NHS England

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

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Contents

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 (AADs) 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). It 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

- Two systematic reviews (SR) and one recently published randomised controlled trial (RCT), fulfilling the PICO criteria for clinical effectiveness and safety, were identified for inclusion. One systematic review (Berger et al 2019) compared catheter ablation (CA) with minimally invasive surgical ablation in patients with AF. The second systematic review (Chen et al 2018) compared CA with medical therapy (rhythm and/or rate control) in AF patients, whilst the RCT (Marrouche et al 2018), published after the search date of the systematic review, compared CA with medical therapy in AF patients with heart failure (HF).
- One systematic review (Neyt et al 2013) of published cost effectiveness studies fulfilling the PICO criteria for cost effectiveness was found.

Clinical effectiveness

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

- **All-cause mortality:** Three out of eight RCTs in one SR (n=559). No significant difference between CA and medical therapy (risk ratio[1] (RR) 0.47, [95%CI 0.22 to 1.02]; p=0.05) (Chen et al 2018).
- **AF Freedom rates:** Three out of eight RCTs (n=262) in one SR (Chen et al 2018). Pooled results found a significant improvement after CA compared with medical therapy (rhythm control) (RR 2.08, [95%CI 1.67 to 2.58]; p<0.00001). Pooled results, from another three out of eight RCTs included in Chen et al (2018) with 338 patients (mean follow-up six to 24 months) who were completely off anti-arrhythmic drugs (AADs) after CA, also showed a significant benefit in favour of CA (RR 1.82, [95%CI 1.33 to 2.49]; p=0.0002).
- **Need for cardioversion:** Three out of eight RCTs (n=394) in one SR (Chen et al 2018) reported rates of p cardioversion after the blanking period[2]. Pooled results showed that, compared to AADs, CA significantly reduced the number of participants needing cardioversion (RR 0.59, [95%CI 0.46 to 0.76]; p < 0.0001). Number needed to treat (NNT) with CA to prevent one case of cardioversion was 4.2.
- **Hospitalisation:** Two out of eight RCTs (n=349) in one SR (Chen et al 2018), showed a significant reduction in hospitalisation after CA compared with AADs (RR 0.54, [95%CI 0.39 to 0.74]; p=0.0002). NNT with CA to prevent one hospitalisation was 6.7.
- **Improvement in LVEF:** One RCT of HF patients with persistent AF (n=63); four out of eight RCTs in one SR (n=205). At 60 months, median left ventricular ejection fraction (LVEF) increased by 10% (interquartile range (IQR) 1 to 20) in 37 HF patients with persistent AF after CA versus -2.5% (IQR -7 to 5) in 26 patients on medical therapy; p=0.004 (Marrouche et al 2018). Pooled data from 4 RCTs (n=205) showed a significant increase in LVEF in patients treated with CA compared with medical therapy (mean

[1] Risk ratio or relative risk is the ratio of the probability of an outcome in an exposed group to the probability of an outcome in an unexposed group.
[2] 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

difference (MD) 7.72, [95%CI 4.78 to 10.67]; p< 0.00001) (Chen et al 2018).

- **Composite of death or hospitalisation for worsening HF:** 1 RCT (n=245). At a median follow up of 37.6 months, the outcome was reported in 34/125 (27.2%) patients after CA versus 48/120 (40.0%) after medical therapy (hazard ratio (HR) 0.64 [95% CI 0.41 to 0.99], p value not reported) (Marrouche et al 2018).
- **Six-minute walk distance (6MWD):** Three out of eight RCTs in one SR (n=150) found no significant difference between CA and medical rate control (MD = 19.17, [95%CI −11.43 to 49.76]; p= 0.22) (Chen et al 2018).
- **Minnesota Living with Heart Failure Questionnaire (MLHFQ):** Three out of eight RCTs in one SR (n=140). A pooled analysis detected a significant reduction in MLHFQ score, indicating improved quality of life after CA versus medical rate control (MD 11.13, [95% CI 2.52 to 19.75]; p=0.01) (Chen et al 2018).

2.2 Catheter ablation versus minimally invasive surgical ablation

- **Freedom from AF:** Berger et al (2019) reported rate of AF freedom at 12 months after surgical ablation (SA) versus CA, based on two direct comparison RCTs (n= 67). These studies showed numerically but not statistically significantly higher AF freedom after SA versus CA (odds ratio (OR) 2.58, [95%CI 0.83 to 8.03], p value not reported).
- Berger et al (2019) also conducted an indirect comparison between CA and SA with and without AADs. AF freedom was higher after SA than after CA. This effect was further enhanced when AADs use was permitted during follow-up. In 7,502 CA patients from 41 studies versus 339 SA (5 studies), without AADs, 51% [95% CI 46 to 56%] CA patients versus 69% [95% CI 64 to 74%] SA patients were free from AF at 12 months; p value not reported. AF freedom rates on AADs were higher with both treatments. In 3,133 CA patients (29 studies) versus 196 SA patients (3 studies) 58% [95% CI 54 to 63%] of CA patients versus 71% [95% CI 64 to 74%] of SA patients were free from AF at 12 months; p value not reported.

Safety

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

- **Ablation or drug-related complication rates:** Eight RCTs in one SR (n=809) (Chen et al 2018). Pooled results from four (n=604) out of eight RCTs showed no significant difference between CA and medical rhythm control with AADs (RR 1.95, [95%CI 0.52 to 7.25]; p=0.32).

2.4 Catheter ablation versus minimally invasive surgical ablation

- **Overall death and procedure-related death**: One SR reported no difference between CA and surgical ablation (SA) in both outcomes. After CA, mortality was 1.1% (38/3264) and procedure-related death 0.1% (3/3052); after SA, the outcomes were 1.1% (5/464) and 0% (o/464) respectively (Berger et al 2019).
- **Bleeding:** Combined major and minor bleeding rates were 7.7% (21/272) and 1.7% (124/7515) in the CA and SA groups respectively (Berger et al 2019).
- **Other adverse events:** Number of RCTs and patients evaluated were not specifically reported. Generally, adverse events after CA were infrequent. The commonest complications were any bleeding (1.7%), pericarditis (1.4% - 54/3981) and pacemaker implantations (0.9% - 3/345); thromboembolic events occurred in 0.7% (53/7169) of patients. After SA, pneumothorax occurred in 6.1% (31/509) of patients, 2.7% (8/301)

required pacemaker implantation, 1.6% (8/489) were converted to sternotomy and thromboembolic events occurred in 1.4% (8/557). Overall, irreversible adverse events occurred more frequently after SA than after CA (Berger et al 2019).

