NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of percutaneous endoscopic laser balloon pulmonary vein isolation for atrial fibrillation

Atrial fibrillation (AF) is the irregular, and typically rapid, beating of the upper 2 chambers of the heart (the atria). It is caused by abnormal electrical impulses thought to start in the pulmonary veins (the blood vessels carrying blood from the lungs to the heart). Symptoms include palpitations, dizziness, shortness of breath and fatigue. Complications can include stroke.

In this procedure, a catheter with a laser is inserted through the femoral vein in the groin and up into the heart. The laser is used to destroy the areas around the pulmonary veins that cause the abnormal electrical impulses, to help maintain a normal heartbeat. This procedure may be suitable for patients whose atrial fibrillation has not responded to medication.

Introduction

The National Institute for Health and Care Excellence (NICE) has prepared this interventional procedure (IP) overview to help members of the Interventional Procedures Advisory Committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This IP overview was prepared in December 2015.

Procedure name

- Percutaneous endoscopic laser balloon pulmonary vein isolation for atrial fibrillation

Specialist societies

- British Heart Rhythm Society

Description

Indications and current treatment

Atrial fibrillation (AF) is the most common type of cardiac arrhythmia. It is caused by the uncoordinated electrical stimulation of the atrial walls, which stop contracting as they fibrillate. This causes the ventricle to beat at an irregular and sometimes rapid rate. It may be classified as paroxysmal, persistent or permanent. Patients with AF may be asymptomatic or have palpitations, dizziness, shortness of breath, fatigue and chest pain.

Atrial fibrillation is associated with increased risk of embolic stroke from atrial thrombus, and death. Depending on risk stratification, oral anticoagulation treatment may be indicated. Such treatment needs monitoring and is associated with risk of haemorrhage. Drugs may be used to prevent AF and maintain sinus rhythm (anti-arrhythmics) or may be used to control the ventricular rate when AF occurs (usually beta blockers).

Ablation procedures are typically used in patients with non-permanent AF when drug therapy is either not tolerated or is ineffective.

What the procedure involves

Percutaneous endoscopic laser balloon pulmonary vein isolation for AF aims to maintain normal heart rhythm. It uses laser ablation to isolate the electrical impulses originating in the pulmonary veins, which are thought to be responsible for triggering AF.

The laser balloon catheter comprises an inflatable balloon mounted on a catheter shaft, an endoscope lumen, and an optical fibre that can also deliver laser energy.

The procedure is done with the patient under general anaesthesia or sedation. A deflectable sheath introducer is inserted in the femoral vein and advanced into the left atrium through a trans-septal puncture. A circular mapping catheter is introduced, which may need a second trans-septal puncture. A balloon catheter is passed through the deflectable sheath and the balloon is inflated at the ostium of the target pulmonary vein. The endoscope tip is positioned at the proximal end of the balloon, allowing direct visualisation of the cardiac tissue and assessment of the degree of contact between the balloon and cardiac muscle. Laser energy is delivered around the circumference of the pulmonary vein to isolate the source of the abnormal electrical activity. The circular mapping catheter is then used to assess whether electrical isolation of the pulmonary vein has been achieved. Ablation and assessment are repeated sequentially for each pulmonary vein. During ablation of the right-sided pulmonary veins, phrenic nerve pacing is done from the superior vena cava to monitor for phrenic nerve injury.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to percutaneous endoscopic laser balloon pulmonary vein isolation for atrial fibrillation. The following databases were searched, covering the period from their start to 26 November 2015: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with atrial fibrillation.
Intervention/test	Percutaneous endoscopic laser balloon pulmonary vein isolation.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on approximately 1,128 patients from 2 randomised controlled trials, 3 non-randomised comparative studies, 2 case series and 2 case reports[1–9].

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

Table 2 Summary of key efficacy and safety findings on percutaneous endoscopic laser balloon pulmonary vein isolation for atrial fibrillation

Study 1 Dukkipati SR (2015)

Details

Study type	**Randomised controlled trial**
Country	USA (19 sites)
Recruitment period	Not reported
Study population and number	**n=353** (178 laser balloon pulmonary vein isolation versus 175 radiofrequency ablation [RFA]) Patients with drug-refractory paroxysmal atrial fibrillation (AF).
Age and sex	Mean 60 years; 66% (227/342) male
Patient selection criteria	2 or more symptomatic AF episodes (1 minute or more) within the previous 6 months; 1 documented episode within the previous 12 months; and refractory or intolerance to an anti-arrhythmic drug (class I, II, or III). Exclusion criteria included: pulmonary vein size >35 mm; left atrial (LA) thrombus; LA diameter >50 mm; left ventricular ejection fraction <30%; previous LA ablation for AF or atrial flutter; New York Heart Association class III or IV symptoms; myocardial infarction within the previous 60 days; unstable angina; cardiac surgery within the previous 3 months; coronary artery bypass grafting within the previous 6 months; any history of cardiac valve surgery; a thromboembolic event within the previous 3 months; uncontrolled bleeding; active infection; atrial myxoma; severe pulmonary disease or gastrointestinal bleeding; a previous valvular cardiac surgical procedure; presence of an implantable cardioverter-defibrillator; women of childbearing potential who were pregnant, lactating or not using adequate birth control; and inability to be removed from anti-arrhythmic drug therapy.
Technique	General anaesthesia was usually used. Laser balloon pulmonary vein isolation was done with the visually guided laser balloon system (Heartlight, CardioFocus Inc., USA). In the control group, ablation was done using an irrigated RFA catheter (Thermo-Cool Navistar, Biosense Webster, USA) and CARTO electroanatomic mapping system (Biosense Webster) guidance. Additional ablation was allowed in the control arm, which could include linear lesions, ablation of electrogram fractionation, and cavotricuspid isthmus ablation. Patients in the control arm were also allowed a repeat ablation within 80 days if they had a documented, symptomatic episode of AF.
Follow-up	**12 months**
Conflict of interest/source of funding	The study was funded by CardioFocus Inc., USA. The first author has received honoraria from CardioFocus and research funding from Biosense Webster. Other authors are consultants to, or have received grant support or honoraria from ,Biosense Webster, St Jude Medical, Medtronic, Biotronic, Janssen Pharmaceuticals, Laguna Pharmaceuticals, Boston Scientific and CardioFocus.

Analysis

Follow-up issues: Of the 353 randomised patients, 11 were not treated (8 randomised to laser balloon ablation and 3 randomised to RFA). The reasons for treatment not being started were: 3 patients did not meet the eligibility criteria, 2 investigator decision (continued alcohol abuse, diagnosis of lung cancer), 2 console non-operational, 1 withdrew consent, 1 thrombus present on day of procedure, 1 difficulty gaining access, 1 congenital defect noted during procedure. Of the 343 treated patients, 11 were not evaluable for the primary endpoint (3 in the laser balloon group and 5 in the RFA group): 3 patients withdrew consent, 1 missed the 12-month visit, 2 were lost to follow-up and 2 patients had adverse events.

Study design issues: The method of randomisation was not described. There was no blinding. There was a 90-day blanking period for the primary efficacy endpoint. Patients were permitted to continue on the same anti-arrhythmic drug as before the procedure until the end of the 90-day blanking period, at which time it was stopped. Transtelephonic monitoring was started at 3 months after the procedure and continued until 12 months after the procedure. The primary efficacy endpoint was freedom from protocol-defined treatment failure, which included: documented symptomatic AF (1 minute or more); ablation-induced LA flutter or atrial tachycardia; failure to acutely isolate all pulmonary veins; use of any anti-arrhythmic drug; or left heart ablation/surgery or implantable cardioverter-defibrillator placement for AF.

Study population issues: There were no significant differences between the groups with regard to age, sex, AF duration, LA size, and left ventricular ejection fraction.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **342 (170 versus 172)** **Number of pulmonary veins isolated** • Laser balloon=97.7% (649/664) • RFA=99.1% (658/664), p=0.05 **Number of pulmonary veins isolated on first attempt** • Laser balloon=87.8% (583/664) • RFA=83.3% (553/664), p=0.02 **Primary efficacy endpoint met (freedom from protocol-defined treatment failure at 12 months)** • Laser balloon=61.1% • RFA=61.7%, p=0.003 for non-inferiority **12-month drug-free rate of freedom from symptomatic AF or atypical atrial flutter/atrial tachycardia** • Laser balloon=63.5% (106/167) • RFA=63.9% (106/166), p=0.94	**Primary adverse event rate (the number of patients experiencing at least 1 primary adverse event)** Laser balloon=11.8% (20/170) RFA=14.5% (25/172), p=0.002 for non-inferiority **Total number of primary adverse events** Laser balloon=14.1% (24/170) RFA=15.7% (27/172), p=not significant **Stroke** Laser balloon=1.2% (2/170) (1 before discharge, 1 a week after discharge) RFA=0.6% (1/172), p=0.56 All 3 strokes completely resolved. **Cardiac tamponade, perforation, or significant effusion** Laser balloon=1.2% (2/170) RFA=1.7% (3/172), p=0.66 **Diaphragmatic paralysis persisting beyond the blanking period** Laser balloon=3.5% (6/170) (3 persisted at 12 months, 1 resolved after 12 months) RFA=0.6% (1/172), p=0.05 (persistent at 12 months) **Significant pulmonary vein stenosis (>50% decrease in diameter diagnosed by CT or cardiac magnetic resonance imaging) at 3 months** Laser balloon=0% (0/170) RFA=2.9% (5/172), p=0.03 Pulmonary vein narrowing (>20% but ≤50% decrease in diameter, evaluated on a per-vein basis) Laser balloon=21.9% RFA=24.7%, p=not reported **Cardioversion for atrial arrhythmia** Laser balloon=8.2% (14/170) RFA=9.3% (16/172), p=0.73 **Major bleeding needing transfusion** Laser balloon=0% (0/170) RFA=0.6% (1/172), p=0.30 There were no atrio-oesophageal fistulas. There was 1 death during follow-up in the laser balloon ablation arm that was not considered to be a primary adverse event. The patient had severe pulmonary hypertension and died approximately 7 months after the index procedure and 3 months after ablation for atypical atrial flutter.
Abbreviations used: RFA, radiofrequency ablation	

Study 2 Schmidt B (2013)

Details

Study type	**Randomised controlled trial**
Country	Germany
Recruitment period	Not reported
Study population and number	**n=99 (33 laser balloon versus 33 radiofrequency versus 33 cryoballoon)** Patients with drug-refractory paroxysmal atrial fibrillation.
Age and sex	Mean 65 years; sex not reported
Patient selection criteria	Patients with drug-refractory paroxysmal atrial fibrillation and indication for catheter ablation. Exclusion criteria included left atrial size >50 mm, left ventricular ejection fraction <45%, any contraindications for MRI scanning, stage III renal failure, presence of an intracardiac thrombus, and a CHADS score >3.
Technique	All procedures were done with the patient under conscious sedation.
Follow-up	**1 day**
Conflict of interest/source of funding	2 authors received research grants and honoraria from CardioFocus and are both consultants to Medtronic; 1 author is a consultant to Medtronic; 1 author was supported by a grant from the European Heart Rhythm Association.

