NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of percutaneous balloon cryoablation for pulmonary vein isolation in atrial fibrillation

Treating atrial fibrillation using a balloon catheter to freeze parts of the heart

Atrial fibrillation is the irregular and rapid beating of the upper two chambers of the heart (the atria). This is caused by the disorganisation of the electrical impulses that control the heartbeat as a result of electrical triggers that may originate at the mouth of the pulmonary veins (large blood vessels that carry blood from the lungs to the left atrium). Typical symptoms can include palpitations, dizziness, shortness of breath and fatigue. Complications can include stroke. This procedure uses a probe attached to a balloon catheter to freeze tissue in one of the chambers on the left side of the heart. The aim is to produce scarring, which may interrupt the electrical signals and help regulate the heartbeat.

Introduction

The National Institute for Health and Clinical Excellence (NICE) has prepared this 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 overview was prepared in October 2011, and updated in March 2012.

Procedure name

- Percutaneous balloon cryoablation for pulmonary vein isolation in atrial fibrillation

Specialty societies

- British Cardiovascular Intervention Society
- Heart Rhythm UK

Description

Indications and current treatment

Atrial fibrillation is the irregular and rapid activation of the atria. It is caused by the uncoordinated electrical stimulation of the atrial walls. Atrial fibrillation may be classified as paroxysmal, persistent or permanent. Patients with atrial fibrillation have an irregular heartbeat, which may be fast or within the normal range. Patients may be asymptomatic or have symptoms such as palpitations, dizziness, shortness of breath, fatigue and chest pain.

Atrial fibrillation is associated with increased risk of embolic stroke from atrial thrombus, and death. Patients considered to be at high risk of thromboembolic stroke are usually treated with anticoagulation therapy. Medical treatment for atrial fibrillation includes drugs to control heart rate or to help maintain a normal cardiac rhythm following cardioversion. Such treatment requires regular monitoring and is associated with a risk of haemorrhage.

Ablation procedures, designed to disrupt abnormal conduction pathways, may be used when drug therapy is either not tolerated or is ineffective. Several methods are available to deliver cardiac ablation including cryoablation with or without a balloon.

What the procedure involves

Percutaneous balloon cryoablation for pulmonary vein isolation in atrial fibrillation helps to maintain normal heart rhythm by isolating or destroying the electrical impulses originating in the pulmonary veins that are thought to be responsible for ‘triggering’ atrial fibrillation.

The procedure may be done either with the patient under general anaesthesia, or using local anaesthesia and sedation. Catheters are introduced percutaneously via one or both femoral veins. One or more electrode catheters may be placed in the heart to allow pacing. An additional electrode catheter is placed in a vein or the heart to allow stimulation of the phrenic nerve. One or two sheaths are advanced into the left atrium transseptally. A multipolar circular catheter (to record electrical signals from the pulmonary vein ostia) and the cryoablation catheter are passed through the two sheaths. The balloon cryoablation catheter is placed at one of the pulmonary vein ostia and the balloon is inflated to allow continuous contact between the balloon and the atrial myocardium. Good contact is confirmed fluoroscopically by injecting contrast into the vein through the lumen of the balloon catheter. When the balloon catheter has been positioned satisfactorily,

it is cooled in bursts of approximately 4 minutes, to achieve circumferential isolation of the cells responsible for the arrhythmia. This is assessed using the circular mapping catheter and each of the pulmonary veins is treated in the same way, until all are electrically isolated.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to percutaneous balloon cryoablation for atrial fibrillation. Searches were conducted of the following databases, covering the period from their commencement to February 2012: 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 balloon cryoablation.
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 overview

This overview is based on about 1748 number of patients from 1 systematic review[1], 4 comparative case series[2-5], 1 case-control study[6] and 3 case series[7-9]. To avoid double counting, patients who were included in studies in

the systematic review and were also included in the main extraction table are not included in the total.

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 balloon cryoablation for atrial fibrillation

Abbreviations used: AF, atrial fibrillation; CT, computed tomography; ECG, electrocardiogram; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; PV, pulmonary vein; RFA, radiofrequency ablation; TTE, transthoracic examination; TOE, transoesophageal echocardiography.

