study might have exaggerated the contribution of CA to the base case analysis. Secondly, 79% of AADs patients crossed over to cryoablation during 12 months of study follow-up due to recurrent, symptomatic AF. This might have been due to the limited choice of antiarrhythmic drugs permitted in the study. Thirdly, there is a dearth of long-term outcome date in PAF. Consequently, the authors limited the time horizon of their model to 5 years, The study was supported by Medtronics International. All the authors had either received honoraria from or were employed by Medtronics (manufacturers of balloon dilation catheters).

AADs- antiarrhythmic drugs; AF-atrial fibrillation; AFL – atrial flutter; AT- atrial tachycardia; CA-catheter ablation; CACAF- Catheter Ablation for the Cure of Atrial Fibrillation; CI-confidence interval; FU – follow up; HF-heart failure; HR-hazard ratio; ICER- incremental cost effectiveness ratio; IQR-interquartile range; LVEF- left ventricular ejection fraction; MCS-mental component scores; MT-medical treatment; NR-not reported; NS-not significant; NYHA-New York Heart Association; PAF-paroxysmal AF; PCS-physical component scores; QALY- quality-adjusted life-year; RFA-radiofrequency ablation; RCT-randomised control trial; RR-risk ratio

b) Use of catheter ablation vs. surgical ablation to treat paroxysmal AF									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Jan et al 2018 Slovenia	P1-Single-centre RCT	Patients with history of paroxysmal AF with average duration of 4.8±3.6 years Age = 59.2 ± 8.9 years Male =74% Female = 26% n = 50 (32 patients had prior treatment with AADs) Mean follow-up = 30.5±6.9 months	Catheter ablation (n=) vs. convergent epicardial & endocardial ablation (n=)	Primary Clinical effectiveness	Incidence of AF/AT/AFL recurrence[12]	**CVP (SA) vs. CA** n=8/24 (33.4%) vs. n=17/26 (65.4%) OR 3.78 (95% CI 1.17 to 12.19); p=0.048	7	Direct	The small number of patients included limits the strengths of the findings of this study. Patients were blinded to the treatment they received: All patients in the SA group and none in the CA group were in general anaesthesia during the procedure, which might have influenced the results of arrhythmia occurrence. Any AF or other atrial arrhythmia lasting 6 minutes or more was defined as a recurrence. This time limit is different from the standard of 30 second stipulated in most current guidelines. Only point-by-point method[13] of CA was used, therefore the results may not be easily extrapolated to continuous cryoballoon technique of CA
				Primary Clinical effectiveness	Re-intervention	**CVP (SA) vs. CA** n=4/24 (16.7%) vs. n=9/26 (34.6%) No tests of statistical significance reported			
				Primary Safety	Major peri-procedural complications	**CVP (SA) vs. CA** n=3/24 (12.5%) vs. n=0/26 (0%) No tests of statistical significance reported			
Phan et al 2016 Sydney Australia 8 comparative studies; 3 RCTs & 5 observational studies. 3 RCTs (n=260) & 1 observational study (n=9) included PAF	S1-SR/MA	Patients with PAF or persistent AF Total number of patients with AF or PAF was not reported. Not clear what proportion of patients had prior treatment with AADs	CA vs. thoracoscopic SA	Primary Clinical effectiveness	Freedom from AF/arrhythmias	**At up to 12 months CVP(SA) vs. CA (4 studies, n=269)** 82% vs. 62.5%; RR, 1.35 (95% CI 1.01 to 1.79); p=0.04	6	Direct	Four of the included studies reported on AF freedom in PAF patients. The systematic review was performed according to the Transparent Reporting of Systematic Reviews and Meta-analyses (PRISMA) guidelines and Assessing the Methodological Quality of Systematic Reviews (AMSTAR) checklist recommendations However, the results of this systematic review are constrained by a number of limitations. The included studies consisted of a combination of retrospective observation studies and prospective randomized evidence. Retrospective studies are susceptible to selection bias, which may undermine the validity of the presented results. While there was no significant publication bias detected in this review, the small sample sizes and relatively short duration of follow-up are significant limitations of the majority of included studies.