Cost effectiveness

2.5 Catheter ablation versus medical therapy (AADs or rate control)

- One SR of health economic studies (Neyt et al 2013) reported data from two studies of persistent AF patients. For first line ablation compared with second line rate control, reported ICERs depended on patients' ages and CHADS2 scores and were between $60,804 USD (£46,837)/QALY (age 65 years; CHADS2 score 1) and $80,615 (£62,100) (age 75 years; CHADS2 score 3).
- For second line ablation compared with second line rate control, reported ICERs were: $73,947 USD (£56,961)/QALY (age 65 years; CHADS2 score 1) to $96,846 (£74,600) (age 75 years; CHADS2 score 3).

Conclusion

- Moderate quality evidence was found for the effectiveness of CA compared with medical therapy, in patients with persistent AF, and very limited data comparing CA with surgical ablation.
- Compared with medical therapy, CA appeared to improve AF freedom, reduce hospitalisation and the need for cardioversion. However, there are no benefits in terms of all-cause mortality. In AF patients with heart failure, CA appears to significantly improve LVEF and hospitalisation for worsening HF. There was no significant difference in ablation or drug-related complications.
- Compared with surgical ablation the quality of evidence was weak, but surgical ablation appears to be more effective than CA at establishing and maintaining sinus rhythm, albeit at the expense of higher bleeding rates. There was however no difference between CA and surgical ablation in overall and procedure-related death.
- There are no good quality studies on the cost effectiveness of CA compared with surgical ablation or medical treatment in patients with persistent AF. The available studies are of very limited quality and not from a perspective that can be easily extrapolated to the UK healthcare system.
- The published data on the effectiveness, safety and cost effectiveness of CA in persistent AF is limited as most studies have been conducted in mixed AF patients (paroxysmal AF, permanent AF and persistent AF), without ensuring adequate matching for all subtypes and without consistently reporting the results separately. Further assessments in large-scale RCTs investigating CA versus medical therapy or surgical ablation specifically in persistent AF, are warranted.

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 01 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[3], 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 persistent 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

Two systematic reviews (SR) and one recently published RCT, fulfilling the PICO criteria for clinical effectiveness and safety, were identified for inclusion. One systematic review compared CA with medical therapy (anti-arrhythmic drugs (AADs) or rhythm control) in patients with AF, whilst the RCT, published after the search date of the systematic review, compared CA with medical therapy in heart failure (HF) patients with AF. The second systematic review compared catheter ablation (CA) with minimally invasive surgical ablation in patients with AF.

One systematic review, of published cost effectiveness studies, fulfilling the PICO criteria for cost effectiveness, was identified for inclusion.

In patients with persistent 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 identified sources included: freedom from AF, need for cardioversion, hospitalisation, all-cause mortality, change in LVEF and a composite of death or hospitalisation for heart failure.

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

4.1.1 All-cause mortality

Three RCTs (n=559), included in the Chen et al (2018) review, contributed to the analysis of all-

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

cause mortality. There was no significant difference between CA and AADs in all-cause mortality (RR 0.47, [95%CI 0.22 to 1.02]; p=0.05).

4.1.2 AF Freedom rates

Chen et al (2018) reported AF freedom rates based on three RCTs that enrolled 262 persistent AF patients. The pooled results found a significant improvement in freedom from AF with CA vs medical therapy (rhythm control) (RR 2.08, [95%CI 1.67 to 2.58]; p<0.00001).

Pooled results, from three RCTs with 338 patients (mean follow-up six to 24 months), who were completely off AADs after CA, also showed a significant benefit in favour of CA (RR 1.82, [95%CI 1.33, 2.49]; p=0.0002).

4.1.3 Need for cardioversion

Chen et al (2018) reported rates of patients needing cardioversion after the blanking period[4]. Pooled results from three RCTs (n=394) showed that, compared to AADs, CA significantly reduced the number of participants needing cardioversion (RR 0.59, [95%CI 0.46, 0.76]; p < 0.0001). Number needed to treat (NNT) with CA to prevent one case of cardioversion was 4.2.

4.1.4 Hospitalisation

In the meta-analysis by Chen et al (2018), two RCTs (n=349) contributed to analysis of hospitalisation. A significant reduction in hospitalisation was detected in patients who were treated with CA compared with AADs (RR 0.54, [95%CI 0.39 to 0.74]; p=0.0002). NNT with CA to prevent one hospitalisation was 6.7.

4.1.5 Improvement in left ventricular ejection fraction (LVEF)

At 60 months, Marrouche et al (2018) reported a median LVEF increase of 10% (interquartile range (IQR) 1 to 20%) in 37 HF patients with persistent AF, treated with CA versus IQR -2.5% -7 to 5%) in 26 HF patients with persistent AF who received medical therapy (p=0.004).

Pooled data from four RCTs (n=205) included in Chen et al (2018) showed that a significant increase in ejection fraction was detected in patients who were treated with CA compared with the medical rate control (MD= 7.72, [95%CI 4.78 to 10.67]; p< 0.00001).

4.1.6 Composite of death or hospitalisation for heart failure (HF)

At a median follow up of 37.6 months, Marrouche et al (2018) reported composite of death or hospitalisation for worsening HF in 34/125 (27.2%) persistent AF patients treated with CA versus 48/120 (40.0%) persistent AF patients treated with medical therapy (HR 0.64 [95% CI 0.41 to 0.99], p value not reported).

4.1.7 Six-minute walk distance changes (6MWD changes)

In the meta-analysis by Chen et al (2018), pooled results from three RCTs (n=150) contributed to the analysis of the 6MWD changes. There was no significant difference between the CA arm and the medical rate control arm (MD = 19.17, [95%CI − 11.43 to 49.76]; p= 0.22).

4.1.8 Reduction in Minnesota living with heart failure questionnaire (MLHFQ) scores

Three studies (n=140) included in the review by Chen et al (2018) provided data on MLHFQ score changes. A pooled analysis detected a significant reduction in MLHFQ score, indicating improved quality of life in the ablation arm compared with that in the medical rate control arm (MD 11.13,

[4] 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

[95% CI 2.52 to 19.75]; p=0.01).