Study details	Key efficacy findings	Key safety findings	Comments
Andrade JG (2011)[1] **Systematic review** USA Search details: studies published between 2000 and 2011. Not restricted to English language articles. Study population: cryoballoon ablation for AF n = **23 articles** (1221 patients treated for paroxysmal AF; 87 for persistent AF) Age: Mean 57.5 years Sex: 73.6% male Study selection criteria: inclusion criteria: study in humans; study design consisting of a case series, case-control study, cohort study or controlled trial; absolute numbers for study endpoints reported or could be derived form available data. Exclusion criteria: animal and in-vitro studies; meta-analyses, abstracts, case reports, reviews, letters, and comments Technique: in 9 of the 23 studies (376 patients), the ablation procedure was performed exclusively with the cryoballoon. In the remaining studies, the cryoballoon was combined with focal ablation in up to 17% of patients (cryocatheter: 13/14 studies; n = 910; irrigated RF in 1/14 studies; n = 22). Follow-up: not stated	**Acute procedural success** (by patient) (Defined as complete isolation of all targeted PVs) Achieved in 98.8% (95% CI 97.9 to 99%) of patients (19 studies; n = 924 patients; I^2 = 0% [no heterogeneity]). **Acute procedural success** (by targeted vein) (Defined as successful electrical disconnection of a targeted PV in which PV potentials previously demonstrated) Achieved complete pulmonary vein isolation in 98.5% (95% CI 98.0 to 98.8%) of patients; (18 studies; I^2 = 83%). Heterogeneity attributed to whether or not focal ablation was used in addition to cryoballoon application. **1-year freedom from AF** Patients with paroxysmal AF after 3-month blanking period: 72.8% (95% CI 68.8 to 76.6) (5 studies; n = 519; I^2 = 0%) Patients with paroxysmal AF without a 3-month blanking period: 60.3% (95% CI 54.5 to 66) (3 studies; n = 316; I^2 = 0%) Patients with persistent AF after 3 month blanking period: 45.2% (95% CI 32.5 to 58.3) (2 studies; n = 62; I^2 = 0%)	**Complication** / **% (n/N)** **Phrenic nerve palsy** Any reported: 6.4 (86/1349) Persisting post procedure: 4.9 (67/1349) Persisting > 1 year: 0.4 (5/1349) **Pulmonary vein stenosis** Any (per patient) (studies reporting systematic screening for PVS with non-invasive imaging): 0.9 (7/773) Requiring intervention: 0.2 (2/1163) **Vascular access complications** Any groin complication: 1.8 (22/1231) Arteriovenous fistula: 0.4 (5/1231) Bleeding requiring transfusion: 0.4 (5/1231) Femoral artery pseudoaneurysm: 0.3 (4/1231) Subclavian vein rupture: 0.1 (1/1231) **Periprocedural events** Stroke or TIA: 0.3 (4/1241) Myocardial infarction (transient due to air embolism; resolved without sequelae): 0.2 (3/1231) Left atrial-oesophageal fistula: 0 Oesophageal ulceration(reported in 3 studies of systematic endoscopy post cryoablation): 5.2 (6/116) Pericardial effusion or tamponade: 1.5 (18/1231) Cardiac tamponade: 0.6 (7/1231) Pulmonary artery rupture: 0.1 (1/1231)	**Study design issues:** • The majority of the data came from case series. • There was variation in study methodologies, patient characteristics, procedural characteristics, presence and composition of comparator groups and duration of follow-up. **Other issues:** • 28 mm cryoballoon used in 80% (681/842) of patients, 23 mm in 13.9% (117/842) and both in 5% (44/842)

Abbreviations used: AF, atrial fibrillation; CT, computed tomography; ECG, electrocardiogram; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; PV, pulmonary vein; RFA, radiofrequency ablation; TTE, transthoracic examination; TOE, transoesophageal echocardiography.			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Conflict of interest/source of funding: One author is a consultant for Medtronic.			

Abbreviations used: AF, atrial fibrillation; CT, computed tomography; ECG, electrocardiogram; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; PV, pulmonary vein; RFA, radiofrequency ablation; TTE, transthoracic examination; TOE, transoesophageal echocardiography.