[12] Every episode of AF/AT/AFL lasting 6 minutes or more was defined as a recurrence

[13] In the point-by-point method, the delivery is applied at each point generally for 60 s and set to find the next site after each ablation.

b) Use of catheter ablation vs. surgical ablation to treat paroxysmal AF									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
patients									There was heterogeneity in the studies (I^2 = 54 for the meta-analysis of AF freedom in PAF patients). Heterogeneity means that the results may not be applicable to the general AF population requiring non-pharmacological intervention. Furthermore, given that new onset AF is a known complication of prior cardiac surgery, patients with prior cardiac surgical procedures may have skewed or bias estimation for freedom from AF. Inter-study risk of publication bias was assessed by funnel plot methodology, and no significant asymmetry was observed using Begg's statistics (p = 0.75) and Egger's statistics (p = 0.49). Trim-and-fill analysis however demonstrated that there were three 'missing' studies from the available literature. The differences in observed efficacy may also be driven by the included study populations, which included a large proportion of patients who had failed prior non-pharmacological interventions. For example, a number of the included studies were based on patients with prior failed CA, and some of the patients had failed prior procedures. As such, the pooled patient population may have more advanced states of AF, predisposing to CA failure. Therefore, caution must be taken in interpreting the results of the present analysis, which is likely applicable to patients with severe refractory AF with prior attempts at CA, but not a general AF population.

AF-atrial fibrillation; AFL – atrial flutter; ASTA - Arrhythmia-Specific questionnaire in Tachycardia and Arrhythmia; AT- atrial tachycardia; CA-catheter ablation; CI-confidence interval; CVP-convergent epicardial and endocardial ablation procedure; MA-meta-analysis; NR-not reported; NS-not significant; OR-odds ratio; PAF-paroxysmal AF; RCT-randomised control trial; RR-risk ratio or relative risk used interchangeably; SA-surgical ablation; SR-systematic review

8 Grade of Evidence Table

For abbreviations see list after each table

a) Use of catheter ablation vs. medical therapy to treat paroxysmal AF					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
All-cause mortality	Skelly et al 2015	8	Direct	B	All-cause mortality was defined as any death past the 30-day peri-procedural time up to 12 (or 13) months or for which timing of mortality was not reported. All-cause mortality included all causes of mortality whether or not it was felt to be due to AF or complications of AF treatment. Skelly et al (2015) reported no difference in all-cause mortality between the intervention groups within 30 days based on pooled results from three RCTs (n=570) [CA 0% to 0.7% versus medical therapy 0%]; however, no test of statistical significance was reported. There was also no difference between the two study arms at up to 12 months [three RCTs (n=333) CA 0% to 1% versus MT 0% to 3.6%)] and at 24 months [two RCTs (n=408) CA 1.4% versus MT 2.8%] p value not reported for both. The systematic review suggests no difference in all-cause mortality between CA and MT. This result should be interpreted with caution because the study sizes were likely insufficient to effectively determine the effect of AF ablation on mortality or detect statistical differences between treatment groups.
Freedom from recurrence of any arrhythmia	Skelly et al 2015	8	Direct	B	Freedom from recurrence was variably defined across trials, with some trials defining it based on the presence of symptoms and others defining it based on duration and frequency of recurrent episodes of arrhythmia (any including AF). The blanking period[14] ranged from 1 to 3 months. Pooled results from 4 RCTs in the HTA by Skelly et al (2015) reported a significant difference in freedom of recurrence of AF between PAF patients treated with CA vs. MT. At 12 months 226/286 (79%) of CA patients vs. 64/245 (26.1%) of MT patients; RR 3.06 (95% CI; 2.35 to 3.90) favours CA, p<0.05. There was equally a significant difference at 24 to 48 months (3 RCTs) 226/311 (72.6%) of CA patients vs. 178/308 (57.8%) in the MT group. RR 1.24 (95% CI 1.11 to 1.47) favours CA, p<0.05. The systematic review suggests that CA is better at preventing

[14] In the period immediately after AF ablation, early recurrences of atrial arrhythmias (ERAA) are common and may not necessarily imply long-term ablation failure. Therefore, guidelines recommended implementation of a "blanking period" post-ablation during which AF or OAT recurrences need not be counted against long-term ablation success.

a) Use of catheter ablation vs. medical therapy to treat paroxysmal AF					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					any arrhythmia than MT. People with AF have higher risks of developing comorbidities such as heart failure and stroke as well as higher all-cause mortality rate. The goal of AF treatment is to establish sinus rhythm and/or achieve rhythm control. Many clinicians believe that achieving either of these goals may lead to a reduction in major cardiovascular events. Following CA, continuation of AADs treatment is sometimes required for some patients to maintain AF freedom. However, avoiding AADs where possible is considered a better outcome especially as it could obviate the ubiquitous undesirable side effects of these drugs. The results should be interpreted with caution because of the limitations of the data included and in the meta-analyses. There was substantial heterogeneity across included studies and a formal assessment of publication bias was not conducted. There was wide variability across studies (in the quality of reporting of study methods, in how outcomes were defined, and in which patients were included). Only one trial was considered to be good quality by the HTA authors; the remaining trials were all considered fair quality. Other important limitations of the evidence base include the small sample size of the available trials, discrepancies in baseline characteristics, unclear randomisation concealment and lack of assessor blinding. These factors make it difficult to draw strong conclusions regarding the effects and benefits of CA.
Freedom from AF burden	Nielsen et al 2017	7	Direct	B	AF burden was defined as the percentage of time in AF (AF episodes longer than 1 minute) according to 7 day Holter recording during follow up. At 5 years, significantly more patients in the RFA group (CA) were free from any AF (n=126/146 (86%) vs. 105/148 (71%), RR 0.82; 95% CI 0.73 to 0.93) p=0.001 and symptomatic AF (137/146 (94%) vs. 126/148 (85%), RR 0.91; 95% CI 0.84 to 0.98) p=0.015. Burden of any AF at 5 years was significantly lower in the RFA than in the AADs group. 85% and 95% percentiles for the CA group were 0%, 56% respectively vs. 7%, 97% respectively for the AADs group; p=0.003. Corresponding percentiles for symptomatic AF were: 0%, 7% (CA) vs. 0%, 11% (AADs), p=0.02. This study suggests that CA is more effective than AADs at reducing AF burden at 5-year follow-up. Freedom from symptomatic paroxysmal AF is of clinical value to patients in