4.2 Catheter ablation versus minimally invasive surgical ablation

4.2.1 Freedom from AF

Berger et al (2019) reported on the rate of AF freedom at 12 months after surgical ablation versus catheter ablation, based on two direct comparison RCTs involving 67 patients with persistent AF. These studies showed numerically but not statistically significantly higher AF freedom after surgical ablation compared to catheter ablation (OR 2.58, [95%CI 0.83 to 8.03], p value not reported).

Berger et al (2019) also conducted an indirect comparison between CA and surgical ablation with and without AADs. AF freedom was higher in the minimally invasive surgical ablation group than in the catheter ablation group. This effect was further enhanced when AADs use was permitted during follow-up. In 7,502 CA patients from 41 studies compared with 339 surgical ablation patients from five studies, without AADs use, 51% (95% CI 46 to 56%) of CA patients versus 69% (95% CI 64 to 74%) surgical ablation patients were free from AF at 12 months; p value was not reported. AF freedom rates on AADs were higher with both treatments. In 3,133 CA patients (29 studies) versus 196 surgical ablation patients (three studies) 58% (95% CI 54 to 63%) of CA patients vs 71% (95% CI 64 to 74%) surgical ablation patients were free from AF at 12 months; p value was not reported.

In patients with persistent AF, what is the safety of percutaneous left atrial catheter ablation compared with medical management?

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

4.3.1 Ablation- or drug-related complications rates

Chen et al (2018) reported ablation or drug-related complication rates between patients receiving CA and medical rhythm control. Pooled results from four studies (n=604), reported by Chen et al (2018), showed no significant difference between CA and medical rhythm control with AADs (RR 1.95, [95%CI 0.52 to 7.25]; p=0.32). However, the studies were highly heterogeneous.

4.4 Catheter ablation versus minimally invasive surgical ablation

4.4.1 Overall death and procedure-related death

Berger et al (2019) reported no difference between CA and surgical ablation procedures in terms of overall death and procedure-related death. Mortality after catheter ablation during the study course was 1.1% (38/3264); procedure-related death 0.1% (3/3052). Mortality after minimally invasive surgical ablation was 1.1% (5/464); 0% procedure-related death.

4.4.2 Bleeding

Combined major and minor bleeding rates were 1.7% (124/7515) and 7.7% (21/272) in the CA and surgical ablation groups respectively.

4.4.3 Other adverse events

Generally, adverse events after CA were infrequent. The commonest complications were pacemaker implantations (0.9% - 3/345), any bleeding (1.7%- 124/7515) and pericarditis (1.4% - 54/3981). Thromboembolic events occurred in 0.7% (53/7169) of patients.

In the surgical ablation group 1.6% (8/489) of patients were converted to sternotomy. Pneumothorax occurred in 6.1% (31/509) of patients and 2.7% (8/301) required pacemaker implantation. Thromboembolic events occurred in 1.4% (8/557).

Taken together, irreversible adverse events occurred more frequently after surgical ablation than after catheter ablation.

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

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

4.5.1 Incremental Cost Effectiveness Ratio (ICER)

In a systematic review of health economic studies, Neyt et al (2013) reported data from two studies that included persistent AF patients. For first line ablation compared with second line rate control, reported ICERs depended on patients' ages and CHADS2 scores and were between $60,804 USD (£46,837)/QALY (age 65 years; CHADS2 score 1) and $80,615 (£62,100) (age 75 years; CHADS2 score 3).

For second line ablation compared with second line rate control, reported ICERs were between $73,947 USD (£56,961)/QALY (age 65 years; CHADS2 score 1) and $96,846 (£74,600) (age 75 years; CHADS2 score 3).

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 or obesity)?

None of the studies identified for inclusion carried out any suitable sub-group analysis 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. 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, 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?

From the evidence selected, is there a maximum number of clinically effective procedures undertaken per patient that can be performed safely in persistent AF?

The evidence selected did not include any suitable sub-group analysis or other comparison that can help identify a maximum number of clinically effective procedures per patient that can be performed safely in persistent AF.

5 Discussion

The systematic review by Chen et al (2018) represents moderate quality evidence for the effectiveness of CA compared with medical therapy (AADs or rate control therapy) in the management of patients with persistent AF. Pooled data from eight different RCTs showed that, compared with AADs, CA significantly improved freedom from AF, need for cardioversion and hospitalisation. However, all-cause mortality was not significantly different between the groups. In the same systematic review, CA treated patients had a significant improvement in LVEF compared to patients who received medical therapy in the form of rate control only.

A moderate quality RCT by Marrouche et al (2018) also reported significant improvements in LVEF in favour of CA. The same study reported a significant difference in rates of a composite of death or hospitalisation for worsening HF. However, the higher range of the 95% confidence interval was very close to unity (0.99).

Chen et al (2018) also reported on two quality of life outcomes relevant to heart failure; 6MWD changes and reduction of MLHFQ. There was no significant difference between the CA arm and medical rate control arm in 6MWD. MLHFQ score on the other hand, a validated measure of therapeutic efficacy which associated with favourable prognostic outcomes, was significantly improved in the CA arm. However, the follow-up duration was only six to 12 months and might not be sufficient for the effect of restoration of sinus rhythm to be fully evaluated.

The systematic review by Berger et al (2019) provided very limited data on the effectiveness and safety of CA compared with minimally invasive surgical ablation. AF freedom was higher in the minimally invasive surgical ablation groups than in the CA groups, and the effect was further enhanced when AADs use was permitted during follow up. However, this was based on indirect comparison of a large number of CA patients from several studies with a small number of SA patients in only a few studies. Besides, in the only two direct comparisons, surgical ablation showed only a numerical, but not statistically significant, improvement compared with CA.

Chen et al (2018) reported no significant differences between CA and medical therapy in terms of ablation or drug-related complications. Berger et al (2019) reported no difference between CA and surgical ablation in terms of overall death and procedure-related death. However, combined minor and major bleeding was remarkably more frequently reported with surgical ablation.

Neyt et al (2013) provided very limited data on the cost effectiveness of CA compared with medical therapy. The comparison was based on the US payer and societal perspective and the generalisability of the results to the NHS in England is not certain.

These results should be interpreted with caution because of the limitations in these studies. There are no large RCTs specifically in persistent AF patients investigating CA versus medical therapy or surgical ablation. The available data have therefore been synthesized from RCTs that reported outcomes on persistent AF patients separately, alongside those for patients with other types of AF. However, we do not know whether the persistent AF patients in these studies were balanced enough in baseline characteristics as to make a conclusive inference on the results. The available comparative data relating to CA versus surgical ablation is even more limited to an indirect comparison and two very small direct comparative studies.