Analysis

Follow-up issues: There were no losses to follow-up.

Study design issues: The method of randomisation is not described. The study was designed to compare the incidence of asymptomatic cerebral lesions between the different ablation technologies. Patients' neurological status was assessed the day after the procedure.

Study population issues: The baseline clinical characteristics did not differ between the groups.

Other issues:

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **99 (33 versus 33 versus 33)** The pulmonary vein isolation rate was 100% in all patients. **Mean procedure times (minutes)** • Laser balloon=149±34 • RFA=103±33 • Cryoballoon=129±29, p≤0.05	None of the patients had asymptomatic cerebral lesions detected in the MRI done before the procedure. **Asymptomatic cerebral lesions detected after the procedure** • Overall=22% (22/99) • Laser balloon=24% (8/33) • RFA=24% (8/33) • Cryoballoon=18% (6/33), p=0.8 Univariate analysis identified a history of arterial hypertension as the sole independent predictor of asymptomatic cerebral lesions in the entire study cohort (p=0.05). No major procedural complications occurred in the study.
Abbreviations used: RFA, radiofrequency ablation.	

Study 3 Bordignon S (2013)

Details

Study type	**Non-randomised comparative study**
Country	Germany
Recruitment period	September 2010–September 2011
Study population and number	**n=140 (70 laser balloon versus 70 cryoballoon** Patients with paroxysmal atrial fibrillation refractory to at least 1 membrane active anti-arrhythmic drug.
Age and sex	Mean 63 years; 66% (92/140) male
Patient selection criteria	Age 18–75 years, no prior pulmonary vein isolation attempt, left atrial (LA) size <50 mm, left ventricular ejection fraction >45%.
Technique	All procedures were done with the patient under conscious sedation. Laser balloon: Heartlight, CardioFocus Inc., USA Cryoballoon: Arctic Front, Medtronic, USA For the laser balloon procedures, a temperature probe was inserted in the oesophagus with an oesophageal temperature cut-off limit of 39°C.
Follow-up	**Median 393 days**
Conflict of interest/source of funding	Two authors received research grants and speaker honoraria from CardioFocus and are both consultants to Medtronic, 1 author was supported by a grant of the European Heart Rhythm Association and received travel support from CardioFocus, 1 author is a consultant to Medtronic.

Analysis

Follow-up issues: There were no losses to follow-up. Five patients in the cryoballoon group and 1 patient in the laser balloon group had a repeat procedure for intractable atrial fibrillation in the 90-day blanking period. These patients were excluded from the primary efficacy analysis. In addition, 1 patient in the cryoballoon group died from lung cancer 420 days after the ablation procedure. Patients were followed up for 12 months using 3-day Holter ECG recording.

Study design issues: Patients were prospectively assigned to the treatment groups (no further details provided). All previously ineffective anti-arrhythmic drugs were stopped immediately after the procedure and a blanking period of 90 days was applied. Electrical or chemical cardioversion was allowed during the blanking period followed by a prescription of anti-arrhythmic drugs. At the end of the blanking period, all anti-arrhythmic drugs had to be stopped. The primary efficacy endpoint was a documented atrial fibrillation recurrence ≥30 seconds between 90 and 365 days after the index ablation. An intention to treat analysis was done, including all patients, with repeat procedures during the 90 day blanking period being counted as true atrial fibrillation recurrences.

Study population issues: There were no significant differences between the groups with regard to baseline clinical characteristics.

Key efficacy and safety findings

<table>
<tr><td>Efficacy</td><td>Safety</td></tr>
<tr><td>Number of patients analysed: 140 (70 versus 70)
1 patient in the laser balloon group did not have ablation because of a femoral venous laceration needing surgical intervention.
In the cryoballoon group, 1 out of 270 pulmonary veins could not be isolated because of imperfect balloon occlusion despite multiple attempts.
In the laser balloon group, 3 out of 273 pulmonary veins could not be isolated: in 2 cases, occlusion was impossible and 1 procedure was interrupted because of phrenic nerve palsy.
Mean procedure time (minutes)
• Laser balloon=144±33
• Cryoballoon=136±30, p=0.13
Mean fluoroscopy time (minutes)
• Laser balloon=15±6
• Cryoballoon=21±9, p<0.001
Atrial fibrillation recurrence between 90 and 365 days after ablation (primary endpoint)
• Laser balloon=27% (18/68)
• Cryoballoon=37% (24/65), p=0.18
Kaplan-Meier analysis with log-rank test confirmed a trend towards increased atrial fibrillation free survival in the laser balloon group (p=0.23).
Atrial fibrillation recurrence between 90 and 365 days after ablation (primary endpoint) – intention to treat analysis
• Laser balloon=29% (20/70)
• Cryoballoon=41% (29/70), p=0.11
Multiple procedure success rate
• Laser balloon=80% (56/70) after median follow-up of 225 days
• Cryoballoon=82% (58/70) after median follow-up of 334 days
Electrophysiological findings during repeat procedures – reconnection of previously isolated pulmonary veins
• Laser balloon=42% (18/42) of pulmonary veins (n=11 patients)
• Cryoballoon=68% (58/85) of pulmonary veins (n=22 patients)
Relative risk 0.63, 95% confidence interval 0.43 to 0.92, p=0.006</td><td>Procedural related complications
<table>
<tr><th></th><th>Laser balloon</th><th>Cryoballoon</th></tr>
<tr><td>Death</td><td>0 (0%)</td><td>0 (0%)</td></tr>
<tr><td>Cardiac tamponade</td><td>1 (1.4%)
(treated by drainage of 300 ml of blood)</td><td>0 (0%)</td></tr>
<tr><td>Minor vascular complications</td><td>3 (4.2%)
(2 false aneurysms, 1 haematoma)</td><td>2 (2.8%)
(2 false aneurysms – treated conservatively)</td></tr>
<tr><td>Major vascular complications</td><td>1 (1.4%) (laceration of the right femoral vein caused by mechanical trauma – treated by surgery)</td><td>0 (0%)</td></tr>
<tr><td>Phrenic nerve palsy*</td><td>3 (4.2%)</td><td>4 (5.7%)</td></tr>
<tr><td>Stroke</td><td>0 (0%)</td><td>0 (0%)</td></tr>
<tr><td>Transient ischaemic attack</td><td>1 (1.4%)
(the patient reported double vision 3 days after ablation and after chemical cardioversion of an early atrial fibrillation recurrence. Symptoms resolved after 10 minutes and MRI did not reveal any ischaemic lesions.)</td><td>0 (0%)</td></tr>
<tr><td>Atrio-oesophageal fistula</td><td>0 (0%)</td><td>0 (0%)</td></tr>
</table>
* Phrenic nerve palsy completely recovered within 6 months in all patients.</td></tr>
</table>

Study 4 Metzner A (2011)

Details

Study type	**Non-randomised comparative study (prospective)**
Country	Germany
Recruitment period	August 2009–October 2010
Study population and number	**n=60 (40 laser balloon versus 20 radiofrequency ablation)** Patients with highly symptomatic, drug-refractory paroxysmal atrial fibrillation.
Age and sex	Mean 56 versus 63 years; 55% (33/60) male
Patient selection criteria	Exclusion criteria were persistent atrial fibrillation, previous pulmonary vein isolation, left atrial diameter >50 mm, severe valvular heart disease, and contraindications to postinterventional oral anticoagulation. A pulmonary vein diameter >32 mm was an additional exclusion criterion.
Technique	All procedures were done with the patient under conscious sedation. Laser balloon: Endoscopic ablation system (EAS, CardioFocus, USA). An oesophageal temperature probe was inserted transorally and the procedure was stopped if the oesophageal temperature exceeded 38.5°C. All patients were treated with proton-pump inhibitors.
Follow-up	**2 days**
Conflict of interest/source of funding	The study was supported by a research grant by CardioFocus, Inc., USA. One of the authors received a research grant and speaker's honoraria from CardioFocus.

Analysis

Follow-up issues: An oesophagogastroduodenoscopy was done in all patients 2 days after ablation to assess for the presence and severity of possible thermal lesions. This was repeated after 5 days when thermal lesions were detected.

Study design issues: Consecutive patients were treated by pulmonary vein isolation using either laser balloon or radiofrequency; the method for assigning patients to treatment groups was not described. The primary aim of the study was to assess the incidence and severity of oesophageal lesions using the laser balloon in comparison with radiofrequency ablation.

Study population issues: Patients in the laser balloon group were statistically significantly younger than those in the radiofrequency group (56 versus 63 years, p=0.019) and the left atrial size was smaller (42 versus 46 mm, p=0.003). Hypertension was present in 50% (20/40) of patients in the laser balloon group and 75% (15/20) of patients in the radiofrequency group (p=0.064).

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>Number of patients analysed: 60 (40 versus 20)
Complete electrical pulmonary vein isolation was achieved in all patients. No additional ablation lines were done in either group.
Mean procedure time (minutes)
• Laser balloon=234±62
• Radiofrequency=185±28, p=0.001
Mean fluoroscopy time (minutes)
• Laser balloon=28±16
• Radiofrequency=26±8, p=0.71
Oesophageal temperature >38.5°C
• Laser balloon=70% (28/40)
• Radiofrequency=90% (18/20), p=0.033
Mean maximum oesophageal temperature (°C) after stopping energy delivery
• Laser balloon=39.0±2.3
• Radiofrequency=41.6±2.3, p<0.0001</td><td>Incidence and quality of oesophageal thermal lesions (identified by endoscopy)
<table><tr><th></th><th>Laser balloon n=40</th><th>Radiofrequency n=20</th></tr><tr><td>No thermal lesions, n (%)</td><td>33 (82)</td><td>17 (85)</td></tr><tr><td>Minimal thermal lesions, n (%)</td><td>3 (8)</td><td>3 (15)</td></tr><tr><td>Ulceration, n (%)</td><td>4 (10)</td><td>0</td></tr><tr><td>Atrio-to-oesophageal fistula</td><td>0</td><td>0</td></tr></table>There was no statistically significant difference in the incidence of thermal lesions but the quality of thermal lesions was more severe in the laser balloon group.
In all patients, repeat imaging done 8 days (laser balloon) or 5 days (radiofrequency) after the initial endoscopy demonstrated healing lesions.</td></tr>
</table>

Study 5 Dukkipati SR (2013)

Details

Study type	**Case series (composite of 4 separate studies)**
Country	USA, Germany, Czech Republic (15 study centres)
Recruitment period	Not reported
Study population and number	**n=200** Patients with symptomatic, recurrent, paroxysmal atrial fibrillation
Age and sex	Mean 57 years; 60% (120/199) male
Patient selection criteria	Key inclusion criteria: age 18–75, recurrent paroxysmal atrial fibrillation refractory to 1 or more anti-arrhythmic drugs. Key exclusion criteria: left ventricular ejection fraction <30%, left atrial diameter >5 cm, pulmonary vein diameters >32 mm, presence of an intracardiac thrombus, previous cardiac ablation, myocardial infarction or cardiac surgery within the previous 3 months, moderate or severe valvular heart disease, or a stroke or transient ischaemic attack within the previous 6 months.
Technique	The procedures were done using either conscious sedation or under general anaesthesia. An oesophageal temperature probe was used and the procedure was stopped if the oesophageal temperature exceeded 38.5°C. Device: balloon-based visually guided laser ablation catheter (CardioFocus Inc., USA).
Follow-up	**12 months**
Conflict of interest/source of funding	The study was supported by CardioFocus, Inc.; 9 authors received research grant support from CardioFocus, Inc., 1 author serves as consultant for CardioFocus Inc., 1 author served on the clinical oversight committee for 1 of the studies (no compensation), and 4 authors received honoraria from CardioFocus, Inc.