a) Use of catheter ablation vs. medical therapy to treat paroxysmal AF					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					terms of reduced risk long-term complications of AF, e.g. stroke and HF. AADs, which may be required due to AF recurrence, are often associated with side effects. Long-term AF freedom is also of economic benefit to the health system in terms of reduced requirement for repeat ablation or hospitalisation. These results should be interpreted with caution because of certain limitations to the conduct of the study. Although Holder[15] analysis was blinded, treatments could not be blinded. There was significant loss to follow up although the majority of patients lost to follow-up were included in the analyses. Only AF episodes >1 minute were taken into account, not >30 seconds as currently recommended. AF freedom was based on a single 7-day Holter recording obtained 5 years after the start of the study. No data regarding the occurrence of burden of AF from 2- to 5- years' follow-up were recorded. It cannot be excluded that comparisons between groups would have been different using more intensive monitoring or another cut-off for AF episode length.
Maintenance of sinus rhythm	Bertaglia et al 2017	6	Direct	C	Sinus rhythm maintenance, which refers to continuation of normal sinus rhythm without appearance of an arrhythmia such as AF, was mainly based on the last ECG recording. Bertaglia et al (2017) reported no significant difference in the long-term maintenance of sinus rhythm between PAF patients treated with CA versus AADs. At 12 years: CA n=22/42 (51.2%) versus AADs n= 22/50 (44%); p=0.402. The goal of AF treatment is to establish sinus rhythm and/or achieve rhythm control. Many clinicians believe that achieving either of these goals may lead to a reduction in major cardiovascular events. Following CA, continuation of AADs treatment is sometimes required for some patients to remain in sinus rhythm. However, avoiding AADs where possible is considered a better outcome especially as it could obviate the ubiquitous undesirable side effects of these drugs. This result should be interpreted with caution because of certain limitations to the study. Sinus rhythm maintenance was mainly based on the last ECG. Without routine ambulatory monitors and ECGs, long-term arrhythmia recurrence rates and sinus rhythm rates could be overestimated because of the inability to detect subclinical arrhythmias. Although amiodarone was the preferred

[15] A Holter monitor is a battery-operated portable device that measures and records your heart's activity (ECG) continuously for 24 to 48 hours or longer depending on the type of monitoring used.

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Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					AADs, the final decision was left to the physician who was not reported to be blinded to the treatment. The physician's belief about the residual risk in each patient could have biased their choice of AADs. Although over 60% of patients had a structural heart disease, most of them had well-preserved systolic function. The data cannot, therefore, be extrapolated to patients with more severe heart disease and impaired systolic function.
Improvement in LVEF	Marrouche et al 2018	7	Direct	B	Improvement in LVEF was defined as the median absolute increase in LVEF from baseline to the 60-month follow-up. At 60 months, Marrouche et al (2018) reported a median LVEF increase in patients with heart failure and AF: CA (n=14) 7% (5 to 16) vs. MT (n=11) 8% (-1 to 23); However, the difference was not statistically significant, p=0.81. The study suggests no difference between CA and MT in improving LVEF. A significant increase in LVEF could have a positive impact on clinical outcomes like hospitalisation and quality of life outcomes like walking distance. Therefore this would be beneficial to the patients. This result should be interpreted with caution because of the relatively small number of paroxysmal AF patients assessed for this outcome (14 CA vs 11 medical therapy). Although patients' characteristics were well balanced between the two treatment arms in this study, the relative characteristics were not compared for the subgroup of paroxysmal AF patients reported on in the study. Furthermore, the study was not blinded and a greater number of patients in the ablation group than in the medical therapy group crossed over to the other treatment group. Patients with a worse LVEF at baseline could therefore have been more likely to cross over to the medical therapy group.
Cardiac hospitalisation/re-admission	Skelly et al 2015	8	Direct	B	Hospitalisation or re-hospitalisation for cardiac causes was reported in two of the RCTs included in the HTA by Skelly et al (2015). The studies did not provide further details regarding reasons for hospitalisation. Skelly et al (2015) reported that at 12 to 24 months following CA, patients had fewer cardiac hospitalisations or re-admissions than those on MT based on results from two RCTs. One RCT (n=67) reported that at 12 months CA 9.4% versus MT 54.3% and the other (n=294) at 24 months CA 0% versus MT 1.4%. However, results were not pooled and no tests of statistical significance were reported. The systematic review suggests that CA is better at