Further assessments in large-scale RCTs investigating CA versus medical therapy or surgical ablation, specifically in persistent AF, are warranted.

6 Conclusion

Moderate quality evidence was found for the effectiveness of CA compared with medical therapy, in patients with persistent AF, and very limited data compared with surgical ablation.

Compared with medical therapy, CA appeared to improve AF freedom, reduce hospitalisation and the need for cardioversion. However, there are no benefits in terms of all-cause mortality. In AF patients with heart failure, CA appears to significantly improve LVEF and hospitalisation for worsening HF. There was no significant difference in ablation or drug-related complications.

The quality of evidence comparing CA with surgical ablation was weak but suggests that surgical ablation may be more effective than CA at establishing and maintaining sinus rhythm albeit at the expense of high bleeding rates. There was however no difference in overall and procedure-related death.

There are no good-quality studies on the cost effectiveness of CA compared with surgical ablation or medical treatment in patients with persistent AF. The available studies are of very limited quality and not from a perspective that can be easily extrapolated to the NHS in England.

The long-term success rate of CA in maintaining sinus rhythm and improving prognosis in persistent AF with or without HF is uncertain. The published data on the effectiveness, safety and cost effectiveness of CA in persistent AF is limited as most studies have been conducted in mixed AF patients (paroxysmal AF, permanent AF and persistent AF), without ensuring adequate matching for all subtypes and without consistently reporting the results separately. Further assessments in large-scale RCTs with longer follow-up duration are needed, to establish the efficacy of CA versus medical therapy or surgical ablation specifically in persistent AF.

7 Evidence Summary Table

For abbreviations see list after each table

a) Use of catheter ablation vs. medical therapy to treat persistent 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: Catheter 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 125 with persistent AF); 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 120 with persistent AF); 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 persistent AF patients	At a median follow up of 37.6 months, CA 34/125 patients (27.2%) vs. MT 48/120 patients (40.0%); HR 0.64 [95% CI, 0.41 to 0.99], p value not reported.	7	Direct	Both groups were well matched for baseline characteristics including the proportion of patients with persistent AF vs PAF. However, it is not clear whether the persistent AF subset of patients in each group were equally well matched. 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. The authors did not comment on the reasons for this. One of the limitations of this trial is the 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 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 and was not reported separately by type of AF. A greater number of patients in the catheter 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;
				Secondary Clinical effectiveness	Improvement in LVEF (median percentage improvement) in persistent AF patients	At 12 months: CA (n=105) 8% [IQR -1 to 14] vs MT (n=108) 0.5% [IQR -5 to 10.5%]; p=0.001 At 36 months: CA (n=62) 6.5% [IQR -2 to 16%] vs MT (n=56) 1.5% [IQR -5.5 to 11%]; p=0.14 At 60 months: CA (n=37) 10% [IQR 1 to 20%] vs MT (n=26) -2.5% [IQR -7 to 5%]; p=0.004			

a) Use of catheter ablation vs. medical therapy to treat persistent AF

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
									this could have affected the outcome in the medical therapy arm; no attempt to assess compliance with medical therapy was reported. In result reported for persistent AF patients in the primary outcome, upper limit of 95%CI was just below unity (0.99).
Chen et al 2018 China 8 RCTs which included patients with persistent AF in the meta-analysis Databases were searched from inception to 27 October 2017	S1 – Meta-analysis	n=809 Patients with persistent AF Mean age (by study): ranged from 55 to 64 years (predominantly male) Mean follow-up (by study): ranged from 6 to 24 months	CA to achieve PVI combined with substrate modification containing linear ablation, complex fractionated atrial electrogram ablation or non-pulmonary vein trigger ablation Versus Medical therapy rhythm control (amiodarone or other class Ic or class III drugs determined by condition) or Versus Medical therapy rate control (beta-blockers and/or digoxin)	Primary Clinical effectiveness	Freedom from AF[5] at follow-up	**Pooled results (3 RCTs; n=262)** RR 2.08, [95%CI 1.67, 2.58]; p<0.00001	8	Direct	All eight of the RCTs (which included patients with persistent AF) included in the analysis had relatively low risks of bias according to the Cochrane Collaboration tool. There was also low risk of selection bias and selective reporting. However, the risk of performance bias and other bias were uncertain. No significant publication bias was found in the funnel plot or the Egger and Begger tests (Egger: p =0.059; Begger: p=0.308) Meta-analyses were performed using a random-effects model. Heterogeneity was assessed using the I^2 statistic. However, there were a number of important limitations to the study. Firstly, the number of RCTs included in the meta-analysis and the sample sizes of most studies were relatively small. Secondly, some results showed moderate heterogeneity among the included studies and different studies had a somewhat dissimilar patient population and different ablation strategies; therefore, the results need to be interpreted with caution. Thirdly, it is unfortunate that results for persistent AF subgroups are often not reported separately for mixed persistent/paroxysmal trials, so these data were not be
				Primary Clinical effectiveness	Freedom from AF off AADs at follow-up	**Pooled results (3 RCTs; n=338)** RR 1.82, [95%CI 1.33, 2.49]; p=0.0002			
				Secondary Clinical effectiveness	Need for cardioversion	**Pooled results (3 RCTs; n=394)** RR 0.59, [95%CI 0.46, 0.76]; p<0.0001. NNT=4.2			
				Secondary Safety	Ablation or drug-related complications	**Pooled results (4 RCTs; n=604)** RR 1.95, [95%CI 0.52, 7.25]; p = 0.32			
				Secondary Safety	Hospitalisation	**Pooled results (2 RCTs; n=349)** RR 0.54, [95%CI 0.39, 0.74]; p = 0.0002			
				Secondary Safety	All-cause mortality	**Pooled results (3 RCTs; n=559)** RR 0.47, [95%CI 0.22, 1.02]; p=0.05			