Analysis

Follow-up issues: Outcome data at 12 months were available for 91% (181/200) of patients. Of the 19 patients with no outcome data, 7 were lost to follow-up, 6 withdrew from the study, and 6 patients had not yet reached 12 months of follow-up. Follow-up methods varied between the study centres and included clinic visits at 3 or 6 month intervals, and either Holter or transtelephonic monitoring at variable intervals.

Study design issues: Composite of 4 open-label non-randomised studies rather than a single study with a uniform protocol. CT scans were not routinely done after the procedure, and those that were done were not assessed by a core laboratory. Anti-arrhythmic drugs were typically continued for 1–3 months after which they were completely discontinued. There was a 3-month blanking period after ablation. Recurrence was defined as any atrial arrhythmia exceeding 60 seconds.

Other issues: The study includes the first 200 patients with paroxysmal atrial fibrillation to be treated by the visually guided laser balloon catheter. There is likely to be some overlap in patient populations between this study and the other studies included in table 2.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **200** Acute electrical isolation was achieved in 78.4% of all pulmonary veins after placement of the initial encircling lesion set and ultimately in 98.8% of pulmonary veins after an average of 1.3 attempts per vein. Mean procedure time=200±54 minutes Mean fluoroscopy time=31±21 minutes (these times decreased with increasing operator experience) At 12 month follow-up, 60.2% (95% CI 52.7% to 67.4%) of patients were free from atrial fibrillation and were off anti-arrhythmic drugs (class I or III).	There was no clinical evidence of pulmonary vein stenosis in any of the patients. Of the 116 patients with baseline and 3 month CT or MRI scans, the mean decrease in pulmonary vein diameter was 3.5% at 3 month follow-up. Mild narrowing (1–25% decrease in diameter) was present in 44% of pulmonary veins and moderate narrowing (26–50%) in 6% of pulmonary veins. Phrenic nerve injury=2.5% (5/200) (1 remained unresolved at 12 month follow-up) Pericardial effusion=3.0% (6/200) (4 patients developed haemodynamic compromise or cardiac tamponade. All of these tamponades occurred during the procedure and were successfully drained.) One patient with cardiac tamponade had pericardiocentesis and was discharged 4 days after the procedure. Two days after discharge, he experienced sudden death. The autopsy showed no pericardial effusion, cardiac perforation, atrio-oesophageal fistula, or pulmonary embolisation. The patient was found to have unrecognised, critical triple vessel coronary artery disease. An independent Data Safety and Monitoring Board adjudicated that this event was not related specifically to the laser ablation catheter. There were no patients who had transient ischaemic attacks, strokes, or atrio-oesophageal fistulas. Catheter failure rate=6.5% (13/200) (attributed to catheter damage; a second catheter was used for all patients)
Abbreviations used: CI, confidence interval	

Study 6 Bordignon S (2015)

Details

Study type	**Non-randomised comparative study**
Country	Germany
Recruitment period	January 2011–December 2012
Study population and number	**n=80 (40 laser balloon versus 40 radiofrequency)** Patients with persistent atrial fibrillation
Age and sex	Laser balloon: mean age=66 years; male=78% (31/40) Radiofrequency: mean age=67 years; male=65% (26/40)
Patient selection criteria	Not reported. All patients had drug refractory early persistent atrial fibrillation.
Technique	All procedures were done under sedation. An oesophageal temperature probe was used and energy delivery was stopped if the temperature exceeded 39.5°C. Additional ablation beyond pulmonary vein isolation was allowed in case of failed restoration of sinus rhythm by cardioversion after pulmonary vein isolation and occurrence of mappable atrial tachycardias. In the laser balloon group, additional ablations were done using an irrigated tip catheter. Most patients in the radiofrequency group had pure pulmonary vein isolation without additional substrate modification. Laser balloon device: endoscopic laser balloon ablation system (HeartLight, CardioFocus, USA)
Follow-up	**Mean 517±170 days**
Conflict of interest/source of funding	Two authors received research grants from CardioFocus; 3 authors received speaker's honoraria from CardioFocus.

Analysis

Follow-up issues: Patients attended follow-up visits, including a 72 hour Holter electrocardiogram, on day 90, 180 and 365.

Study design issues: Patients treated by laser balloon pulmonary vein isolation were matched with patients treated by radiofrequency ablation. They were matched for age, gender, atrial fibrillation duration, left atrial size, left ventricular ejection fraction, and date of procedure. The primary efficacy endpoint of the study was recurrence of any atrial tachyarrhythmia lasting longer than 30 seconds between 90 and 365 days after the procedure off anti-arrhythmic drugs. The study protocol included a 3 month blanking period. A repeat procedure during the blanking period was according to the protocol a primary endpoint event. Anti-arrhythmic drug therapy was stopped immediately after the procedure. If arrhythmia recurred within 90 days after the procedure, the previous ineffective anti-arrhythmic drug was resumed and electrical cardioversion was done if necessary.

Study population issues: The baseline characteristics did not differ significantly between the groups, with the exception of atrial fibrillation episode duration. Patients presenting in atrial fibrillation at the time of the ablation (65% in the laser balloon group and 68% in the radiofrequency group) had a median atrial fibrillation duration of 3 months in the laser balloon group and 1 month in the radiofrequency group (p=0.001). The history of atrial fibrillation was 3 and 4 years respectively (p=0.51).

Key efficacy and safety findings

Efficacy

Number of patients analysed: **80 (40 versus 40)**

Acute pulmonary vein isolation was achieved in all patients in both groups.

Procedural data

	Laser balloon n=40	Radiofrequency n=40	p value
Procedural time (min)	133±35	100±37	<0.01
Fluoroscopy time (min)	13±	12±7	0.28
left atrial linear ablation for perimitral flutter	2.5% (1/40)	2.5% (1/40)	1.00
right atrial isthmus ablation	5% (2/40)	5% (2/40)	1.00

Repeat pulmonary vein isolation in the blanking period

- Laser balloon=7.5% (3/40)
- Radiofrequency=2.5% (1/40)

Primary endpoint reached (1-year single procedure recurrence)

- Laser balloon=27.5% (11/40)
- Radiofrequency=22.5% (9/40), p=0.79

1-year atrial fibrillation or atrial tachycardia-free survival (Kaplan-Meier analysis)

- Laser balloon=72%
- Radiofrequency=76%, p=0.83

During the entire follow-up, 32.5% (13/40) and 40% (16/40) of patients in the laser balloon and radiofrequency groups respectively, had atrial fibrillation or atrial tachycardia recurrences (p=0.64). The mean time to recurrence was 221±200 days in the laser balloon group and 318±158 days in the radiofrequency group (p=0.87).

Repeat procedures

- Laser balloon=25% (10/40)
- Radiofrequency=22.5% (9/40)

Safety

Complications

Complication	Laser balloon n=40	Radiofrequency n=40	p value
Cardiac tamponade	0	0	1.00
Pericardial effusion (managed conservatively)	0	1	1.00
False aneurysm	1	1	1.00
Arteriovenous-fistula	0	1	1.00
Groin haematoma	0	1	1.00
Mild to moderate asymptomatic pulmonary vein stenosis	0	2	0.49
Phrenic nerve palsy	0	0	1.00

Study 7 Sediva L (2014)

Details

Study type	**Case series (retrospective)**
Country	Czech Republic
Recruitment period	January 2009–May 2013
Study population and number	**n=194** Patients with either drug-refractory paroxysmal atrial fibrillation (n=178) or persistent atrial fibrillation (n=16)
Age and sex	Mean 61 years; 66% (127/194) male
Patient selection criteria	Patients were classified as having symptomatic, drug-refractory paroxysmal atrial fibrillation (atrial fibrillation episode <7 days), symptomatic persistent atrial fibrillation (atrial fibrillation episode duration ≤365 days) or symptomatic long-standing persistent atrial fibrillation (atrial fibrillation episode duration >365 days). Patients with signs of thrombus in the left atrial appendage were excluded.
Technique	The procedures were done under conscious sedation. A single trans-septal puncture was used for the laser balloon catheter, which was then removed and replaced by a circular mapping catheter. An oesophageal temperature probe was used and energy delivery was stopped if the temperature exceeded 38.5°C. After January 2013, all patients were treated with proton pump inhibitors for at least 2 weeks after the procedure. Before this time, only patients whose oesophageal temperature exceeded 38.5°C were treated with proton pump inhibitors. Device: visually guided laser ablation (VGLA) system (CardioFocus Inc.).
Follow-up	**Mean 30 months (range 4–48)**
Conflict of interest/source of funding	Not reported

Analysis

Follow-up issues: Patients were followed up routinely between 4 and 6 months after the procedure, with a 7-day Holter recording. For most patients, this was repeated after 12 months follow-up. Continuing follow-up of longer term patients took place at 24, 36 and 48 months follow-up and included 7 days Holter recordings, resting electrocardiograms, and patient history. A small cohort of 27 patients, who were included on a prospective feasibility study, were followed up more rigorously than the remaining patients who were followed up according to the centre's regular clinical procedures.

Study design issues: Retrospective, single centre cohort study. The authors note that patients with non-symptomatic episodes of atrial fibrillation during follow-up may have been missed because 7-day Holter recordings were repeated only in patients reporting symptoms, or for other reasons based on the judgement of the physician.