a) Use of catheter ablation vs. medical therapy to treat paroxysmal AF					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					hospitalisation or re-hospitalisation than MT. This can have a positive impact on complications and morbidity, for example due to infection. In general, acute hospital beds are a limited resource and increased hospital admissions are an important burden to health resources as well as for the patients. This result should be interpreted with caution because of the small size of the studies included. In addition, the studies did not provide further details regarding reasons for hospitalisation and the extent to which hospitalisation for re-ablation procedures or crossover from medical therapy to ablation was included.
Reablation	Skelly et al 2015	8	Direct	B	Repeat ablations (i.e., reablation for arrhythmia recurrence) were reported only if they occurred after the blanking period, which was typically three months. Skelly et al (2015) reported that, based on data from three RCTs (n=184), the frequency of reablation following RFA ranged from 0% to 43% within 12 months of CA. The results were not pooled. Over follow-up periods ranging from longer than 12 months to 48 months, frequency of reablation varied across four trials including 619 patients, this ranged from 12.5% to 49.2% with a pooled risk of 24.2% (95% CI 12.6 to 41.5). The HTA suggests that reablation is very common in patients who have undergone CA. These results are important because they reflect whether or not the primary or secondary treatment of AF with CA has been successful. These results should be interpreted with caution because the criteria for deciding which patients required reablation was not specified and could have varied between the different trials and clinical centres.
Composite of death or hospitalisation for worsening HF	Marrouche et al 2018	7	Direct	B	This refers to a composite of death from any cause or worsening of heart failure that led to an unplanned overnight hospitalisation. Patients requiring intravenous medication for HF or substantial increase and/or addition of thiazide to a loop were deemed to have worsening HF. Reasons for worsening of HR may include AF, acute coronary syndrome and hypertension. At a median follow-up of 37.6 month, Marrouche et al (2018) reported composite of death or hospitalisation for worsening HF in: CA n=17/54 (31.5%) vs. MT n=34/64 (53.1%); HR 0.60 (95% CI 0.34 to 1.08), in favour of CA, p value was not reported. This study suggests no difference between CA and MT at reducing composite of death or hospitalisation for worsening HF

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Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					than MT. AF and HR are common co-existing conditions, with AF increasing the risk of stroke, hospitalisation for HF and death. Successful treatment of AF can therefore substantially alter long-term outcomes in patients with HF. These results should be interpreted with caution because there was a lack of blinding with regard to randomisation and treatment. It would have been quite difficult to perform a truly blinded trial with a sham ablation procedure, but the lack of blinding could have led to bias in such decisions as whether to admit a patient for worsening heart failure. A greater number of patients in the ablation group than in the medical therapy group crossed over to the other treatment group, but the results of per-protocol and as-treated analyses were similar to those of the primary analysis. Finally, although medical therapy (for both atrial fibrillation and heart failure) was managed systematically, we cannot exclude the possibility that a different or more aggressive approach to medical management might have influenced the trial results. Furthermore, side effects and unwillingness to take antiarrhythmic drugs were listed as recruitment criteria, and it was not clear whether this could have affected the outcome in the medical therapy arm.
Stroke occurrence	Skelly et al 2015	8	Direct	B	None of the trials included in this study provided criteria or definitions for stroke diagnosis although they distinguished stroke from TIA. Skelly et al (2015) reported no difference in stroke occurrence within 30 days based on pooled results from three RCTs (n=481) [CA 0% to 0.7% versus medical therapy 0%; no test of statistical significance reported] and beyond 30 days based on two RCTs [CA n=0/98 (0%) versus MT n=0/96 (0%), p=NS]. No transient ischaemic attacks (TIAs) were reported at 12 or 48 months; however, one RCT (n=294) reported 0.7% in both the CA (1/146) and MT (1/148) groups. No p values were reported. The systematic review suggests no difference between CA and MT in the occurrence of stroke. AF is associated with an increased risk of stroke, which affects nearly 7% of AF patients with heart failure each year. Furthermore, ischaemic stroke that occurs in the setting of AF tends to be either fatal or of moderate to high severity in most patients. Therefore avoiding this would be beneficial to patients. This result should be interpreted with caution because none of the studies included in this systematic review provided criteria or