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Kojodjojo (2011)[2]
Comparative case series
UK
Recruitment period: May 2006–2009.
Study population: patients with paroxysmal and persistent AF undergoing their first left atrial ablation
n = 177
Age: 58.5 years vs 59.3 years (mean)
Sex: 77% vs 77% male
Patient selection criteria: patients with symptomatic, medically refractory AF referred for ablation.
Technique: all antiarrhythmic drugs except amiodarone were stopped at least 5 half lives before the procedure. Warfarin was stopped 5 days before the procedure with bridging tinzaparin. TOE excluded intracardiac thrombus.
Cryoballoon ablation (Arctic Front, Medtronic cryocath) with applications to the right-sided PV (1500 ms CL, 20mA output) or conventional RFA (Thermocool, Biosense Webster) with 25-35W and 17 ml/min flow guided by fluoroscopy or 3D mapping system (Carto, Biosense Webster). Postoperative oral anticoagulation with warfarin was resumed with bridging tinzaparin.
Follow-up: mean 13.3 ± 7.4 months
Conflict of interest/source of funding: none</td>
<td>Number of patients analysed: 124 (492 PVs) vs 53 (211 PVs).
Freedom from AF after single procedure at 12 months
<table>
<tr><th></th><th>Paroxysmal AF</th><th>Persistent AF</th><th>p value</th></tr>
<tr><td>Cryoballoon ablation (n = 124)</td><td>77%</td><td>48%</td><td>0.002</td></tr>
<tr><td>RFA (n = 53)</td><td>72%</td><td>n/a</td><td></td></tr>
</table>
Among cryoballoon-treated patients free from AF at 12 months, 9/69 paroxysmal AF and 3/15 persistent AF patients were still on antiarrhythmic medication for frequent atrial ectopy.
Requirement for repeat ablation for recurrent AF during follow-up
Cryoablation group: 14% (17) of patients
RFA group: 23% (12) of patients
In the cryoablation group all but 3 persistent AF subjects required cardioversion at the end of the procedure to restore sinus rhythm. In the 2 subjects, AF organised into typical atrial flutter, which terminated into sinus rhythm during cavotricuspid isthmus ablation. After left atrial cryotherapy, 17 patients with paroxysmal AF and 4 patients with persistent AF had cavotricuspid isthmus ablation.</td>
<td>Transient phrenic nerve palsy
2 in cryoablation group which resolved within 3 and 14 months (phrenic nerve palsy taking 14 months to resolve was caused by unmonitored cryoablation of the right lower PV).
No cases reported in the RFA group.
Pericardial effusion
1 patient in cryoballoon group (due to guidewire perforating the side branch of the left upper pulmonary vein before any cryoablation was delivered). 2 patients in RFA group (unrelated to transseptal puncture requiring drainage).</td>
<td>Follow-up issues:
Follow-up 24-hour Holter monitoring performed by clinic visits at 1, 3 and 6 months and subsequent 6-month intervals.
All patients had at least 6 months' follow-up.
Study design issues:
Aim of study was to investigate the effect on efficacy of a strategy using a large cryoablation balloon to perform antral cryoablation with 'touch-up' ostial cryoablation for PV isolation in patients with paroxysmal and persistent AF.
After cryoballoon therapy, each PV was assessed for isolation and if necessary, treated with focal ostial cryoablation until PV isolation was achieved. Follow-up with Holter monitoring.
Study population</td>
</tr>
</table>

Abbreviations used: AF, atrial fibrillation; CT, computed tomography; ECG, electrocardiogram; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; PV, pulmonary vein; RFA, radiofrequency ablation; TTE, transthoracic examination; TOE, transoesophageal echocardiography.

Study details	Key efficacy findings	Key safety findings	Comments
			issues: • 90 patients with paroxysmal AF and 34 patients with persistent AF had cryoballoon ablation. • Only patients with paroxysmal AF had RFA (n = 53). • The group with persistent AF was significantly older and had significantly larger left atria compared with the paroxysmal group. **Other issues**: • Large balloon used (28 mm). • Procedural and fluoroscopic times during cryoablation were significantly shorter than RFA.

Abbreviations used: AF, atrial fibrillation; CT, computed tomography; ECG, electrocardiogram; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; PV, pulmonary vein; RFA, radiofrequency ablation; TTE, transthoracic examination; TOE, transoesophageal echocardiography.