Study population: the mean duration of atrial fibrillation was 60.7 (range 11–300) months for patients with paroxysmal atrial fibrillation and 62.8 (range 12–200) months for patients with persistent atrial fibrillation.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **194** 99.2% of veins were isolated acutely; 95.3% of veins were isolated at first attempt. **Freedom from atrial fibrillation – paroxysmal atrial fibrillation** • 12 month follow-up=82.3% (130/158) • 24 month follow-up=75.9% (66/87) • 36 month follow-up=75.9% (41/54) • 48 month follow-up=75% (24/32) **Freedom from atrial fibrillation – persistent atrial fibrillation** • 12 month follow-up=75% (9/12) Repeat procedures=5.7% (11/194)	**Complications** • Stroke/transient ischaemic attack=0.5% (1/194) (the patient showed symptoms of verbal confusion 2 hours after the procedure, but this resolved within 24 hours) • Tamponade/pericardial effusion=0.5% (1/194) • Acute phrenic nerve injury=2.1% (4/194) • Persistent phrenic nerve injury (>6 months)=0% (0/194) • Vascular injury=3.1% (6/194) (prolonged hospitalisation because of bleeding=4, vascular surgical repair=2) • Pulmonary vein stenosis=0% (0/194) • Atrio-oesophageal fistula=0% (0/194)

Study 8 Kumar N (2015)

Details

Study type	**Case report**
Country	The Netherlands
Recruitment period	Not reported
Study population and number	**n=1** Patient with persistent atrial fibrillation
Age and sex	65-year old man
Patient selection criteria	Not reported
Technique	Laser balloon (HeartLight, CardioFocus, Marlborough, Massachusetts) ablation of all 4 pulmonary veins
Follow-up	**6 months**
Conflict of interest/source of funding	Not reported

Analysis

Other issues: The full text article was unavailable so data has been extracted from the first of the 2 pages only.

Key efficacy and safety findings

Safety
Pulmonary vein stenosis The pre-procedure high-resolution CT scan and intraprocedural left atrial angiogram of pulmonary veins were normal. The CT scan 6 months after the procedure revealed fusiform stenosis of the left inferior pulmonary vein ostium. Its dimension at the ostium was 15 mm x 10 mm, and at 1 cm after the ostium, was 22 mm x 14 mm. This was corroborated during the subsequent epicardial ablation of the left pulmonary veins, showing remarkable segmental fibrosis leading to a narrowing of the left inferior pulmonary vein. In this patient, none of the laser applications was within the pulmonary vein. Visual assessment during the procedure confirmed that all applications were delivered in the ostium. However, because of the unsuccessful first attempt to isolate the pulmonary vein during the same procedure, additional energy applications were given, which might have contributed to its stenosis.

Study 9 Gal P (2015)

Details

Study type	**Case report**
Country	The Netherlands
Recruitment period	Not reported
Study population and number	**n=1** Patient with drug-refractory, symptomatic, paroxysmal atrial fibrillation
Age and sex	58-year old woman
Patient selection criteria	Not reported
Technique	Endoscopically assisted laser balloon ablation system
Follow-up	**Not reported**
Conflict of interest/source of funding	None

Analysis

Key efficacy and safety findings

Safety
Endoscopically visible steam pop During ablation at the antrum of the left superior pulmonary vein, a sudden steam pop was witnessed, with displacement of the laser balloon catheter. Visualisation of the left superior pulmonary vein antrum showed a red discolouration, most likely a haematoma in the antral wall. A successful pulmonary vein isolation was done. The red discolouration was still present 1 hour later. The patient did not develop any symptoms related to the steam pop and echocardiography did not reveal any abnormalities.

Efficacy

Freedom from atrial fibrillation

In a randomised controlled trial of 342 patients with AF treated by laser balloon pulmonary vein isolation or radiofrequency ablation, 61% and 62% of patients (actual numbers not reported) respectively (p=0.003 for non-inferiority) did not have protocol-defined treatment failure (documented symptomatic AF of 1 minute or more; ablation-induced left atrial flutter or atrial tachycardia; failure to acutely isolate all pulmonary veins; use of any anti-arrhythmic drug; or left heart ablation or surgery, or implantable cardioverter-defibrillator placement for AF) at 12-month follow-up[1]. The percentage of patients who were drug-free at 12 months and free from symptomatic AF or atypical atrial flutter or atrial tachycardia was 64% (106/167 and 106/166) in both treatment groups (p=0.94). In a non-randomised comparative study of 140 patients treated by laser balloon pulmonary vein isolation or cryoballoon ablation, AF recurred between 90 and 365 days after ablation in 27% (18/68) and 37% (24/65) of patients respectively (p=0.18)[3]. In a case series of 200 patients, 60% (95% confidence interval [CI] 53% to 67%) of patients were free from AF and were off anti-arrhythmic drugs (class I or III) at 12-month follow-up[5]. In a non-randomised comparative study of 80 patients with early persistent AF treated by laser balloon pulmonary vein isolation or radiofrequency ablation, AF recurred in 28% (11/40) and 23% (9/40) of patients respectively (p=0.79) after a single procedure at 12-month follow-up[6]. In a case series of 194 patients 82% (130/158) of patients with paroxysmal AF and 75% (9/12) of patients with persistent AF were free from AF at 12-month follow-up[7]. For patients with paroxysmal AF, 76%, 76% and 75% of patients were free from AF at 24-, 36- and 48-month follow-up respectively.

Repeat procedures

In the non-randomised comparative study of 80 patients with early persistent AF treated by laser balloon pulmonary vein isolation or radiofrequency ablation, 25% (10/40) and 23% (9/40) of patients respectively had a repeat procedure. In the case series of 194 patients, 6% (11/194) of patients had a repeat procedure.

Safety

Stroke/transient ischaemic attack

Stroke was reported in 2 patients treated by laser balloon pulmonary vein isolation (1 before discharge and 1 a week after discharge) and in 1 patient treated by radiofrequency ablation (p=0.56) in a randomised controlled trial of 342 patients[1]. All 3 strokes completely resolved. Transient ischaemic attack was reported in 1 patient treated by laser balloon pulmonary vein isolation in a non-randomised comparative study of 140 patients[3]. Stroke or transient ischaemic attack was reported in 1 patient in a case series of 194 patients; the patient showed symptoms of verbal confusion 2 hours after the procedure, but this resolved within 24 hours[7].

Cardiac tamponade, perforation or pericardial effusion

Cardiac tamponade, perforation, or significant effusion was reported in 1% (2/170) of patients treated by laser balloon pulmonary vein isolation and 2% (3/172) of patients treated by radiofrequency ablation (p=0.66) in the randomised controlled trial of

342 patients[1]. Cardiac tamponade was reported in 1 patient in the non-randomised comparative study of 140 patients; this was treated by drainage of 300 ml of blood[3]. Pericardial effusion was reported in 3% (6/200) of patients in a case series of 200 patients; 4 patients developed haemodynamic compromise or cardiac tamponade. All of these tamponades occurred during the procedure and were successfully drained. One of the patients with cardiac tamponade had pericardiocentesis and was discharged 4 days after the procedure. Two days after discharge, he died suddenly. The autopsy showed no pericardial effusion, cardiac perforation, atrio-oesophageal fistula or pulmonary embolisation. The patient was found to have unrecognised critical triple vessel coronary artery disease. An independent Data Safety and Monitoring Board considered that this event was not related specifically to the laser ablation catheter[5]. Cardiac tamponade or pericardial effusion was reported in 1 patient in the case series of 194 patients[7].

Diaphragmatic paralysis or phrenic nerve palsy

Diaphragmatic paralysis persisting beyond 90 days was reported in 4% (6/170) of patients treated by laser balloon pulmonary vein isolation (3 persisted at 12 months, 1 resolved after 12 months) and 1% (1/172) of patients treated by radiofrequency ablation (persistent at 12 months; p=0.05) in the randomised controlled trial of 342 patients[1]. Phrenic nerve palsy was reported in 4% (3/70) of patients treated by laser balloon pulmonary vein isolation and 6% (4/70) of patients treated by cryoballoon ablation in the non-randomised comparative study of 140 patients[3]. Phrenic nerve injury was reported in 3% (5/200) of patients in the case series of 200 patients (1 remained unresolved at 12-month follow-up)[5]. Acute phrenic nerve injury was reported in 2% (4/194) of patients in the case series of 194 patients, none persisted beyond 6 months[7].

Vascular complications

Laceration of the right femoral vein by mechanical trauma was reported in 1 patient in the non-randomised comparative study of 140 patients[3]. This was treated by surgery. In the same study, minor vascular complications (false aneurysms or haematoma) were reported in 4% (3/40) of patients treated by laser balloon pulmonary vein isolation and 3% (2/70) of patients treated by cryoballoon ablation. False aneurysm was reported in 1 patient treated by laser balloon and 1 patient treated by radiofrequency ablation in a non-randomised comparative study of 80 patients[6]. Vascular injury was reported in 3% (6/194) of patients in the case series of 194 patients; 2 had surgical repair and 4 patients had prolonged hospitalisation because of bleeding[7].

Cardioversion for atrial arrhythmia

Cardioversion for atrial arrhythmia was reported in 8% (14/170) of patients treated by laser balloon pulmonary vein isolation and 9% (16/172) of patients treated by radiofrequency ablation (p=0.73) in the randomised controlled trial of 342 patients[1].

Asymptomatic cerebral lesions

Asymptomatic cerebral lesions were detected by MRI 1–2 days after the procedure in 24% (8/33) of patients treated by laser balloon pulmonary vein isolation, 24% (8/33) of patients treated by radiofrequency ablation and 18% (6/33) of patients treated by cryoballoon ablation (p=0.8) in a randomised controlled trial of 99 patients[2].

Thermal damage

Thermal lesions in the oesophagus, identified by endoscopy, were reported in 82% (33/40) of patients treated by laser balloon pulmonary vein isolation and 85% (17/20) of patients treated by radiofrequency ablation in a non-randomised comparative study of 60 patients; ulceration was reported in 10% (4/40) of patients treated by laser balloon and no patients treated by radiofrequency ablation[4].

A patient with pulmonary vein stenosis 6 months after laser balloon pulmonary vein isolation was described in a case report[8]. The first attempt to isolate the pulmonary vein was unsuccessful and additional energy applications were needed, which might have contributed to the stenosis. Significant pulmonary vein stenosis (more than a 50% decrease in diameter on CT or cardiac MRI) at 3 month follow-up was reported in no patients treated by laser balloon pulmonary vein isolation and 3% (5/172) of patients treated by radiofrequency ablation (p=0.03) in the randomised controlled trial of 342 patients[1]. Pulmonary vein narrowing (more than 20% but not more than 50% decrease in diameter, evaluated on a per-vein basis was reported in 22% and 25% of patients respectively, in the same study (p value not reported). The mean decrease in pulmonary vein diameter was 4% at 3-month follow-up in the case series of 200 patients. Mild narrowing (1–25% decrease in diameter) was present in 44% of pulmonary veins and moderate narrowing (26–50%) in 6% of pulmonary veins[5].