[5] Freedom from AF refers to freedom from atrial arrhythmia lasting at least 30 s

a) Use of catheter ablation vs. medical therapy to treat persistent AF									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
				Secondary Clinical effectiveness	Change in LVEF[i]	**Pooled results (4 RCTs; n=205)** MD 7.72, [95%CI 4.78, 10.67]; p<0.00001			included in this meta-analysis. Fourthly, the follow-up duration ranging from 6 to 24 months was short. The authors state that 'prior studies have shown a higher rate of late AF recurrence in persistent AF patients with HF compared with those with a structurally normal heart.
				Secondary Safety	Change in 6MWD[i]	**Pooled results (3 RCTs; n=150)** MD 19.17, [95%CI −11.43 to 49.76]; p=0.22			
				Secondary Safety	Reduction in MLHFQ[i]	**Pooled results (3 RCTs; N=140)** MD 11.13, [95% CI 2.52 to 19.75]; p=0.01			
				Secondary Safety	Ablation or drug-related complications	**Pooled results (4 RCTs; N=206)** RR 1.64, [95%CI 0.39 to 6.84]; p= 0.50			
Neyt et al 2013 Belgium 7 studies of which 2 studies included persistent AF Search date: August 2012. No restrictions on the	R1 – Cost effectiveness study based on 7 studies	Patients with AF	Radiofrequency catheter ablation VERSUS Medical rate therapy or rhythm control therapy including electric cardioversion	Primary Cost effectiveness	**Analysis from one study** ICER: Cost/QALY	**For first-line ablation compared with second line rate control** Model 1: 65-year-old male group with persistent AF and CHADS2 of 1. $60,804USD/ QALY Model 2: 75-year-old male group with persistent AF and CHADS2 of 3. $80,615USD/QALY. **For second line ablation compared to**	5	Direct	Only two of the seven studies in this review included patients with persistent AF; of these, only one reported the results for persistent AF patients separately. The authors of this one study used an unpublished systematic review of published literature and other sources, to inform a primary cost-utility analysis of a variety of management strategies for adults with atrial fibrillation. The method of systematic review was not described, but it included studies with conflicting results, and there was likely to be significant heterogeneity among these studies. The authors made no explicit conclusion about the cost effectiveness of the compared treatment strategies. The review was conducted for Belgium but the study that informed the outcome for persistent AF was

a) Use of catheter ablation vs. medical therapy to treat persistent AF									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
time period						**second line rate control** Model 1: 65-year-old male group with persistent AF and CHADS2 of 1. $73,947USD/QALY Model 2: 75-year-old male group with persistent AF and CHADS2 of 3. $96,846USD/QALY			calculated from a US payer and societal perspective. Therefore the relevance of these results to the NHS in England is not known.

6MWD-6-min walk distance; AADs-anti-arrhythmic drugs; AF-atrial fibrillation; CA-catheter ablation; CHADS2-Cardiac failure, Hypertension, Age ≥75 years, Diabetes, prior Stroke; CRT-D-cardiac resynchronization therapy defibrillator; HF-heart failure; ICD- implantable cardioverter–defibrillator; ICER-incremental cost effectiveness ratio; LVEF-Left ventricular ejection fraction; MD-mean difference; MLHFQ-Minnesota living with heart failure questionnaire; MT-medical therapy; N-Number of patients in the study; n-Number of patients in the treatment arm; PAF-paroxysmal atrial fibrillation; QOL-quality of life; RCT-randomised controlled trial; RD-risk difference; RR-Risk ratio; SA-surgical ablation; SR-sinus rhythm;

b) Use of catheter ablation vs. surgical ablation to treat persistent AF									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Berger et al 2019 Netherlands 60 RCTs which included patients persistent AF in the meta-analysis (two of which were direct comparisons of CA vs SA) Databases were searched from inception to July 2018 Search date not reported	S1 – Meta-analysis	Patients with persistent AF or longstanding persistent AF Studies of both paroxysmal and persistent AF were included when persistent AF or longstanding persistent AF data was extractable for efficacy defined as freedom of AF or any atrial tachycardia n=7624 (persistent AF) Mean age = 59.4 years (range 50–69) Mean follow-up period = 12 months (efficacy	CA (n=7183) to achieve PVI using: radiofrequency, cryoballoon (97%), or any other type of AF ablation **Versus** Minimally invasive surgical ablation (n=388) to achieve PVI using mini-thoracotomy and (hybrid) thoracoscopy to isolate PV, but concomitant AF ablation during open-chest cardiac surgery was excluded The numbers of patients reported here do not add up to the total overall figures	Primary Clinical Effectiveness	AF Freedom (freedom from AF or any atrial tachycardia)	At 12 months: CA (n=40) 69% [95% CI 64 to 74%] SA (n=17) 51% [95% CI 46 to 56%]; OR 2.58, [95%CI 0.83 to 8.03], p value not reported	6	Direct	The majority of the 5 RCTs with 7 treatment arms on minimally invasive surgical ablation studies were small and/or single-centre studies, whereas larger, more frequently multi-centre RCTs were available on catheter ablation. Potentially, the minimally invasive surgery studies reflect dedicated programs in specialised centres. The blanking period[6], during which arrhythmia episodes are considered no recurrence, ranged from 0 to 3 months. The variation among the studies was large, with limited direct comparison between invasive treatment strategies and CA for persistent AF. Funnel plots showed publication bias in catheter ablation studies, but not in minimally invasive surgical ablation studies. Meta-analysis was performed using a random-effects model, and all meta-analyses demonstrated heterogeneity (I^2 > 40%). Sensitivity analyses were performed for: 12 months vs >12 months, persistent AF vs long longstanding persistent AF. This was also carried out for different criteria for AF freedom and year of publication (before 2000 vs 2010 to 2015 vs 2016 to 2018, and study size <100 vs >100).
				Primary Clinical Effectiveness	AF Freedom (freedom from AF or any atrial tachycardia) without AADs	After 12 months: CA (n=7502) 51% [95% CI 46 to 56%] vs SA (n=339) 69% [95% CI 64 to 74%], p value not reported			
				Primary Clinical Effectiveness	AF Freedom (freedom from AF or any atrial tachycardia) with AADs allowed	After 12 months: CA (n=3133) 58% [95% CI 54 to 63%] vs SA (n=196) 71% [95% CI 46 to 56%], p value not reported			
				Secondary Safety	Overall death	CA 1.1% (38/3264) vs SA 1.1% (5/464) No tests of statistical significance reported			
				Secondary Safety	Procedure-related death	CA 0.1% (3/3052) vs. SA 0% (0/464) No tests of statistical significance reported			

6 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.