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Chierchia GB (2010)[3]
Comparative case series (as described)
Belgium
Recruitment period: December 2007–February 2009
Study population: all patients needing AF ablation for highly symptomatic paroxysmal AF.
n = 133 (46 vs 87)
Age: 56 years (mean)
Sex: 79% (105) male
Patient selection criteria: frequent recurrent episodes of AF, self-terminating within 7 days and developing despite treatment with at least 2 antiarrhythmic drugs.
Technique: cryoballoon ablation with a minimum of 2 applications lasting 5 minutes each (Arctic Front, Medtronic Cryocath) or point-by-point RFA pulses applied for a maximum of 60 seconds outside the ostium with a power limit of 35 W, each guided by electroanatomical mapping (Carto, Navistar, Lasso: Biosense Webster). Oral anticoagulation stopped 5 days before ablation and replaced with low-molecular weight heparin. 2D TOE within 24 hours postoperatively. Oral anticoagulation resumed within 1 week of the procedure in all patients.
Follow-up: maximum 24 hours
Conflict of interest/source of funding: none declared</td>
<td>Number of patients analysed: 133 (46 vs 87)
Procedure time
Mean procedure time was shorter with cryoballoon ablation compared with RFA (168 ± 30 vs 188 ± 28; p < 0.001).</td>
<td>Pericardial effusion: Postoperative pericardial effusion reported for cryoballoon ablation and RFA: 11% (5/46) vs 16% (14/87), p = 0.623. Drainage was needed in 1 patient in each group; all other effusions resolved spontaneously.
<table>
<tr><th>Pericardial effusion</th><th>Cryoballoon ablation (n = 5)</th><th>RFA (n = 14)</th></tr>
<tr><td>Mild[a] (< 10 mm)</td><td>4/5</td><td>12/14</td></tr>
<tr><td>Moderate[b] (> 10 mm posteriorly)</td><td>0/5</td><td>1/14</td></tr>
<tr><td>Large (> 20 mm in all diastole)</td><td>0/5</td><td>0/14</td></tr>
<tr><td>Pericardial tamponade[c]
> 20 mm with haemodynamic compromise (related to transseptal puncture)</td><td>1/5</td><td>1/14</td></tr>
</table>
[a] No prolonged hospital stay. No invasive treatment. No symptoms related to pericardial effusion. All resolved at an average 3-month follow-up; [b] Discharged after 2 additional observational days in hospital without complications; [c] Haemodynamic compromise readily reversed by subxiphoidal puncture. Both patients required 4 adjunctive hospital days.
Intraoperative phrenic nerve palsy: 3 patients had phrenic nerve palsy during cryoballoon ablation energy delivery in the right superior pulmonary vein. Diaphragmatic contraction completely recovered before the end of the procedure in all patients (recovery time 20 ± 9 min).
Arteriovenous fistula: 1 patient in RFA group had arteriovenous fistula requiring vascular intervention and 2-day prolongation of hospital stay.
No cerebrovascular accidents occurred during or after any procedure.</td>
<td>Follow-up issues:
• None.
Study design issues:
• Single centre non-randomised study. Results may not be generalisable.
• Study aimed to investigate incidence and outcome of pericardial effusion
• Echocardiographists not blinded.
Study population issues:
• Some overlap in reporting with Sorgente et al. 2010.
• None of the patients exhibited pericardial effusion at a preprocedural 2D TTE.
Other issues:
• All procedures done with 28 mm cryoballoon (relatively large).</td>
</tr>
</table>

Abbreviations used: AF, atrial fibrillation; CT, computed tomography; ECG, electrocardiogram; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; PV, pulmonary vein; RFA, radiofrequency ablation; TTE, transthoracic examination; TOE, transoesophageal echocardiography.

Study details	Key efficacy findings	Key safety findings	Comments
Sorgente A (2010)[4] **Retrospective comparative case series** Belgium Recruitment period: Patients having a single PV isolation procedure between June 2007–December 2009 Study population: patients referred for drug-refractory symptomatic AF n = **94 (30 vs 29 vs 35)** Age: 55.9 years (mean) Sex: 79 males Patient selection criteria: Patients excluded if had undergone a previous AF ablation procedure, if lost to follow-up or if they were included in another ongoing study. Technique: 2D TTE, CT and TOE 1 day before ablation. Cryoballoon ablation with 2 applications 5 minutes each (Flexcath,Arctic Front, Medtronic Cryocath) or conventional manual RFA limit 35 Watts for 60 seconds (Lasso, Carto, Navistar Thermocool ablation catheter: Biosense Webster) or remote magnetic navigation assisted RF ablation (Carto RMT system, Niobe II remote magnetic system, Thermocool RMT Navistar ablation catheter: Biosense Webster). All patients discharged on oral anticoagulation. antiarrhythmic drugs stopped after blanking period of 2 months. Follow-up: **maximum 1 year** Conflict of interest/source of funding: none declared.	Number of patients analysed: **94 (30 vs 29 vs 35)** **Success[a] rate without antiarrhythmic drugs at mean follow-up 12.64 ± 6.41 months.** Cryoballoon ablation: 66% (23) RFA: 66% (19) Robotic assisted RFA: 67% (20) p value: 0.625 [a] Ablation was considered successful if there were no symptomatic or asymptomatic atrial tachyarrhythmias lasting ≥ 30 seconds, identified on surface ECG, Holter monitoring or 7-day ECG recording, without antiarrhythmic drug therapy.	**Pseudoaneurysm** Left femoral artery pseudoaneurysm in 4 patients at 1-day follow-up (1 cryoballoon, 2 RFA, 1 robotic assisted RFA). **Phrenic nerve palsy** Intraoperative transient phrenic nerve palsy in 3 patients in cryoballoon group. Diaphragmatic contraction recovered completely before the end of the procedure. **Fistula** 1 patient in RFA group had an arteriovenous fistula which required vascular intervention and 2-day prolongation of hospital stay. **Pericardial effusion** 1 patient in RFA group had moderate asymptomatic pericardial effusion at 1-day follow-up. ECG showed complete resolution at 1 month.	**Follow-up issues**: • 92 patients had physical examination and Holter recordings at 1, 3, 6 months and 1 year after the procedure. • Follow-up was longer in patients who had cryoballoon ablation. **Study design issues**: • Retrospective analysis, observational design. • Only clinicians experience with > 30 patients using each technique were included. Plus the first 5 patients having PV isolation with each technique were excluded from analysis. • In cases of persistence of PV potentials, extra cryoballoon applications were carried out to complete PV isolation.