An endoscopically visible steam 'pop' was described in a case report[9]. During ablation at the antrum of the left superior pulmonary vein, a sudden steam pop was witnessed, with displacement of the laser balloon catheter. The left superior pulmonary vein antrum showed a red discolouration, most likely a haematoma in the antral wall. A successful pulmonary vein isolation was done. The discolouration was still present 1 hour later. The patient did not develop any symptoms related to the steam 'pop' and echocardiography did not reveal any abnormalities.

Validity and generalisability of the studies

- There were no studies reported from the UK.
- There are several studies reported from the same centres and there is likely to be some patient overlap between them.
- Most of the studies include patients with paroxysmal atrial fibrillation; 2 studies included patients with persistent atrial fibrillation[6,7].
- The randomised controlled trial used an atrial fibrillation duration of 60 seconds as a marker of treatment failure, rather than 30 seconds as in the other studies.
- Some patients were followed up with routine 7-day Holter recording whereas others were only assessed with 7-day Holter recording if they had symptoms. So some patients with asymptomatic episodes of atrial fibrillation may have been missed.

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B gives details of the recommendations made in each piece of guidance listed.

Interventional procedures

- Percutaneous balloon cryoablation for pulmonary vein isolation in atrial fibrillation. NICE interventional procedure guidance 427 (2012). Available from http://www.nice.org.uk/guidance/IPG427
- Thoracoscopic exclusion of the left atrial appendage (with or without surgical ablation) for non-valvular atrial fibrillation for the prevention of thromboembolism. NICE interventional procedure guidance 400 (2011). Available from http://www.nice.org.uk/guidance/IPG400
- Percutaneous endoscopic catheter laser balloon pulmonary vein isolation for atrial fibrillation. NICE interventional procedure guidance 399 (2011). This guidance is currently under review and is expected to be updated in 2016. For more information, see http://www.nice.org.uk/guidance/IPG399
- Percutaneous occlusion of the left atrial appendage in non-valvular atrial fibrillation for the prevention of thromboembolism. NICE interventional procedure guidance 349 (2010). Available from http://www.nice.org.uk/guidance/IPG349
- Percutaneous (non-thoracoscopic) epicardial catheter radiofrequency ablation for atrial fibrillation. NICE interventional procedure guidance 294 (2009). Available from http://www.nice.org.uk/guidance/IPG294
- Thoracoscopic epicardial radiofrequency ablation for atrial fibrillation. NICE interventional procedure guidance 286 (2009). Available from http://www.nice.org.uk/guidance/IPG286
- High-intensity focused ultrasound for atrial fibrillation in association with other cardiac surgery. NICE interventional procedure guidance 184 (2006). Available from http://www.nice.org.uk/guidance/IPG184
- Percutaneous radiofrequency ablation for atrial fibrillation. NICE interventional procedure guidance 168 (2006). Available from http://www.nice.org.uk/guidance/IPG168

- Cryoablation for atrial fibrillation in association with other cardiac surgery. NICE interventional procedure guidance 123 (2005). Available from http://www.nice.org.uk/guidance/IPG123
- Microwave ablation for atrial fibrillation in association with other cardiac surgery. NICE interventional procedure guidance 122 (2005). Available from http://www.nice.org.uk/guidance/IPG122
- Radiofrequency ablation for atrial fibrillation in association with other cardiac surgery. NICE interventional procedure guidance 121 (2005). Available from http://www.nice.org.uk/guidance/IPG121

Technology appraisals

- Apixaban for preventing stroke and systemic embolism in people with nonvalvular atrial fibrillation. NICE technology appraisal guidance 275 (2013). Available from http://www.nice.org.uk/guidance/TA275
- Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation. NICE technology appraisal guidance 256 (2012). Available from http://www.nice.org.uk/guidance/TA256
- Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation. NICE technology appraisal guidance 249 (2012). Available from http://www.nice.org.uk/guidance/TA249
- Dronedarone for the treatment of non-permanent atrial fibrillation. NICE technology appraisal guidance 197 (2010). Available from http://www.nice.org.uk/guidance/TA197

NICE guidelines

- Atrial fibrillation: the management of atrial fibrillation. NICE guideline CG180 (2014). Available from www.nice.org.uk/guidance/CG180

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their specialist society or Royal college. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by specialist advisers, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. Three specialist adviser

questionnaires for percutaneous endoscopic laser balloon pulmonary vein isolation for atrial fibrillation were submitted and can be found on the NICE website

Patient commentators' opinions

NICE's Public Involvement Programme was unable to gather patient commentary for this procedure.

Issues for consideration by IPAC

Ongoing trials

- Catheter Ablation of Drug-refractory Persistent Atrial Fibrillation With the HeartLight(TM) Laser Balloon in Comparison With Irrigated Radiofrequency Current Ablation (NCT01863472); Czech Republic, Germany and Spain; randomised controlled trial; estimated enrolment 150; estimated primary completion date August 2016.
- Eagle AF - Endoscopically Guided Laser Ablation of Persistent Atrial Fibrillation (NCT02234102); Germany; non-randomised study; estimated enrolment 160; estimated study completion date June 2017.

References

1. Dukkipati SR, Cuoco F, Kutinsky I et al. (2015) Pulmonary Vein Isolation Using the Visually Guided Laser Balloon: A Prospective, Multicenter, and Randomized Comparison to Standard Radiofrequency Ablation. Journal of the American College of Cardiology 66: 1350-1360
2. Schmidt B, Gunawardene M, Krieg D et al. (2013) A prospective randomized single-center study on the risk of asymptomatic cerebral lesions comparing irrigated radiofrequency current ablation with the cryoballoon and the laser balloon. Journal of Cardiovascular Electrophysiology 24: 869-874
3. Bordignon S, Chun KR, Gunawardene M et al. (2013) Comparison of balloon catheter ablation technologies for pulmonary vein isolation: the laser versus cryo study. Journal of Cardiovascular Electrophysiology 24: 987-994
4. Metzner A, Schmidt B, Fuernkranz A et al. (2011) Esophageal temperature change and esophageal thermal lesions after pulmonary vein isolation using the novel endoscopic ablation system. Heart Rhythm 8: 815-820
5. Dukkipati SR, Kuck KH, Neuzil P et al. (2013) Pulmonary vein isolation using a visually guided laser balloon catheter: the first 200-patient multicenter clinical experience. Circulation: Arrhythmia and Electrophysiology 6: 467-472
6. Bordignon S, Boehmer MC, Klostermann A et al. (2015) Visually guided pulmonary vein isolation in patients with persistent atrial fibrillation. Europace doi: 10.1093/europace/euv208
7. Sediva L, Petru J, Skoda J et al. (2014) Visually guided laser ablation: a single-centre long-term experience. Europace 16:1746-1751
8. Kumar N, Pison L, Blaauw Y et al. (2015) Pulmonary vein stenosis after laser balloon ablation for atrial fibrillation. JACC: Clinical Electrophysiology 1: 220-221
9. Gal P, Smit JJ, Elvan A. (2015) Endoscopically visible steam pop during high-energy laser pulmonary vein ablation. Netherlands Heart Journal doi:10.1007/s12471-015-0711-8

Appendix A: Additional papers on percutaneous endoscopic laser balloon pulmonary vein isolation for atrial fibrillation