b) Use of catheter ablation vs. surgical ablation to treat persistent AF

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
		rate at 12 months was extracted no range provided)	reported	Secondary Safety	Thrombo-embolic events	CA 0.7% (53/7169) vs. SA 1.4% (8/557). No tests of statistical significance reported			As studies generally did not compare different strategies directly, care must be taken in comparing absolute numbers, especially in the safety outcomes. P values were not reported for the persistent AF patients; therefore, the significance of the reported outcomes is not certain.
				Secondary Safety	Combined major and minor bleeding	CA 1.7% (124/7515) vs. SA 7.7% (21/272). No tests of statistical significance reported			
				Secondary Safety	Haemothorax	CA 1.3% (1/80) vs. SA 1.3% (6/448) No tests of statistical significance reported			
				Secondary Safety	Cardiac tamponade	CA 1.0% (81/8090) vs. SA 0.6% (2/301) No tests of statistical significance reported			
				Secondary Safety	Infection (e.g. pneumonia, urinary tract infection)	CA 0.7% (21/2754) vs. SA 1.0% (3/301) No tests of statistical significance reported			

6MWD-6-min walk distance; AADs-anti-arrhythmic drugs; AF-atrial fibrillation; CA-catheter ablation; CHADS2-Cardiac failure, Hypertension, Age ≥75 years, Diabetes, prior Stroke; CRT-D-cardiac resynchronization therapy defibrillator; HF-heart failure; ICD- implantable cardioverter–defibrillator; ICER-incremental cost effectiveness ratio; LVEF-Left ventricular ejection fraction; MD-mean difference; MLHFQ-Minnesota living with heart failure questionnaire; MT-medical therapy; N-Number of patients in the study; n-Number of patients in the treatment arm; OR – odds ratio; PAF-paroxysmal atrial fibrillation; QOL-quality of life; RCT-randomised controlled trial; RD-risk difference; RR-Risk ratio; 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 persistent AF					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
All-cause mortality	Chen et al 2018	8	Direct	B	All-cause mortality included all causes of mortality whether or not it was felt to be due to AF or complications of AF treatment. Chen et al (2018) reported all-cause mortality between patient receiving CA treatment and those receiving antiarrhythmic drugs (AADs) for rate control. Three randomised controlled trials (RCTs) (n=559) contributed to the analysis of all-cause mortality. Reduction in all-cause mortality was not significantly different between the two groups (risk ratio (RR) 0.47, [95% CI 0.22 to 1.02]; p=0.05). The meta-analysis suggests that there is no difference in all-cause mortality between CA and medical therapy. This result should be interpreted with caution because of the short-term follow-up in the studies included in the systematic review (median six to 24 months). The method excluded zero total event trials assuming that they make no contribution to the magnitude of the treatment effect. Some experts insist that inclusion of zero total event trials would enable the inclusion of all available RCT data in a meta-analysis, thereby providing the most generalisable estimate of treatment effect. However, the authors also calculated the results using risk difference (RD) as the effect measure and found the result was robust (RD −0.02, [95%CI −0.09 to 0.05]; p=0.55).
Freedom from AF	Chen et al 2018	8	Direct	B	Freedom from AF was defined as freedom from atrial arrhythmia lasting at least 30 seconds at follow-up. Chen et al (2018) reported AF freedom rates based on results from 3 RCTs that enrolled 262 persistent AF patients. The pooled results found a significant improvement in freedom from AF with CA compared with medical therapy (rhythm control) (RR 2.08, [95%CI 1.67, 2.58]; p<0.00001). Pooled results from three RCTs with 338 patients who were completely off AADs at follow up (mean follow-up six to 24 months) also showed a significant benefit in favour of CA (RR 1.82, [95%CI 1.33, 2.49]; p=0.0002). The systematic review suggests that CA is better at improving freedom from AF than medical therapy. People with AF have higher risks of developing comorbidities such as heart failure (HF) and stroke as well as higher all-cause mortality rate. The goal of AF treatment is to establish sinus rhythm 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. These results should be interpreted with caution because the number of RCTs included in the meta-analysis and the sample sizes of most studies were relatively small. There was moderate heterogeneity among the included studies for this outcome and different studies had a somewhat dissimilar patient population and different ablation strategies; therefore, the results may not be generalisable. The follow-up duration ranged from six to 24 months, which is not long enough to

a) Use of catheter ablation vs. medical therapy to treat persistent AF					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					detect late AF recurrence.
Need for cardioversion	Chen et al 2018	8	Direct	B	Need for cardioversion is defined as requirement for cardioversion after the blanking period (usually three months after CA), during the follow up period. Chen et al (2018) reported rates of patients needing cardioversion after the blanking period. Pooled results from three RCTs (n=394) showed that, compared to AADs, CA significantly reduced the number of participants needing cardioversion (RR 0.59, 95%CI [0.46, 0.76]; p < 0.0001). Number needed to treat (NNT) with CA to prevent one case of cardioversion was 4.2. The systematic review suggests that CA is better at preventing the need for cardioversion than medical therapy. Requiring cardioversion after the blanking period is an objective indication of treatment failure. These results are important because they reflect whether or not the primary or secondary treatment of AF with CA or medical therapy has been successful or not. These results should be interpreted with caution because the criteria for deciding which patients required cardioversion was not specified and could have varied between the different trials and clinical centres.
Hospitalisation	Chen et al 2018	8	Direct	B	Hospitalisation was not specifically defined by the authors of this review. However, in other related reviews hospitalisation refers to admission related to the condition or complications of the treatment. In the meta-analysis by Chen et al (2018), two RCTs (n=349) contributed to analysis of hospitalisation. A significant reduction in hospitalisation was detected in patients who were treated with CA compared with AADs (RR 0.54, [95%CI 0.39 to 0.74]; p=0.0002). NNT with CA to prevent one hospitalisation was 6.7. The meta-analysis suggests that CA is better at reducing hospitalisation than medical therapy. Hospitalisation, especially when it involves overnight stay is an important contribution to burden of illness. Depending on the nature of hospitalisation it could consume significant healthcare resources, and increase the risk of further complications like infection, therefore avoiding this would be valuable to the patient. These results should be treated with caution as it is not certain what the nature of the hospitalisations were and whether or not they were always related to AF, HF or other cardiovascular conditions.
Improvement in LVEF	Marrouche et al 2018	7	Direct	A	Improvement in LVEF was defined as the median absolute increase in LVEF from baseline to the 60-month follow-up. Four RCTs (n=205) included in Chen et al (2018) compared CA with medical rate control therapy in patients with persistent AF and concomitant HF. A significant increase in EF was detected in patients who were treated with CA compared with the medical therapy (rate control) [MD = 7.72, 95%CI 4.78 to 10.67; P < 0.00001]. This result should be interpreted with caution because of the relatively small number and size of the studies included in the meta-analysis. Although the studies showed no heterogeneity, the different