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Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					definitions for stroke diagnosis. Anticoagulation was used in all patients receiving RFA but anticoagulant used was variable reported for the medical group. The follow up period was too short to give any conclusive insight into the risk of strokes in the longer term.
Major bleeding	Skelly et al 2015	8	Direct	B	Major bleeding complications were defined as the occurrence of cardiac tamponade or haemopericardium that required intervention or caused symptoms, the need for transfusion, haematoma requiring intervention, massive haemoptysis, haemothorax, and retroperitoneal bleeding. There was no difference in the risk of 30-day major bleeding, haemorrhage, or transfusion between treatment groups. Major bleeding occurred in 2/32 (6.3%) RFA patients vs. 1/35 (1.9%) in the MT group. No tests of statistical significance were reported. The systematic review suggests no difference in bleeding between CA and MT. Bleeding, including requirement for hospitalisation and transfusion, is a known risk in the management of AF. The requirement for effectiveness anticoagulation in the pre, peri and post procedure stages further contribute to this risk. Major bleeding could lead to complications like subarachnoid haemorrhage, intestinal bleeding and subdural bleeding. These results are limited as they are based on only one study. The risk could also be heterogeneous depending on the method of ablation and experience of the centre. Further larger multicentre trials are required to establish the risk of bleeding in this population.
Other complications	Skelly et al 2015	8	Direct	B	Adverse events (AE) or complications were not specifically defined by Skelly et al (2015). However, the WHO defines this as any unfavourable and unintended outcomes temporarily associated with the use of an intervention. Skelly et al (2015) reported on other complications attributable to CA such as cardiac tamponade within 24 months (n=512) [pooled risk from four RCTs of 1.7% (95% CI 0.8 to 3.6)], pericardial effusion within 48 months (n=519) [pooled risk from three RCTs 0.6% (95% CI 0.2 to 1.8)], pulmonary vein stenosis at 12 months [pooled risk based on two studies (n=122) was 1.6% (95% CI 0.4 to 6.3) and pooled risk based on two studies (n=283) with 24-month follow-up was 0.7% (95% CI 0.2 to 2.8). Other ablation-related harms reported in the SR included

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Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					perforation at the trans-septal puncture (one RCT n=194, 0.5%), perimyocarditis (two RCTs n=333, 0% to 1.7%) and haematoma at catheter insertion site (2 RCTs n=276, 1.6% to 2.2%). There were no reports of atrio-oesophageal fistula, diaphragmatic paralysis, heart block and pneumothorax. The authors also reported drug intolerance requiring discontinuation based on one RCT (n=99) in 23.2% of patients in the MT arm and 0% in the CA arm. This HTA suggests that CA is associated with intervention-related complications and that drug intolerance to AADs is very common. It is important to patients that treatment of AF represents a favourable balance of successful treatment over complications. These results should be interpreted with caution because of the heterogeneity found among studies comparing CA with MT which may be due to dissimilar patient populations and extent of ablation.
Quality of life	Nielsen et al 2017	7	Direct	A	QoL was assessed using the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) physical and mental component scores (range 0 to 100, higher scores indicating better well-being). Skelly et al (2015) reported no statistical differences between treatment groups for the SF-36 MCS at 12 months based on two RCTs (n=406); this held true whether the analysis was done using the difference in mean scores at follow-up 2.26 (95% CI -2.12 to 7.40) or using the difference in change from baseline scores 1.88 (95% CI -0.47 to 4.50). For PCS, RFA was favoured over medical therapy when the pooled estimate was calculated using differences in mean follow-up scores (overall effect 2.85; 95% CI 0.93 to 4.82), however when the analysis was based on

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Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
	Skelly et al 2015	8	Direct		the change from baseline the effect was no longer statistically meaningful (overall effect 2.88; 95% CI 0.18 to 5.25). No p values were reported. The authors also reported no difference in both QoL measures at 24 months, MCS scores [one RCT (n=294) CA: 51.1 ± SD 9.2 versus MT 50.9 ± SD 8.0] and PCS scores [one RCT (n=294) CA: 50.0 ± SD 8.8 versus MT 47.9 ± SD 8.9] and 48 months for MCS scores [one RCT (n=198) CA: 52.9 ± SD 9 versus MT 51.9 ± SD 9] and PCS scores [one RCT (n=198) CA: 52.3 ± SD 9 versus MT 52.6 ± SD 8]. No other details were reported. The study suggests no difference in QoL between CA and MT at 24-month follow-up. Quality of life is likely to be valuable to patients. These results should be interpreted with caution because of the heterogeneity found among studies comparing CA with MT which may be due to dissimilar patient populations and extent of ablation.
Cost effectiveness	Reynolds et al 2014	7	Direct	B	ICER, usually measured as cost/QALY, and is a summary measure representing the economic value of an intervention, compared with an alternative. An ICER is calculated by dividing the difference in total costs (incremental cost) by the difference in the chosen measure of health outcome or effect (incremental effect) to provide a ratio of 'extra cost per extra unit of health effect'. In a cost effectiveness analysis from a UK NHS perspective, Reynolds et al (2014) reported an ICER of £21,957 per QALY gained, with the use of cryoballoon ablation vs AADs. The authors concluded that, beyond a threshold of £22 000 per QALY gained, ablation becomes the more cost effective intervention, with probabilities of 86% and 97.2% of being cost effective at thresholds of £30,000 and £40,000 per QALY gained, respectively. In the UK the QALY is most frequently used as the measure of health effect, enabling ICERs to be compared across disease areas. In decision-making ICERs are most useful when the new intervention is more costly but generates improved health effect. ICERs reported by economic evaluations are compared with a pre-determined threshold in order to decide whether choosing the new intervention is an efficient use of resources. There is no published official ratio that defines what is cost effective, but in