Abbreviations used: AF, atrial fibrillation; CT, computed tomography; ECG, electrocardiogram; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; PV, pulmonary vein; RFA, radiofrequency ablation; TTE, transthoracic examination; TOE, transoesophageal echocardiography.			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
			Study population issues: • Some overlap in reporting with Chierchia et al. 2010. • 75 patients with paroxysmal, 16 persistent, 3 permanent AF. **Other issues**: • 28-mm cryoballoon catheter was used. • Lower procedural and fluoroscopy times recorded with cryoablation.

Abbreviations used: AF, atrial fibrillation; CT, computed tomography; ECG, electrocardiogram; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; PV, pulmonary vein; RFA, radiofrequency ablation; TTE, transthoracic examination; TOE, transoesophageal echocardiography.

Study details	Key efficacy findings	Key safety findings	Comments
Gaita F (2011)[5] **Comparative case series** Italy Recruitment period: Between January to August 2010 Study population: Patients with paroxysmal AF n = **108** (36 patients each in 3 groups) Age: mean 56 years Sex: 67% male Patient selection criteria: Patients with a history of paroxysmal AF, defined according to guidelines on management of AF (European Society of Cardiology), refractory to antiarrhythmic drugs. Exclusion criteria: age < 20 and > 80 years, severe valvular heart disease, acute coronary syndrome in last 3 months, previous pacemaker of implantable cardioverter-defibrillator or contraindication to perform cerebral MRI. Technique: Antithrombotic therapy was discontinued 5 days before admission and replaced by low molecular weight heparin dosed according to the body weight. Anticoagulation therapy for at least 1 month before the procedure was maintained with an international normalised ratio between 2 to 3. Cryoballoon ablation with either 23 mm or		**Cerebral lesions** (% of patients who presented new asymptomatic ischaemic lesions; number of lesions) Cerebral MRI performed the day before and the day after the procedure. Cryoballoon (n = 36): 5.6% (2/36); 9 lesions Irrigated RF ablation (n = 36): 8.3% (3/36) ; 3 lesions Non-irrigated multi-electrode catheter: 38.9% (14/36) ;24 lesions; Statistical significant difference among the 3 groups (p = 0.023). The difference in number of lesions for the cryoballoon versus non-irrigated multi-electrode catheter group was not significant (p = 0.112). There was a trend in favour of major number of new silent thromboembolic events using the non-irrigated multi-electrode catheter vs cryoballoon although this was not statistically significant (8.3% vs 5.6% ; p = 0.5; RR 1.5). Multivariate analysis showed that non-irrigated multi-electrode catheter was independently associated with an increased incidence of new asymptomatic cerebral lesions after pulmonary vein isolation of 48% (OR 1.48 ; 95% CI 1.19 to 1.62; p<0.001), compared with cryoballoon or irrigated RF ablation. **Phrenic nerve palsy** Cryoballoon (n = 36): Transient phrenic nerve palsy reported in 14% (5/36) patients during cryoablation of the right superior PV (23-mm balloon: 1 patient; 28 mm balloon: 4 patients). Full recovery of right phrenic function observed in all patients. **Other complications** In 1 patient in the irrigated RF ablation group, during the ablation AF was induced and still present at the end of the procedure. Cardioversion was performed after 1 month of effective anticoagulation and post ablation cerebral MRI was negative.	**Follow-up issues:** • No loss to follow-up reported **Study design issues:** • Patients enrolled in a consecutive manner. • Results may not be generalisable to patients undergoing AF with an aggressive anticoagulation protocol. • It is unclear which confounding factors were taken into account in the adjusted multivariate analysis. **Study population issues:** • No significant differences in relation to baseline characteristics.

Abbreviations used: AF, atrial fibrillation; CT, computed tomography; ECG, electrocardiogram; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; PV, pulmonary vein; RFA, radiofrequency ablation; TTE, transthoracic examination; TOE, transoesophageal echocardiography.			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
28 mm balloon. Application delivered at least 2 times for each vein and ranged from 4 to 5 minutes per freeze. During right PVs cryoablation, superior vena cava pacing was performed to verify right phrenic nerve integrity or irrigated RF ablation with multipolar catheter and RF applied to 30W and irrigation rate of 20-35 ml/min or non-irrigated multielectrode catheter at 10 W application lasted for 60 seconds. Follow-up: not stated Conflict of interest/source of funding: none declared			

Abbreviations used: AF, atrial fibrillation; CT, computed tomography; ECG, electrocardiogram; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; PV, pulmonary vein; RFA, radiofrequency ablation; TTE, transthoracic examination; TOE, transoesophageal echocardiography.