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Bordignon S, Chun K-R, Gunawardene M et al. (2013) Endoscopic ablation systems. Expert Review of Medical Devices 10: 177-183	Review	The endoscopic ablation system makes direct pulmonary vein ostium visualisation possible, despite the large anatomy variation thanks to its compliant balloon. The laser generator delivers precise lesions that in the first clinical studies seem to be durable, with a safety and efficacy profile similar to the other pulmonary vein isolation techniques.	Review with no meta-analysis.
Bordignon S, Chun KR, Gunawardene M et al. (2013) Energy titration strategies with the endoscopic ablation system: lessons from the high-dose vs. low-dose laser ablation study. Europace 15: 685-689	Case series n=60 FU=median 311 days	During median follow-up of 311 days (261-346) recurrence rate was 17 and 40% in the high dose and low dose group, respectively. In both groups one phrenic nerve palsy was observed.	Small case series.
Casella M, Russo AD, Russo E et al. (2014) Biomarkers of myocardial injury with different energy sources for atrial fibrillation catheter ablation. Cardiology Journal.21: 516-523	Non-randomised comparative study n=110 FU=mean 369 days	Highest markers for myocardial injury were observed in the cryoballoon group. It is possible that a longer delivery energy duration and other factors affecting lesion size resulted in higher amount of cardiac injury in cryoablation. The higher levels of cardiac biomarkers did not translate into a better outcome and its physiologic significance is unknown.	Study focuses on biomarkers of myocardial injury.
Deneke T, Nentwich K, Schmitt R et al. (2014) Exchanging Catheters Over a Single Transseptal Sheath During Left Atrial Ablation is Associated with a Higher Risk for Silent Cerebral Events. Indian Pacing & Electrophysiology Journal 14: 240-249	Non-randomised comparative study n=88 (27 laser balloon)	Exchanging catheters over a single transseptal access to perform left atrial ablation is associated with a significantly higher incidence of silent cerebral events compared to an ablation technique using different transseptal accesses for therapeutic and diagnostic catheters.	Study focuses on technique of single transseptal access.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Dukkipati SR, Neuzil P, Kautzner J et al. (2012) The durability of pulmonary vein isolation using the visually guided laser balloon catheter: multicenter results of pulmonary vein remapping studies. Heart Rhythm 9: 919-925	Case series n=56 FU=12 months	After 2 procedures and 12.0 +/- 1.9 months of follow-up, the drug-free rate of freedom from atrial fibrillation was 71.2%.	Small case series.
Dukkipati SR, Woollett I, McElderry HT et al. (2015) Pulmonary vein isolation using the visually guided laser balloon: Results of the U.S. feasibility study. Journal of Cardiovascular Electrophysiology 26: 944-949	Case series n=86 FU=12 months	Of 84 patients completing follow-up, the primary effectiveness endpoint was achieved in 50 (60%) patients. Freedom from symptomatic or asymptomatic AF was 61%. The primary adverse event rate was 16% (8% pericarditis, phrenic nerve injury 6%, and cardiac tamponade 4%). There were no cerebrovascular events, atrioesophageal fistulas, or significant PV stenosis.	Small case series.
Dukkipati SR, Neuzil P, Skoda J et al. (2010) Visual balloon-guided point-by-point ablation: reliable, reproducible, and persistent pulmonary vein isolation. Circulation: Arrhythmia and Electrophysiology 3:266-273	Case series n=27 FU=3 months	17% (4/23) of patients had recurrent AF symptoms.	Small case series. (included in table 2 of 2010 overview)
Gal P, Ooms JF, Ottervanger JP et al. (2015) Association between pulmonary vein orientation and atrial fibrillation-free survival in patients undergoing endoscopic laser balloon ablation. European heart journal cardiovascular Imaging 16:799-806	Case series n=43	PV orientation is associated with AF-free survival after endoscopically assisted laser balloon ablation system (EAS) PVI. PV orientation assessment may be useful for selecting the most suitable patients for EAS PVI.	Small case series.
Gal P, Smit JJ, Adiyaman A et al. (2015) First Dutch experience with the endoscopic laser balloon ablation system for the treatment of atrial fibrillation. Netherlands Heart Journal 23: 96-99	Case series n=50 FU=median 17 months	One procedure was complicated by a temporary phrenic nerve palsy (2 %). During follow-up, 58 % of patients remained free of AF without the use of anti-arrhythmic drugs.	Small case series.
Guijian L, Wenqing Z, Xinggang W et al. (2014) Association between ablation technology and asymptomatic cerebral injury following atrial fibrillation ablation. PACE 37: 1378–91	Systematic review 2 laser balloon studies (n=77)	Using a random effects model, the pooled incidence of asymptomatic cerebral injury was 17.3% (95% CI 0.079 to 0.339; I^2=79.7%).	The review only includes 2 studies on laser balloon ablation.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Khurram IM, Catanzaro JN, Zimmerman S et al. (2015) MRI Evaluation of Radiofrequency, Cryothermal, and Laser Left Atrial Lesion Formation in Patients with Atrial Fibrillation. Pacing & Clinical Electrophysiology 38: 1317-1324	Non-randomised comparative study n=17	No statistically significant difference was noted in the extent of left atrial fibrosis induced by any modality.	Larger studies are included.
Koruth JS, Reddy VY, Miller MA et al. (2012) Mechanical esophageal displacement during catheter ablation for atrial fibrillation. Journal of Cardiovascular Electrophysiology 23: 147-154	Case series n=20 (4 laser balloon)	Mechanical oesophageal deviation is feasible and allows for uninterrupted energy delivery along the posterior wall during catheter ablation of atrial fibrillation.	Small case series.
Kumar N, Blaauw,Y, Timmermans C et al. (2014) Adenosine testing after second-generation balloon devices (cryothermal and laser) mediated pulmonary vein ablation for atrial fibrillation. Journal of Interventional Cardiac Electrophysiology 41: 91-97	Non-randomised comparative study n=60 (20 laser) FU=267 days	Adenosine testing after PV isolation using second-generation balloon based energy devices (laser and cryothermal) reveals dormant conduction in initially isolated PVs with similar long-term success rate.	Small case series.
Metzner A, Kivelitz D, Schmidt B et al. (2012) Impact of pulmonary vein anatomy assessed by cardiac magnetic resonance imaging on endoscopic pulmonary vein isolation in consecutive patients. Europace 14: 474-480	Case series n=51 FU=3 months	The majority of pulmonary veins could have been targeted and successfully isolated using exclusively the novel endoscopic ablation system irrespective of their anatomy assessed by pre-interventional Cardiac MRI.	Most patients were also included in other studies that are described in table 2 (Schmidt et al., 2010 and Metzner et al., 2011).
Metzner A, Wissner E, Schoonderwoerd B et al. (2012) The influence of varying energy settings on efficacy and safety of endoscopic pulmonary vein isolation. Heart Rhythm 9: 1380-1385	Case series n=30	The use of higher energy settings increases the efficacy of acute endoscopic ablation system-based PVI without comprising safety. Further investigation is mandatory before final conclusions can be drawn.	Small case series.
Metzner A, Wissner E, Schmidt B et al. (2013) Acute and long-term clinical outcome after endoscopic pulmonary vein isolation: results from the first prospective, multicenter study. Journal of Cardiovascular Electrophysiology 24: 7-13	Case series n=72 FU=12 months	A very high rate of acute electrical PVI is achieved using exclusively the endoscopic ablation system. The 1-year single-procedure success rate in patients with paroxysmal AF is comparable to conventional PVI. PV reconduction is the major determinant for AF recurrence.	Small case series.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Metzner A, Schmidt B, Fuernkranz A et al. (2011) One-year clinical outcome after pulmonary vein isolation using the novel endoscopic ablation system in patients with paroxysmal atrial fibrillation. Heart Rhythm 8: 988-993	Case series n=40 FU=median 402 days	Patients after endoscopic ablation system (EAS)-based PVI due to paroxysmal AF demonstrate 1-year single-procedure success rates similar to those of other ablation techniques and ablation energies. The major determinant for AF recurrence after EAS treatment seems to be reconnection of previously isolated PVs.	Small case series.
Osca J, Andres A, Cano O et al. (2016) Electrical isolation of pulmonary veins using laser catheter in the treatment of paroxysmal and persistent atrial fibrillation. One-year results. Revista Espanola de Cardiologia *[in press]* DOI:10.1016/j.rec.2015.08.022	Case series n=71 FU=mean 420 days	89% of veins were isolated at the first attempt. Arrhythmia recurrence=12% for paroxysmal AF and 30% for persistent AF. The most common complication was phrenic nerve paralysis (5.6%), which appeared only in the first 18 cases.	Larger studies are included.
Perrotta L, Bordignon S, Dugo D et al. (2014) How to learn pulmonary vein isolation with a novel ablation device: learning curve effects using the endoscopic ablation system. Journal of Cardiovascular Electrophysiology 25: 1293-1298	Case series n=150 FU=median 467 days	With the endoscopic ablation system even first time users may achieve acute PVI in a high number of patients with favourable clinical outcomes after 1 year. But acute procedural efficacy and safety are further improved after passing a learning curve of 50 patients.	Larger studies are included.
Reddy VY, Neuzil P, Themistoclakis S et al. (2009) Visually-guided balloon catheter ablation of atrial fibrillation: experimental feasibility and first-in-human multicenter clinical outcome. Circulation 120:12-20	Case series n=30 FU=12 months	Proportion of patients who were drug-free and no AF at 12 months: 60% (18/30)	Small case series. (included in table 2 of 2010 overview)
Reddy VY, Neuzil P, d'Avila A et al. (2008) Balloon catheter ablation to treat paroxysmal atrial fibrillation: what is the level of pulmonary venous isolation? Heart Rhythm 5:353-360	Case series n=4 FU= mean 352 days	Successful isolation of pulmonary veins (confirmed by electroanatomical bipolar voltage amplitude substrate mapping): (100% (4/4)	Small case series. (included in table 2 of 2010 overview)
Schmidt B, Metzner A, Chun KR et al. (2010) Feasibility of circumferential pulmonary vein isolation using a novel endoscopic ablation system. Circulation: Arrhythmia and Electrophysiology 3:481-8	Case series n=30 Median FU=168 days	Proportion of patients free of any asymptomatic AF recurrence lasting >1 minute at median follow-up: 80% (24/30)	Small case series. (included in table 2 of 2010 overview)
Schmidt B, Gunawardene M, Urban V et al. (2012) Visually guided sequential pulmonary vein isolation: insights into techniques and predictors of acute success. Journal of Cardiovascular Electrophysiology 23: 576-582	Case series n=35 FU=median 266 days	One pericardial tamponade and 1 right-sided phrenic nerve palsy occurred. During a median follow-up of 266 days, 27 of 35 patients (77%) remained free of any tachyarrhythmia recurrence off anti-arrhythmic drugs.	Small case series.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Tsyganov A, Petru J, Skoda J et al. (2015) Anatomical predictors for successful pulmonary vein isolation using balloon-based technologies in atrial fibrillation. Journal of Interventional Cardiac Electrophysiology 44: 265–71	Non-randomised comparative study n=100 (50 laser) FU=1 year	Over a 12-month follow-up, AF recurrence was documented in 11/45 (24%) and 7/43 (16%) patients in the cryoablation and the laser ablation groups, respectively (p=0.21). In the laser ablation group, a larger left superior PV size (p=0.003) and more oval right inferior PV were associated with worse acute success (p=0.038). There was no absolute cutoff between PV anatomy and clinical success.	Larger studies are included.
Ucer E, Fredersdorf S, Jungbauer CG et al. (2015) Unmasking the dormant pulmonary vein conduction with adenosine administration after pulmonary vein isolation with laser energy. Europace 2015	Case series n=26	A total of 104 PVs were targeted. The balloon catheter could not be placed in two PVs. Of the remaining 102 PVs, 97% could be successfully isolated. Adenosine was administered for each isolated PV in 25 patients. Only six PVs (7%) in five patients (20%) showed a PV reconnection during adenosine provocation.	Small case series.
Wissner E, Metzner A, Neuzil P et al. (2014) Asymptomatic brain lesions following laserballoon-based pulmonary vein isolation. Europace 16: 214-219	Non-randomised comparative study n=86 (44 laser) FU=6 months	There was no statistically significant difference between the groups with regard to new asymptomatic brain lesions detected on post-procedural MRI: 11% (5/44) of patients in the laser balloon group, 5% (1/20) patients in the cryoballoon group, and 18% (4/22) of patients in the irrigated RF group, respectively. In the laser balloon group, one additional patient with a new cerebral lesion experienced transient diplopia.	A randomised controlled trial reporting the same outcome is included.
Wissner E, Metzner A, Reissmann B et al. (2014) Wide circumferential versus individual isolation of pulmonary veins using the endoscopic ablation system. Journal of Cardiovascular Electrophysiology 25: 253-258	Case series n=38	Using the endoscopic ablation system in patients with AF, separate isolation of individual PVs rather than wide circumferential PVI should be the preferred ablation strategy.	Small case series, focusing on technique.