a) Use of catheter ablation vs. medical therapy to treat paroxysmal AF					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					the UK, a threshold of £20,000 to £30,000 is generally assumed to reflect cost effectiveness. These results should be treated with caution because, although the analysis took a UK NHS perspective, there were limitations to the methodology and other factors that could have biased the results. The efficacy assessment was based on a single RCT cryoablation vs AADs, which showed a beneficial effect of CA over AADs, however this effect size is considerably greater than that observed in other CA vs AADs studies, mostly due to a higher recurrence rate in the AADs group. The results of this study might have exaggerated the contribution of CA to the base case analysis. The study was supported by Medtronics International, and all the authors of the study had either received honoraria from or worked for Medtronics (manufacturers of balloon dilation catheters).

b) Use of catheter ablation vs. surgical ablation to treat paroxysmal AF					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Incidence of AF/AT/AFL recurrence	Jan et al 2018	7	Direct	B	Freedom from AF is normally defined as freedom from atrial arrhythmia lasting at least 30 seconds at follow-up. However recurrence was defined as any episode lasting 6 minutes or more. Jan et al (2018) reported a significant reduction in recurrence of AF/AT/AFL with SA compared with CA. At a mean follow-up of 30.5 months, recurrence was observed in 8/24 (33.4%) of SA vs. 17/26 (65.4%) CA patients; OR 3.78 (95% CI 1.17 to 12.19), p=0.048. The study suggests that SA is better at reducing recurrence of AF/AT/AFL compared with CA. People with AF have higher risks of developing comorbidities such as heart failure and stroke as well as higher all-cause mortality rate. The goal of AF treatment is to establish and maintain sinus rhythm and/or achieve rhythm control. Many clinicians believe that achieving either of these goals may lead to a reduction in major cardiovascular events. This result should be interpreted with caution because of limitations to the study. Firstly, the small number of patients included limits the strength of its findings. Secondly, all patients received an Implantable Loop Recorder (ILR); recurrence of AF/AT/AFL was defined as any episode lasting 6 minutes or more. This remarkably longer than the usual definition for AF recurrence. It is still not clear whether this threshold for recurrence represent significant reduction in the risk of AF complications, or what the impact of this level of reduced recurrence is on the patients' quality of life. Finally, only point-by-point method of CA was used, therefore the results may not be easily extrapolated to continuous cryoballoon technique of CA.
	Phan et al 2016	6	Direct		
Re-intervention	Jan et al 2018	7	Direct	B	Re-intervention refers to cardioversion or re-ablation after a 3-month blanking period. In the RCT by Jan et al (2018), through the entire follow-up period (30.5±6.9 months), 9/26 (34.6%) patients after CA and 4/24 (16.7%) after SA required re-intervention. No test of statistical significance was reported. It is unclear from the RCT whether there is a significant difference in the re-intervention rates between SA and CA. The requirement for re-intervention, which signifies failure of the initial intervention, exposes the patients to further risks of complications and is a significant burden on healthcare resources. This result is inconclusive because it is based on very small numbers and no statistical analysis of significance was recorded.

b) Use of catheter ablation vs. surgical ablation to treat paroxysmal AF					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Major peri-procedural complications	Jan et al 2018	7	Direct	B	Major peri-procedural complications were defined as events within 30 days from the ablation procedure resulting in prolonged or repeat hospitalization, bleeding requiring transfusion or intervention, and long-term disability. Jan et al (2018) reported a trend of major peri-procedural complication rates higher in SA treated 3/24 patients (12.5%) vs. 0/26 (0%) who underwent CA. No test of statistical significance was reported. The RCT suggests a higher incidence of major peri-operational complications associated with SA compared to CA however, it is uncertain whether this is significant. In general, minimally invasive surgical approaches to AF ablation carry a higher risk of peri-procedural complications compared to CA. The result of this study has shown a similar pattern. This result is limited in its generalisability because it is a small single-centre study and the statistical significance of the difference is not reported.