a) Use of catheter ablation vs. medical therapy to treat persistent AF					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
	Chen et al 2018	8	Direct		studies use different methods to determine the left ventricular ejection fraction; sensitivity analysis was not carried out. The follow up period (12 to 24 months) was also too short to give sufficient insight into the long-term outcomes in this population.
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 (HF) that led to an unplanned overnight hospitalisation. Patients requiring intravenous medication for HF or substantial increase and/or addition of thiazide to a loop diuretic were deemed to have worsening HF. Reasons for worsening of HF may include AF, acute coronary syndrome and hypertension. At a median follow up of 37.6 months, Marrouche et al (2018) reported composite of death or hospitalisation for worsening HF in 34/125 persistent AF patients treated with CA (27.2%) vs. 48/120 persistent AF patients treated with medical therapy (40.0%) (hazard ratio (HR) 0.64 [95% CI, 0.41 to 0.99], p value not reported). AF and HF 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, therefore valuable to patients. This study suggests that CA is better at reducing this this composite outcome compared with medical therapy although the HR for the difference between groups was only just statistically significant. These results should be interpreted with caution because there was a lack of blinding with regards 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 decisions such as whether to admit a patient for worsening HF. A greater number of patients in the CA group than in the MT 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 MT (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 AADs were listed as recruitment criteria; it is therefore not clear whether this affected the outcome in the MT arm.
Change in 6-minute walk distance (6MWD)[i]	Chen et al 2018	8	Direct	B	The six-min walk distance (6MWD) is mainly used to therapeutically evaluate exercise tolerance in HF patients. In the meta-analysis by Chen et al (2018) pooled results from three RCTs (n=150) contributed to the analysis of the 6MWD changes. There was no significant difference between the CA arm and the medical rate control arm (MD = 19.17, [95%CI −11.43 to 49.76]; p= 0.22). The meta-analysis suggests that there is no difference in 6MWD between CA and medical therapy. Walking distance and general exercise capacity is an important outcome to patients with heart failure and is a measure of deterioration of disease and general morbidity. An improvement in this would be valuable to patients; no difference was reported between CA and medical therapy in this study. This result should be interpreted with caution because, although heterogeneity was not significant among the included studies, the number of patients in these studies was particularly small and a follow-up duration of only 6 to 12 months might not be sufficient for the effect of restoration of sinus

a) Use of catheter ablation vs. medical therapy to treat persistent AF					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					rhythm to fully manifest.
Reduction in Minnesota Living with Heart Failure Questionnaire (MLHFQ) scores	Chen et al 2018	8	Direct	B	MLHFQ score is a validated measure of therapeutic efficacy which is associated with favourable prognostic outcomes in HF. Three studies, reported by Chen et al (2018), provided data on MLHFQ (n=140) score changes. A pooled analysis detected a significant reduction in MLHFQ score, indicating improved quality of life in the ablation arm compared with that in the medical rate control arm (MD 11.13, [95% CI 2.52 to 19.75]; p=0.01). The meta-analysis suggests a significant reduction in MLHFQ scores after CA compared with MT, although the clinical significance of this is not clear. With comprehensive evaluation of QoL, MLHFQ score reflects not only exercise tolerance but also HF symptoms, mental states, and sexual function. It may be attributed to reinstatement of stable sinus rhythm, lesser burden of symptoms, and better cardiac function. This would be valuable to patients. This result should be interpreted with caution because, although heterogeneity was not significant among the included studies, the number of patients in these studies was small.
Ablation- or drug-related complications	Chen et al 2018	8	Direct	B	The most important severe complications related to CA procedure are stroke/transient cerebral ischaemia (TIA), bradycardia, cardiac tamponade, pulmonary vein stenosis, and atrio-oesophageal fistula. AADs adverse effects include thyroid toxicity, pulmonary toxicity, liver dysfunction, bradycardia, and a potential pro-arrhythmic[7] effect. Chen et al (2018) reported ablation or drug-related complication rates between patients receiving CA and medical rhythm control. Pooled results from four studies, reported by Chen et al (2018), showed no significant difference between the CA and medical rhythm control with AADs (RR 1.95, [95%CI 0.52 to 7.25]; p=0.32). However, the studies were highly heterogeneous. Pooled results from another four studies reported no significant difference was between CA and medical rate control (RR 1.64, [95%CI 0.39 to 6.84]; p=0.50). The systematic review suggests that there is no difference in complication rates between CA and medical therapy. Stroke is one of the most severe, and potentially fatal, complications of CA and other procedures used in the treatment of AF. On the other hand, stroke and other thromboembolic events could also result from unsuccessful management of AF. 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 moderate to high heterogeneity found among studies comparing CA with rhythm control and which the authors suspected may be due to somewhat dissimilar patient populations, different ablation strategies, and extent of ablation.
Incremental cost effectiveness ratio (ICER): Cost/QALY	Neyt et al 2013	5	Direct	C	ICER, usually measured as cost/QALY, 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'.

[7] Proarrhythmia is a new or more frequent occurrence of pre-existing arrhythmias, this can be a side effect of antiarrhythmic therapy

a) **Use of catheter ablation vs. medical therapy to treat persistent AF**					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					In a systematic review of health economic studies, Neyt et al (2013) reported data from two studies that included persistent AF patients. For first line ablation compared with second line rate control, reported ICERs ranged from: $60,804 (£46,837)/QALY (age 65 years; CHADS2 score 1) to $80,615 (£62,100) (age 75 years; CHADS2 score 3). 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 the UK, a threshold of £20,000 to £30,000 is generally assumed to reflect cost effectiveness. These results should be treated with a lot of caution because their reliability of the underpinning data is questionable. The outcome measure and the two models used were based on an unpublished systematic review of literature and other undisclosed sources. Some of the studies had conflicting results, so there was likely to be significant heterogeneity in the analyses. The study was from a US payer and societal perspective and relevance to the NHS in England is not known.