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Linhart M (2009)[6]
Case–control
Germany
Recruitment period: not reported
Study population: patients with AF matched to patients treated with RFA from PV ablation register
n = 20 vs 20
Age: range 38–77 years
Sex: 75% male
Patient selection criteria: ECG-documented symptomatic non-valvular paroxysmal AF and failure of at least 2 antiarrhythmic drugs. No patients had undergone prior PV ablation. Patients matched to those treated during same time interval from PV ablation register.
Technique: TTE and TOE 1 day before ablation. All patients had segmental PV isolation. Cryoballoon (Arctic Front, Medtronic Cryocath) with cryoenergy applied for 2x max 6 minutes per application.
RFA using irrigated tip ablation catheter (Thermocool, Biosense Webster). RF energy applied 25–30 Watts with max temperature of 47°C.
Follow-up: 6 months
Conflict of interest/source of funding: none declared</td>
<td>Number of patients analysed: 40
Procedure success
In cryoballoon group 81% (63/78) of veins could be isolated using the balloon only (cryocatheter also used in 11 veins (6 patients, 14%).
In RFA group 100% (77/77) of veins successfully isolated.
<table>
<tr><th></th><th>Freedom from AF within 3 months</th><th>Success rate[a] at 6 months</th></tr>
<tr><td>Cryoballoon only (n = 14)</td><td>50% (7/14)</td><td>50% (7/14)</td></tr>
<tr><td>Cryoballoon + cryotip catheter (n = 6)</td><td>55%</td><td>66% (4/6)</td></tr>
<tr><td>RFA (n = 20)</td><td>45% (9/20)</td><td>45% (9/20)</td></tr>
</table>
[a] Defined as the % of patients who did not have any documented AF episode or any symptoms suggesting AF recurrence after the blanking period of 4 weeks. Only for patients without recurrent AF.
Repeat procedures
4 patients treated by balloon cryoablation and 7 patients treated by RFA had repeat ablation procedures at 6 months.</td>
<td>Intraoperative complications
Cryoballoon group:
<table>
<tr><th>Intraoperative complications[a]</th><th>Patients</th></tr>
<tr><td>Temporary right-sided phrenic nerve palsy (spontaneous recovery after procedure and confirmed by fluoroscopy).</td><td>3</td></tr>
<tr><td>Bradycardia with heart rate < 50/min requiring temporary ventricular pacing</td><td>2</td></tr>
<tr><td>Severe headaches, nausea and dry cough</td><td>3</td></tr>
</table>
[a] All occurred during ablation. None resulted in complications or prolonged stay in hospital.

RFA group:
No complications.</td>
<td>Follow-up issues:
Patients had ECG 1 day before procedure and submitted 1 ECG per day via telephone and to do additional recordings if they felt any symptoms of AF for 3 months.
First 4 weeks of follow-up were excluded from analysis.
At 12 month follow-up patients were asked about AF symptoms with standardised questionnaires.
Study design issues:
Patients from AF register of the University Hospital of Bonn.
Patients were matched for sex, age, LVEF and AF history.
Study population issues:
Small population.
Data on procedural success in</td>
</tr>
</table>

Abbreviations used: AF, atrial fibrillation; CT, computed tomography; ECG, electrocardiogram; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; PV, pulmonary vein; RFA, radiofrequency ablation; TTE, transthoracic examination; TOE, transoesophageal echocardiography.

Study details	Key efficacy findings	Key safety findings	Comments
			cryoballoon group does not add account for all procedures. **Other issues**: • 23-mm cryoballoon used in 2 cases, 28-mm in 15 and both in 3 cases. • 23-mm balloon had been used in 3 cases of phrenic nerve palsy.

Abbreviations used: AF, atrial fibrillation; CT, computed tomography; ECG, electrocardiogram; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; PV, pulmonary vein; RFA, radiofrequency ablation; TTE, transthoracic examination; TOE, transoesophageal echocardiography.