9 Literature Search Terms

Search strategy	
P – Patients / Population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?	Adults (aged 18 and above) with paroxysmal AF [Further subgroups that may be identified: • AF with heart failure • Symptomatic vs Asymptomatic[16] • Obesity, diabetes, sleep apnoea etc.]
I – Intervention Which intervention, treatment or approach should be used?	Catheter ablation for AF [Include any type of catheter ablation for AF. Types of catheter techniques are: 1. Radiofrequency ablation 2. Cryoablation 3. Laser balloon ablation 4. Multi-array catheters][17]
C – Comparison What is/are the main alternative(s) to compare with the intervention being considered?	Medical (drug) management (rhythm control, rate control)[18] Surgical (epicardial ablation), excluding "concomitant surgical ablation" AV node ablation and pacemaker ("pace and ablate")
O – Outcomes What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission; return to work, physical and social functioning, resource use.	<u>Critical to decision-making</u> 1. Efficacy (short and long-term outcomes) a. Symptomatic improvement / quality of life b. Freedom from AF (1 year, 3 years, 10 years etc.) c. Recurrence of AF / other atrial arrhythmias d. Repeat procedure(s) 2. Safety a. Stroke / transient ischaemic attack b. Asymptomatic cerebral lesions c. Cardiac tamponade d. Pericardial effusion e. Phrenic nerve palsy f. Pulmonary vein stenosis g. Vascular complications (haematoma, fistula, pseudoaneurysm) h. Haemoptysis i. Oesophageal ulceration / perforation / atrio-oesophageal fistula (long-term up to 6 months) j. Other events <u>Important to decision-making</u> k. Haemodynamic improvement l. Length of stay m. Cost effectiveness n. Repeat hospitalisation and causes

[16] It may not be possible to separate out the literature into cohorts of asymptomatic versus symptomatic patients.
[17] If any information on the type of anaesthesia (i.e. general anaesthesia versus local anaesthesia) is identified from the evidence selected, it would be useful if this could be stated in the summary of evidence tables. This is important as this may have resource usage implications.
[18] The majority of the evidence identified will most likely relate to catheter ablation versus medical management. Electrical cardioversion is not included as a comparator as this is an acute treatment rather than related to the long-term management of atrial fibrillation.

	o. Impact on clinical frailty score
ASSUMPTIONS / LIMITS APPLIED TO SEARCH	
Inclusions	
Study design:	Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies. If no higher level quality evidence is found, case series can be considered.
Language:	English only
Patients:	Human studies only
Age:	All ages
Date limits:	2005 – 2019[19]
Exclusions	
Publication Type:	Conference abstracts, narrative reviews, commentaries, letters and editorials
Study design:	Case reports, resource utilisation studies

10 Search Strategy

We searched Medline, Embase and Cochrane Library limiting the search to papers published in England from **1 January 2005 to 8 March 2019**. Conference abstracts, commentaries, letters, editorials and case reports were excluded.

Search date: 08 March 2019

Embase search:

1. paroxysmal atrial fibrillation/ or persistent atrial fibrillation/
2. *Atrial Fibrillation/
3. ((atrial or atrium or heart) adj fibrillation).ti.
4. 2 or 3
5. (paroxysm* or persisten*).ti,ab.
6. 4 and 5
7. ((paroxysm* or persisten*) and ((atrial or atrium or heart) adj fibrillation)).ti,ab.
8. ((paroxysm* or persisten*) adj af).ti,ab.
9. 1 or 6 or 7 or 8
10. catheter ablation/
11. ((catheter* or radiofrequen* or radio-frequen* or laser balloon* or multiarray* or multi-array*) adj2 ablat*).ti,ab.
12. (cryoablat* or cryo-ablat*).ti,ab.
13. 10 or 11 or 12
14. 9 and 13
15. (exp animals/ or nonhuman/) not human/
16. 14 not 15
17. limit 16 to (english language and yr="2005 -Current")
18. limit 17 to ("reviews (maximizes sensitivity)" or "therapy (best balance of sensitivity and specificity)" or "economics (best balance of sensitivity and specificity)")
19. (editorial or letter or note or conference*).pt. or case report.ti.

[19] Expansion of date limits to 2005 as seminal papers related to left atrial catheter ablation were released in 2006/7.