Appendix B: Related NICE guidance for percutaneous endoscopic laser balloon pulmonary vein isolation for atrial fibrillation

Guidance	Recommendations
Interventional procedures	**Percutaneous endoscopic catheter laser balloon pulmonary vein isolation for atrial fibrillation. NICE interventional procedure guidance 399 (2011) [current guidance]** 1.1 Current evidence on the safety and efficacy of percutaneous endoscopic catheter laser balloon pulmonary vein isolation for atrial fibrillation (AF) is inadequate because of the limited number of patients reported. Therefore this procedure should only be used with special arrangements for clinical governance, consent and research. 1.2 Clinicians wishing to undertake percutaneous endoscopic catheter laser balloon pulmonary vein isolation for AF should take the following actions. • Inform the clinical governance leads in their Trusts. • Ensure that patients and their carers understand the uncertainty about the procedure's safety and efficacy and provide them with clear written information. In addition, the use of NICE's information for patients ('Understanding NICE guidance') is recommended. 1.3 Patient selection and treatment should be carried out only by interventional cardiologists with expertise in electrophysiology and with experience in performing complex ablation procedures. 1.4 This procedure should be carried out only in units with arrangements for emergency cardiac surgical support in case of complications. 1.5 Clinicians should enter details about all patients undergoing percutaneous endoscopic catheter laser balloon pulmonary vein isolation for AF onto the UK Central Cardiac Audit Database. 1.6 Further research should define patient-selection criteria and should clearly describe adverse events and long-term control of AF. NICE may review this guidance on publication of further evidence. **Percutaneous balloon cryoablation for pulmonary vein isolation in atrial fibrillation. NICE interventional procedure guidance 427 (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. **Thoracoscopic exclusion of the left atrial appendage (with or without surgical ablation) for non-valvular atrial fibrillation for the prevention of thromboembolism. NICE interventional procedure guidance 400 (2011)** 1.1 Current evidence on the safety and efficacy of thoracoscopic exclusion of the left atrial appendage (LAA) for non-valvular atrial fibrillation (AF) for the prevention of thromboembolism as an adjunctive procedure to surgical ablative techniques is inadequate in quantity and quality. Therefore this procedure should only be used as an adjunct to surgical ablation with special arrangements for clinical governance, consent and audit or research. 1.2 Clinicians wishing to undertake thoracoscopic exclusion of the LAA for non-valvular AF for the prevention of thromboembolism as an adjunct to surgical ablation should take the following actions. • Inform the clinical governance leads in their Trusts. • Ensure that patients and their carers understand the uncertainty about the procedure's safety and efficacy, and provide them with clear written information. In addition, the use of NICE's information for patients ('Understanding NICE guidance') is recommended (available from www.nice.org.uk/guidance/IPG400/publicinfo). • Audit and review clinical outcomes of all patients having thoracoscopic exclusion of the LAA for non-valvular AF for the prevention of thromboembolism as an adjunctive procedure to ablative techniques (see section 3.1). 1.3 Current evidence on the safety and efficacy of thoracoscopic exclusion of the LAA for non-valvular AF for the prevention of thromboembolism when used in isolation is inadequate. Therefore this procedure should only be used in the context of research. Research

	studies should clearly define patient selection. They should report the cardiac rhythm achieved after surgery and also adverse events, particularly stroke and death, in both the short and longer term. 1.4 Patient selection should be carried out by a multidisciplinary team including a cardiac surgeon and other clinicians experienced in the management of patients with AF who are at risk of stroke. Patients should be considered for alternative treatments to reduce the risk of thromboembolism associated with AF, and should be informed about these alternatives. 1.5 This procedure should be carried out only by cardiac surgeons with experience in thoracoscopic surgery and specific training in the procedure. **Percutaneous occlusion of the left atrial appendage in non-valvular atrial fibrillation for the prevention of thromboembolism. NICE interventional procedure guidance 349 (2010)** 1.1 Current evidence suggests that percutaneous occlusion of the left atrial appendage (LAA) is efficacious in reducing the risk of thromboembolic complications associated with non-valvular atrial fibrillation (AF). With regard to safety, there is a risk of life-threatening complications from the procedure, but the incidence of these is low. Therefore, this procedure may be used provided that normal arrangements are in place for clinical governance, consent and audit. 1.2 Patient selection should be carried out by a multidisciplinary team including a cardiologist and other appropriate clinicians experienced in the management of patients with AF at risk of stroke. Patients should be considered for alternative treatments to reduce the risk of thromboembolism associated with AF, and should be informed about these alternatives. 1.3 Percutaneous occlusion of the LAA is a technically challenging procedure which should only be carried out by clinicians with specific training and appropriate experience in the procedure. 1.4 This procedure should be carried out only in units with on-site cardiac surgery. 1.5 Any device-related adverse events resulting from the procedure should be reported to the Medicines and Healthcare products Regulatory Agency (MHRA). **Percutaneous (non-thoracoscopic) epicardial catheter radiofrequency ablation for atrial fibrillation. NICE interventional procedure guidance 294 (2009)** 1.1 Current evidence on the safety and efficacy of percutaneous (non-thoracoscopic) epicardial catheter radiofrequency ablation for atrial fibrillation (AF) is inadequate in quantity. Therefore this procedure

	should only be used with special arrangements for clinical governance and consent. 1.2 Clinicians wishing to undertake percutaneous (non-thoracoscopic) epicardial catheter radiofrequency ablation for AF should take the following actions. • Inform the clinical governance leads in their Trusts. • Ensure that patients understand the uncertainty about the procedure's safety and efficacy and provide them with clear written information. In addition, the use of NICE's information for patients ('Understanding NICE guidance') is recommended. 1.3 Patient selection and treatment should be carried out only by a team specialising in the treatment of cardiac arrhythmias that includes experts in electrophysiology and ablation. 1.4 The procedure should only be carried out by interventional cardiologists with specific training in electrophysiology, and in accessing the pericardial space and performing complex ablation procedures. 1.5 The procedure should only be carried out in units with arrangements for emergency cardiac surgical support in case of complications. 1.6 The NHS Information Centre for health and social care runs the UK Central Cardiac Audit Database, and clinicians should enter details about all patients undergoing percutaneous (non-thoracoscopic) epicardial catheter radiofrequency ablation for AF onto this database. 1.7 Clinicians are encouraged to enter patients into research studies that aim to provide more information about patient selection, the use of this procedure as an adjunct to other procedures, freedom from AF in the long term and relief of associated symptoms, and the safety profile of the procedure. NICE may review the procedure on publication of further evidence. **Thoracoscopic epicardial radiofrequency ablation for atrial fibrillation. NICE interventional procedure guidance 286 (2009)** 1.1 There is evidence of efficacy for thoracoscopic epicardial radiofrequency ablation for atrial fibrillation (AF) in the short term and in small numbers of patients. The assessment of cardiac rhythm during follow-up varied between studies, and some patients were concomitantly treated with anti-arrhythmic medication. Evidence on safety shows a low incidence of serious complications but this is also based on a limited number of patients. Therefore the procedure should only be used with special arrangements for clinical governance, consent and audit or research. 1.2 Clinicians wishing to undertake thoracoscopic epicardial

	radiofrequency ablation for AF should take the following actions. • Inform the clinical governance leads in their Trusts. • Ensure that patients understand the uncertainty about the procedure's safety and efficacy, and provide them with clear written information. In addition, the use of NICE's information for patients ('Understanding NICE guidance') is recommended. 1.3 Patient selection for thoracoscopic epicardial radiofrequency ablation for AF should involve a multidisciplinary team including a cardiologist and a cardiac surgeon, both with training and experience in the use of intraoperative electrophysiology. 1.4 The procedure should only be carried out by surgeons with specific training and experience in both thoracoscopic surgery and radiofrequency ablation. 1.5 The NHS Information Centre for Health and Social Care runs the UK Central Cardiac Audit Database (CCAD), and is developing a database for this procedure. Clinicians should collect data on the procedure and submit them to the database when it becomes available. 1.6 NICE encourages further comparative research into the treatment and management of AF, with clearly defined outcomes. NICE may review this procedure on publication of further evidence. **High-intensity focused ultrasound for atrial fibrillation in association with other cardiac surgery. NICE interventional procedure guidance 184 (2006)** 1.1 Current evidence on the safety and efficacy of high-intensity focused ultrasound (HIFU) for atrial fibrillation in association with other cardiac surgery is insufficient for this procedure to be used without special arrangements for consent and for audit or research. 1.2 Clinicians wishing to undertake HIFU for atrial fibrillation in association with other cardiac surgery should take the following actions. • Inform the clinical governance leads in their Trusts. • Ensure that patients understand the uncertainty about the procedure's safety and efficacy and provide them with clear written information. In addition, use of the Institute's information for patients is recommended. • Audit and review clinical outcomes of all patients undergoing HIFU for atrial fibrillation in association with other cardiac surgery. 1.3 Patient selection and follow-up should be carried out by a multidisciplinary team. Cardiac surgeons undertaking this procedure should have specific training in the use of high-intensity focused ultrasound equipment. 1.4 Publication of safety and efficacy outcomes will be useful. The

	Institute may review the procedure upon publication of further evidence. **Percutaneous radiofrequency ablation for atrial fibrillation. NICE interventional procedure guidance 168 (2006)** 1.1 Current evidence on the safety and efficacy of percutaneous radiofrequency ablation for atrial fibrillation appears adequate to support the use of this procedure in appropriately selected patients (see section 2.1.4) provided that normal arrangements are in place for audit and clinical governance. 1.2 Clinicians should ensure that patients fully understand the potential complications, the likelihood of success and the risk of recurrent atrial fibrillation associated with this procedure. In addition, use of the Institute's information for the public is recommended. 1.3 This procedure should only be performed in specialist units and with arrangements for cardiac surgical support in the event of complications. 1.4 This procedure should only be performed by cardiologists with extensive experience of other types of ablation procedures. 1.5 The Department of Health runs the Central Cardiac Audit Database (CCAD), and clinicians are encouraged to enter all patients undergoing percutaneous radiofrequency ablation for atrial fibrillation onto this database. **Cryoablation for atrial fibrillation in association with other cardiac surgery. NICE interventional procedure guidance 123 (2005)** 1.1 Current evidence on the safety and efficacy of cryoablation for atrial fibrillation in association with other cardiac surgery appears adequate to support the use of this procedure provided that the normal arrangements are in place for consent, audit and clinical governance. 1.2 Patient selection and follow-up should be carried out by a multidisciplinary team. Cardiac surgeons undertaking this procedure should have specific training in the use of cryoablation equipment. **Microwave ablation for atrial fibrillation in association with other cardiac surgery. NICE interventional procedure guidance 122 (2005)** 1.1 Current evidence on the safety and efficacy of microwave ablation for atrial fibrillation in association with other cardiac surgery appears adequate to support the use of this procedure provided that the normal arrangements are in place for consent, audit and clinical governance. 1.2 Patient selection and follow-up should be carried out by a multidisciplinary team. Cardiac surgeons undertaking this procedure should have specific training in the use of microwave energy