Study details	Key efficacy findings	Key safety findings	Comments
Neumann T (2008)[7] **Case series** Germany Recruitment period: not reported Study population: Patients with symptomatic, drug refractory paroxysmal (n = 293) or persistent (n = 53) AF. n = **346** Age: 59 years (mean) Sex: 62% (214) male Patient selection criteria: Exclusion criteria: advanced structural heart disease including moderate-to-severe valvular stenosis or insufficiency, previous MI, congenital heart disease, LVEF < 45%, CABG surgery within the last 3 months, chronic obstructive pulmonary disease treated with β-sympathomimetic drugs, severe respiratory insufficiency, known bleeding diathesis or intolerance of heparin or oral anticoagulation, attempted AF ablation in the past, left atrial thrombus, pregnancy and severe comorbidity. Technique: Ablation by circumferential antral PV isolation using a cryoballoon (Arctic Front, Medtronic Cryocath) 240–360 seconds per freeze. If a PV could not be reached with cryoballoon or no isolation could be achieved after 5 applications, an 8-mm tip cryoablation catheter (Freezor Max, Medtronic Cryocath) was used to finish PV isolation. Procedure covered with heparin, oral anticoagulation with Coumadin was started 1 day after PV isolation. All	Number of patients analysed: **different for each outcome** **Procedure success** At least 1 cryoenergy application with grade 4 occlusion (full retention of contrast medium without visible outflow on injection of 50% diluted contrast medium into the PV) achieved in 90% of PVs. Sinus rhythm maintained without antiarrhythmic drugs in 159 (74%) patients with paroxysmal AF and 42% (13/31) patients with persistent AF (timing of assessment not provided). In 41 patients (12%) antiarrhythmic drug therapy was not discontinued at 3-month follow-up because patients had ongoing highly symptomatic episodes of AF. In 58 patients complete isolation of PV could not be completed with cryoballoon alone due to anatomical features. A large catheter tip was needed to finish PV isolation. 33 (10%) patients needed more than 1 size of cryoballoon for PV isolation. None of these patients had a grade 4 occlusion. **Additional procedures** 26 patients with atrial flutter needed an additional right atrial isthmus block. Repeat ablation needed for recurrent AF at 6 months in 35 patients (procedure failed).	**Early periprocedural complications:** 2 pericardial tamponades successfully treated with pericardial drainage; no surgery needed. 5 groin haematoma **Vascular complications (all managed conservatively)** 2 femoral arterial pseudoaneurysms 1 femoral arteriovenous fistula. **Right phrenic nerve palsy** 26/346 during cryoablation of the right superior PV. In 24/26 patients this occurred when using 23-mm balloon, 2/26 with 28-mm balloon. 2/26 phrenic nerve palsies resolved during the procedure. Full recovery of right phrenic function observed in all patients during follow-up of less than 1 year. **Transient ST-segment elevation** 2 patients had transient ST-segment elevation because of bubbles inside the sheath in the inferior leads without haemodynamic compromise. Resolved within < 2 minutes in both patients. **Left atrial flutter** Left atrial flutter in 2 patients within 3 months. Both resolved successfully with a further left atrial ablation. **PV stenosis** No stenosis (defined as reduction of > 30% in PV diameter on MRI) seen after the procedure in 239 patients.	**Follow-up issues**: • In 264 patients follow-up was ≥ 6 months. In 133 patients follow-up was more than 12 months. • 55 patients only available for analysis of acute results. • 9 patients lost to follow-up plus 14 patients refused follow-up visits. • Telephone interview used to follow up patients. During follow-up of 3–12 months at least 1 MRI or CT scan was carried out. • 55 patients (16%) of patients not accounted for at final follow-up because they did not complete follow-up beyond the blanking period. **Study design issues**: • No control. • Preoperative TTE, MR/CT and postoperative TTE, chest X-ray and

Abbreviations used: AF, atrial fibrillation; CT, computed tomography; ECG, electrocardiogram; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; PV, pulmonary vein; RFA, radiofrequency ablation; TTE, transthoracic examination; TOE, transoesophageal echocardiography.

Study details	Key efficacy findings	Key safety findings	Comments
patients had antiarrhythmic drugs for 3 months. Follow-up: **median 12 months** Conflict of interest/source of funding: authors have received speakers' and trainers' honoraria from cryocath. They also serve on advisory boards to Cryocath.			ECG undertaken. **Study population issues**: • Patients with paroxysmal and persistent AF included. • AF documented on separate ECGs within the previous 3 months **Other issues**: • In 116 patients, small balloons were initially selected. In 230 patients the procedure was started with a 28-mm balloon. No significant differences observed in the number of cryoballoon applications, total cryo time per PV, procedure time and incidence of acute PV isolation between 23-mm and 28-mm balloon. Median fluoroscopy time was significantly higher with 28-mm balloon than with 23-mm

Abbreviations used: AF, atrial fibrillation; CT, computed tomography; ECG, electrocardiogram; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; PV, pulmonary vein; RFA, radiofrequency ablation; TTE, transthoracic examination; TOE, transoesophageal echocardiography.

Study details	Key efficacy findings	Key safety findings	Comments
			balloon (46 min vs 33 min). • Learning curve may influence results.

Abbreviations used: AF, atrial fibrillation; CT, computed tomography; ECG, electrocardiogram; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; PV, pulmonary vein; RFA, radiofrequency ablation; TTE, transthoracic examination; TOE, transoesophageal echocardiography.