20. 18 not 19
21. 2 or 3
22. 13 and 21
23. limit 22 to (english language and yr="2005 -Current")
24. limit 23 to "reviews (maximizes specificity)"
25. 20 or 24

11 Evidence Selection

- Total number of publications reviewed: 241
- Total number of publications considered potentially relevant: 78
- Total number of publications selected for inclusion in this briefing: 7

References from the PWG supplied in the PPP		Paper selection decision and rationale if excluded
1	Jais P, Cauchemez B, Macle L, Daoud E, Khairy P, Subbiah R, Hocini M, Extramiana F, Sacher F, Bordachar P, Klein G, Weerasooriya R, Clementy J, Haissaguerre M. Catheter ablation versus antiarrhythmic drugs for atrial fibrillation (The A4 Study). Circulation 2008; 118: 2498-2505.	Not included separately as this is included in the HTA by Skelly et al 2015
2	Marrouche N, Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L, Merkely B, Pokushalov E, Sanders P, Proff J, Schunkert H, Christ H, Vogt J, Bansch D, for the CASTLE-AF investigators. Catheter ablation for atrial fibrillation with heart failure. New England Journal of Medicine. 2018; 378: 417-427.	Included
3	Ganesan A, Shipp N, Brooks AG, Kuklik P, Lau DH, Lim HS, Sullivan T, Roberts-Thompson KC, Sanders P. Long-term outcomes of catheter ablation of atrial fibrillation: A systematic review and meta-analysis. Journal of American Heart Association 2013;2: e004549.	Excluded as this mainly included un-controlled studies. We have included a more recent HTA, Skelly et al 2015, which is a SR of RCTs

12 References

Adderley NJ, Ryan R, Nirantharakumar, Marshall T. 2019. Prevalence and treatment of atrial fibrillation in the UK general practice from 2000 to 2016. Heart, 105: 27-33.

Bertaglia E, Senatore G, De Michieli L, De Simone A, Amellone C, Ferretto S, La Rocca V, Giuggia M, Corrado D, Zoppo F, Stabile G. 2017. Twelve-year follow-up of catheter ablation for atrial fibrillation: A prospective, multicenter, randomized study. *Heart Rhythm*, 14(4): 486-492.

Haïssaguerre M, Gencel L, Fischer B, Le Métayer P, Poquet F, Marcus FI, Clémenty J. 1994. Successful catheter ablation of atrial fibrillation. J Cardiovasc Electrophysiol, 5: 1045-52.

Jan M, Žižek D, Geršak Ž, Geršak B. 2018. Comparison of treatment outcomes between convergent procedure and catheter ablation for paroxysmal atrial fibrillation evaluated with implantable loop recorder monitoring. *Journal of Cardiovascular Electrophysiology*, 29(8): 1073-1080.

Marrouche N, Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L, Merkely B, Pokushalov E, Sanders P, Proff J, Schunkert H, Christ H, Vogt J, Bansch D, for the CASTLE-AF investigators. 2018. Catheter ablation for atrial fibrillation with heart failure. New England Journal of Medicine, 378: 417-427.

National Institute for Health and Clinical (NICE). 2012. Percutaneous balloon cryoablation for pulmonary vein isolation in atrial fibrillation. NICE Interventional Procedures Guidance (IPG 427). www.nice.org.uk/guidance/ipg427

National Institute for Health and Clinical (NICE). 2014. Atrial Fibrillation: Management. NICE Clinical Guideline (CG 180), www.nice.org.uk/guidance/cg180

National Institute for Health and Clinical (NICE). 2016. Percutaneous endoscopic laser balloon pulmonary vein isolation for atrial fibrillation. NICE Interventional Procedures Guidance (IPG 563). www.nice.org.uk/guidance/ipg563

Nielsen J, Johannessen A, Raatikainen P, Hindricks G, Walfridsson H, Pehrson S, Englund A, Hartikainen J, Mortensen L, Hansen P. 2016. Long-term efficacy of catheter ablation as first-line therapy for paroxysmal atrial fibrillation: 5-year outcome in a randomised clinical trial. *Heart*, 103(5):368-376.

Phan K, Phan S, Thiagalingam A, Medi C, Yan, T. 2015. Thoracoscopic surgical ablation versus catheter ablation for atrial fibrillation. *European Journal of Cardio-Thoracic Surgery*, 49(4):1044-1051.

Public Health England (PHE). 2017. Atrial fibrillation prevalence estimates in England: Application of recent population estimates of AF in Sweden https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/644869/atrial_fibrillation_AF_briefing.pdf

Reynolds M, Lamotte M, Todd D, Khaykin Y, Eggington S, Tsintzos S, Klein G. 2014. Cost effectiveness of cryoballoon ablation for the management of paroxysmal atrial fibrillation. *EP Europace*, 16(5): 652-659.

Skelly A, Hashimoto R, Al-Khatib S, Sanders-Schmidler G, Fu R, Brodt E, McDonagh M. 2015. Catheter ablation for treatment of atrial fibrillation. Rockville: Agency for Healthcare Research and Quality (AHRQ). Technology Assessment Report.