	equipment. **Radiofrequency ablation for atrial fibrillation in association with other cardiac surgery. NICE interventional procedure guidance 121 (2005)** 1.1 Current evidence on the safety and efficacy of radiofrequency ablation (RFA) for atrial fibrillation in association with other cardiac surgery appears adequate to support the use of this procedure provided that the normal arrangements are in place for consent, audit and clinical governance. 1.2 Patient selection and follow-up should be carried out by a multidisciplinary team. Cardiac surgeons undertaking this procedure should have specific training in the use of radiofrequency equipment.
Technology appraisals	**Apixaban for preventing stroke and systemic embolism in people with nonvalvular atrial fibrillation. NICE technology appraisal guidance 275 (2013)** 1.1 Apixaban is recommended as an option for preventing stroke and systemic embolism within its marketing authorisation, that is, in people with nonvalvular atrial fibrillation with 1 or more risk factors such as: • prior stroke or transient ischaemic attack • age 75 years or older • hypertension • diabetes mellitus • symptomatic heart failure. 1.2 The decision about whether to start treatment with apixaban should be made after an informed discussion between the clinician and the person about the risks and benefits of apixaban compared with warfarin, dabigatran etexilate and rivaroxaban. For people who are taking warfarin, the potential risks and benefits of switching to apixaban should be considered in light of their level of international normalised ratio (INR) control. **Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation. NICE technology appraisal guidance 256 (2012)** 1.1 Rivaroxaban is recommended as an option for the prevention of stroke and systemic embolism within its licensed indication, that is, in people with nonvalvular atrial fibrillation with one or more risk factors such as: • congestive heart failure • hypertension • age 75 years or older • diabetes mellitus, • prior stroke or transient ischaemic attack. 1.2 The decision about whether to start treatment with rivaroxaban

	should be made after an informed discussion between the clinician and the person about the risks and benefits of rivaroxaban compared with warfarin. For people who are taking warfarin, the potential risks and benefits of switching to rivaroxaban should be considered in light of their level of international normalised ratio (INR) control. **Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation. NICE technology appraisal guidance 249 (2012)** 1.1 Dabigatran etexilate is recommended as an option for the prevention of stroke and systemic embolism within its licensed indication, that is, in people with nonvalvular atrial fibrillation with one or more of the following risk factors: • previous stroke, transient ischaemic attack or systemic embolism • left ventricular ejection fraction below 40% • symptomatic heart failure of New York Heart Association (NYHA) class 2 or above • age 75 years or older • age 65 years or older with one of the following: diabetes mellitus, coronary artery disease or hypertension. 1.2 The decision about whether to start treatment with dabigatran etexilate should be made after an informed discussion between the clinician and the person about the risks and benefits of dabigatran etexilate compared with warfarin. For people who are taking warfarin, the potential risks and benefits of switching to dabigatran etexilate should be considered in light of their level of international normalised ratio (INR) control. **Dronedarone for the treatment of non-permanent atrial fibrillation. NICE technology appraisal guidance 197 (2010)** 1.1 Dronedarone is recommended as an option for the maintenance of sinus rhythm after successful cardioversion in people with paroxysmal or persistent atrial fibrillation: • whose atrial fibrillation is not controlled by first-line therapy (usually including beta-blockers), that is, as a second-line treatment option and after alternative options have been considered and • who have at least 1 of the following cardiovascular risk factors: – hypertension requiring drugs of at least 2 different classes – diabetes mellitus – previous transient ischaemic attack, stroke or systemic embolism – left atrial diameter of 50 mm or greater or – age 70 years or older and • who do not have left ventricular systolic dysfunction and • who do not have a history of, or current, heart failure. 1.2 People who do not meet the criteria in section 1.1 who are currently

	receiving dronedarone should have the option to continue treatment until they and their clinicians consider it appropriate to stop.
NICE guidelines	**Atrial fibrillation: the management of atrial fibrillation. NICE guideline CG180 (2014)** *1.6 Rate and rhythm control* When to offer rate or rhythm control 1.6.1 Offer rate control as the first-line strategy to people with atrial fibrillation, except in people: • whose atrial fibrillation has a reversible cause • who have heart failure thought to be primarily caused by atrial fibrillation • with new-onset atrial fibrillation • with atrial flutter whose condition is considered suitable for an ablation strategy to restore sinus rhythm • for whom a rhythm control strategy would be more suitable based on clinical judgement. [new 2014] **Rate control** 1.6.2 Offer either a standard beta-blocker (that is, a beta-blocker other than sotalol) or a rate-limiting calcium-channel blocker as initial monotherapy to people with atrial fibrillation who need drug treatment as part of a rate control strategy. Base the choice of drug on the person's symptoms, heart rate, comorbidities and preferences when considering drug treatment. [new 2014] 1.6.3 Consider digoxin monotherapy for people with non-paroxysmal atrial fibrillation only if they are sedentary (do no or very little physical exercise). [new 2014] 1.6.4 If monotherapy does not control symptoms, and if continuing symptoms are thought to be due to poor ventricular rate control, consider combination therapy with any 2 of the following: • a beta-blocker • diltiazem • digoxin. [new 2014] 1.6.5 Do not offer amiodarone for long-term rate control. [new 2014] **Rhythm control** 1.6.6 Consider pharmacological and/or electrical rhythm control for people with atrial fibrillation whose symptoms continue after heart rate has been controlled or for whom a rate-control strategy has not been successful. [new 2014] **Cardioversion** 1.6.7 For people having cardioversion for atrial fibrillation that has

	persisted for longer than 48 hours, offer electrical (rather than pharmacological) cardioversion. [new 2014] 1.6.8 Consider amiodarone therapy starting 4 weeks before and continuing for up to 12 months after electrical cardioversion to maintain sinus rhythm, and discuss the benefits and risks of amiodarone with the person. [new 2014] 1.6.9 For people with atrial fibrillation of greater than 48 hours' duration, in whom elective cardioversion is indicated: • both transoesophageal echocardiography (TOE)-guided cardioversion and conventional cardioversion should be considered equally effective • a TOE-guided cardioversion strategy should be considered: – where experienced staff and appropriate facilities are available and – where a minimal period of precardioversion anticoagulation is indicated due to the person's choice or bleeding risks. [2006] **Drug treatment for long-term rhythm control** 1.6.10 Assess the need for drug treatment for long-term rhythm control, taking into account the person's preferences, associated comorbidities, risks of treatment and likelihood of recurrence of atrial fibrillation. [new 2014] 1.6.11 If drug treatment for long-term rhythm control is needed, consider a standard beta-blocker (that is, a beta-blocker other than sotalol) as first-line treatment unless there are contraindications. [new 2014] 1.6.12 If beta-blockers are contraindicated or unsuccessful, assess the suitability of alternative drugs for rhythm control, taking comorbidities into account. [new 2014] 1.6.13 Dronedarone is recommended as an option for the maintenance of sinus rhythm after successful cardioversion in people with paroxysmal or persistent atrial fibrillation: • whose atrial fibrillation is not controlled by first-line therapy (usually including beta-blockers), that is, as a second-line treatment option and after alternative options have been considered and • who have at least 1 of the following cardiovascular risk factors: – hypertension requiring drugs of at least 2 different classes – diabetes mellitus – previous transient ischaemic attack, stroke or systemic embolism – left atrial diameter of 50 mm or greater or – age 70 years or older and • who do not have left ventricular systolic dysfunction and

	• who do not have a history of, or current, heart failure. [This recommendation is from Dronedarone for the treatment of non-permanent atrial fibrillation (NICE technology appraisal guidance 197).] [2010, amended 2012] 1.6.14 People who do not meet the criteria in recommendation 1.6.13 who are currently receiving dronedarone should have the option to continue treatment until they and their clinicians consider it appropriate to stop. [This recommendation is from Dronedarone for the treatment of non-permanent atrial fibrillation (NICE technology appraisal guidance 197).] [2010, amended 2012] 1.6.15 Consider amiodarone for people with left ventricular impairment or heart failure. [new 2014] 1.6.16 Do not offer class 1c anti-arrhythmic drugs such as flecainide or propafenone to people with known ischaemic or structural heart disease. [new 2014] 1.6.17 Where people have infrequent paroxysms and few symptoms, or where symptoms are induced by known precipitants (such as alcohol, caffeine), a 'no drug treatment' strategy or a 'pill-in-the-pocket' strategy[5] should be considered and discussed with the person. [2006] 1.6.18 In people with paroxysmal atrial fibrillation, a 'pill-in-the-pocket' strategy should be considered for those who: • have no history of left ventricular dysfunction, or valvular or ischaemic heart disease and • have a history of infrequent symptomatic episodes of paroxysmal atrial fibrillation and • have a systolic blood pressure greater than 100 mmHg and a resting heart rate above 70 bpm and • are able to understand how to, and when to, take the medication. [2006] ***Left atrial ablation and a pace and ablate strategy*** **Left atrial ablation** 1.6.19 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[6]. [new 2014] 1.6.20 Consider left atrial surgical ablation at the same time as other cardiothoracic surgery for people with symptomatic atrial fibrillation[7]. [new 2014]

	Pace and ablate strategy 1.6.21 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. [new 2014] 1.6.22 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. [new 2014] 1.6.23 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. [new 2014]

Appendix C: Literature search for percutaneous endoscopic laser balloon pulmonary vein isolation for atrial fibrillation

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	26/11/2015	Issue 11 of 12, November 2015
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	26/11/2015	Issue 10 of 12, October 2015
HTA database (Cochrane Library)	26/11/2015	Issue 4 of 4, October 2015
MEDLINE (Ovid)	26/11/2015	1946 to November Week 2 2015
MEDLINE In-Process (Ovid)	26/11/2015	November 24, 2015
EMBASE (Ovid)	26/11/2015	1974 to 2015 Week 47
PubMed	26/11/2015	n/a
JournalTOCS [for update searches only]	26/11/2015	n/a

Trial sources searched on 09/07/2015

- Clinicaltrials.gov
- ISRCTN
- WHO International Clinical Trials Registry

Websites searched on 09/07/2015

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- EuroScan
- General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1	Atrial Fibrillation/
2	((atrial or auricular or atrium) adj4 fibrill*).tw.
3	AF.tw.
4	or/1-3
5	Angioplasty, Balloon, Coronary/
6	Catheter Ablation/
7	(balloon* or catheter*).tw.
8	Pulmonary Veins/
9	(pulmon* adj4 vein*).tw.
10	(pv adj2 isolat*).tw.
11	pvi.tw.
12	or/5-11
13	Endoscopy/
14	Endoscopes/
15	Angioscopes/
16	Lasers/
17	Laser Therapy/
18	angioplasty, laser/ or angioplasty, balloon, laser-assisted/
19	(endoscop* or angioscop* or laser* or cardiofocus or heartlight).tw.
20	or/13-19
21	4 and 12 and 20
22	animals/ not humans/
23	21 not 22