6MWD-6-min walk distance; AADs-anti-arrhythmic drugs; AF-atrial fibrillation; CA-catheter ablation; CHADS2-Cardiac failure, Hypertension, Age ≥75 years, Diabetes, prior Stroke; CRT-D-cardiac resynchronization therapy defibrillator; HF-heart failure; ICD- implantable cardioverter–defibrillator; ICER-incremental cost effectiveness ratio; LVEF-Left ventricular ejection fraction; MD-mean difference; MLHFQ-Minnesota living with heart failure questionnaire; MT-medical therapy; N-Number of patients in the study; n-Number of patients in the treatment arm; PAF-paroxysmal atrial fibrillation; QOL-quality of life; RCT-randomised controlled trial; RD-risk difference; RR-Risk ratio; SA-surgical ablation; SR-systematic review;

b) **Use of catheter ablation vs. surgical ablation to treat persistent AF**					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
AF Freedom (freedom from AF or any atrial tachycardia)	Berger et al 2019	6	Direct	C	AF freedom was defined as absence of any atrial arrhythmia (AF, atrial flutter and atrial tachycardia). Berger et al (2019) reported on the rate of AF freedom; at 12 months, after surgical ablation vs catheter ablation, based on two direct comparison RCTs involving 67 patients with persistent AF. These studies showed numerically but not statistically significantly higher AF freedom after surgical ablation compared to catheter ablation (OR 2.58, [95%CI 0.83 to 8.03], p value not reported). Patients were off AADs after the procedure. Berger et al (2019) also reported the results of indirect comparison between CA and SA with and without AADs. AF freedom was higher after minimally invasive SA than after CA. This effect was further enhanced when AADs use was permitted during follow-up. In 7,502 CA patients from 41 studies vs 339 SA patients from five studies, without AADs, 51% [95% CI 46 to 56%] of CA patients vs 69% [95% CI 64 to 74%] SA patients were free from AF at 12 months; p value was not reported. AF freedom rates on AADs were higher with both treatments. In 3133 CA patients (29 studies) versus 196 SA patients (3 studies) 58% [95% CI 54 to 63%] of CA patients vs 71% [95% CI 64 to 74%] SA patients were free from AF at 12 months; p value not reported.

b) **Use of catheter ablation vs. surgical ablation to treat persistent AF**					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					The systematic review suggests that there are no statistically significant differences in rates of AF freedom between surgical ablation patients and CA patients when compared directly. However, SA appears better at increasing the rate of AF freedom when indirect comparisons are made. Achieving freedom from AF is of importance to patients because it may reduce the need for cardioversion and cardiac-related hospitalisations. This will therefore be valuable to patients. These results should be interpreted with caution. The results from the direct comparisons are based on two small studies (67 patients), and the confidence interval is very wide. In all the meta-analyses, there were considerable heterogeneity, which reduces the reliability of the results and any conclusive inferences about the clinical implications. The majority of the RCTs with treatment arms on minimally invasive surgical ablation were small and/or single-centre studies, whereas larger, more frequently multicentre RCTs were available on catheter ablation. Potentially, the minimally invasive surgery studies reflect dedicated programs in specialised centres.
Adverse effects	Berger et al 2019	6	Direct	C	Adverse events (AE) were not specifically defined by Berger et al (2019). However, the WHO defines an AE as any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of an intervention. Berger et al (2019) reported no difference between CA and surgical ablation procedures in terms of overall death and procedure-related death. Bleeding including cardiac tamponade and haemothorax were the most common adverse effects. Combined minor and major bleeding was remarkably more frequently reported with surgical ablation. CA (1.7%) versus SA (7.7%), but no p values were reported. Thromboembolic events were also higher with surgical ablation (1.4% vs 0.7%). Infection rates were 0.7% and 1.0% for CA and surgical ablation respectively. Taken together, irreversible adverse events occurred more frequently after minimally invasive surgery than after catheter ablation. The systematic review suggests that SA is associated with more adverse effects compared with CA, although there appears to be no difference in overall or procedure related deaths. These results should be interpreted with caution because in all the meta-analyses, the studies were considerably heterogeneous, which reduces the reliability of the result and any conclusive inferences about the clinical implications. The majority of the RCTs with treatment arms on minimally invasive surgical ablation were small and/or single-centre studies, whereas larger, more frequently multicentre RCTs were available on catheter ablation.

6MWD-6-min walk distance; AADs-anti-arrhythmic drugs; AF-atrial fibrillation; CA-catheter ablation; CHADS2-Cardiac failure, Hypertension, Age ≥75 years, Diabetes, prior Stroke; CRT-D-cardiac resynchronization therapy defibrillator; HF-heart failure; ICD- implantable cardioverter–defibrillator; ICER-incremental cost effectiveness ratio; LVEF-Left ventricular ejection fraction; MD-mean difference; MLHFQ-Minnesota living with heart failure questionnaire; MT-medical therapy; N-Number of patients in the study; n-Number of patients in the treatment arm; PAF-paroxysmal atrial fibrillation; QOL-quality of life; RCT-randomised controlled trial; RD-risk difference; RR-Risk ratio; SA-surgical ablation; SR-systematic review;

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 persistent AF [Further subgroups that may be identified: • AF with heart failure • Symptomatic vs Asymptomatic[8] • 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][9]
C – Comparison What is/are the main alternative(s) to compare with the intervention being considered?	Medical (drug) management (rhythm control, rate control)[10] 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 o. Impact on clinical frailty score

[8] It may not be possible to separate out the literature into cohorts of asymptomatic versus symptomatic patients.
[9] 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.
[10] 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.

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[11]
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. We excluded conference abstracts, commentaries, letters, editorials and case reports.

Search date: 8 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.
20. 18 not 19

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

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: 226
- Total number of publications considered potentially relevant: 68
- Total number of publications selected for inclusion in this briefing: 4

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.	Excluded as paper focuses on paroxysmal AF
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 paper focuses on paroxysmal AF

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.

Berger WR, Meulendijks, ER, Limpens J, Van Den Berg NWE, Neefs J, Driessen AHG, Krul, SPJ, Van Boven WJP, De Groot JR. 2019. Persistent atrial fibrillation: A systematic review and meta-analysis of invasive strategies. Int J Cardiol, 278: 137-143.

Chen C, Zhou X, Zhu M, Chen S, Chen J, Cai H, Dai J, Xu, Mao W. 2018. Catheter ablation versus medical therapy for patients with persistent atrial fibrillation: a systematic review and meta-analysis of evidence from randomized controlled trials. *J Interv Card Electrophysiol,* 52: 9-18.

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.

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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

Neyt M, Van Brabandt H, Devos C. 2013. The cost-utility of catheter ablation of atrial fibrillation: a systematic review and critical appraisal of economic evaluations. BMC Cardiovasc Disord, 13: 78.

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

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.

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[i] CA vs Medical rate control therapy