Study details	Key efficacy findings	Key safety findings	Comments
Van Belle Y (2008)[8] **Case series** Netherlands Recruitment period: August 2005 – August 2007 Study population: patients with paroxysmal AF. n = **141** Age: 56 years (mean) Sex: 100 males Patient selection criteria: Inclusion criteria: symptomatic paroxysmal AF without major structural heart disease (normal LVEF, no or only minor mitral insufficiency, normal to slightly enlarged left atrial diameter, assessed in the long parastemal axis). No patients had previously been ablated in the left atrium, all had episodes of AF despite concomitant antiarrhythmic drug treatment. Technique: Cryoballoon PV isolation (Arctic Front, Medtronic Cryocath). Daily Transtelephinuc ECG monitoring, 24h Holter-ECG and an arrhythmia-focused questionnaire were used to document AF. Antiarrhythmic drugs stopped 1 week before ablation. After PV isolation, patients returned to antiarrhythmic drug regime until 3-month follow-up. If no recurrence by 3-months, antiarrhythmic drugs stopped. Follow-up: **457 ± 252 days** Conflict of interest/source of funding: first author received a minor consultancy fee from Cryocath.	Number of patients analysed: **139** **Procedure success** PV isolation achieved in 139 patients in 1 procedure. (23-mm balloon in 33 patients, 28-mm balloon in 99 patients, both sizes in 7 patients). A cryocatheter (Freezor Max) was used to complete PV isolation in 56 patients (86 veins). **Atrial fibrillation** 1-month preoperative: Presence of AF on 24h Holter ECG (lasting more than 30 seconds): 45% (58/128); Continuous AF on 24h Holter ECG (AF present for entire recording): 16% (21/128); Mean AF burden measured by rhythm strips (% of days on 3-month follow-up: Presence of AF on 24h Holter ECG (lasting more than 30 seconds): 11% (14/129); Continuous AF on 24h Holter ECG (AF present for entire recording): 1% (1/129); Mean AF burden measured by rhythm strips (% of days on: 9% (686/7978)	**Pericardial effusion** 8 patients had pericardial effusion. 1 due to rupture of the left superior pulmonary vein caused by distal cryoballoon inflation. 1 had haematopneumothorax which resolved completely. **Phrenic nerve palsy** 4 patients had right phrenic nerve palsy persisting at discharge. 3 resolved at 3 months – all resolved within 6 months. **Haemoptysis** 2 patients had haemoptysis in the first month after PV isolation but no PV stenosis observed on CT. Temporary cessation of anticoagulation therapy resolved problems and it did not recur in either patient. **Haematoma and bleeding** 2 patients needed transfusion for 1 haematoma in groin and 1 retroperitoneal bleeding. **Fistula** 2 arteriovenous fistula. **Perimitral flutter** 1 perimitral valve flutter was successfully ablated. **Pulmonary vein stenosis** There was no change in mean PV diameter on postoperative CT scan (timing not stated).	**Follow-up issues**: • 2 patients excluded from analysis: 1 because of equipment failure at the time of ablation, 1 developed acute pulmonary oedema before the ablation. • Compliance with daily event recording over the telephone after 3 months was difficult. **Study design issues**: • Observational. **Study population issues**: • None. **Other issues**: • 28-mm balloon used from February 2007 onwards (preferred).

Abbreviations used: AF, atrial fibrillation; CT, computed tomography; ECG, electrocardiogram; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; PV, pulmonary vein; RFA, radiofrequency ablation; TTE, transthoracic examination; TOE, transoesophageal echocardiography.

Study details	Key efficacy findings	Key safety findings	Comments
	which AF episode transmitted)		

Recurrence of AF after 1 procedure

- 51% (71/139) had AF recurrence

Recurrence of AF after second procedure

- 17% (24/139) had a 'redo' procedure.
- 46% (11/24) had recurrence of AF after second procedure (8 at mean 15 days, 3 after 3 months).

Event-free survival rate (from any AF) of 44% at 365 days.

Quality of life

Data available for 125 patients

Postoperative symptom change	Patients %
Improved	72% (90/125)
Equal	18% (22/125)
Worse	10% (13/125)

Abbreviations used: AF, atrial fibrillation; CT, computed tomography; ECG, electrocardiogram; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; PV, pulmonary vein; RFA, radiofrequency ablation; TTE, transthoracic examination; TOE, transoesophageal echocardiography.

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Ahmed H (2009)[9]
Comparative case series
USA
Recruitment period: not reported
Study population: patients with drug-resistant paroxysmal AF
n = 74 (67 vs 7)
Age: 48–69 years (range)
Sex: 61% vs 71% male
Patient selection criteria: not reported.
Technique: cryoablation performed using a cryoablation balloon system (Arctic Front, Medtronic Cryocath) (cryoballoon group) for 240 seconds per lesion or spot 4-mm tip cryocatheter (Cryocor, Cryocath) to complete irrigated RF lesion sets at PV regions close to the oesophagus (cryofocal group).
Follow-up: maximum 3 months
Conflict of interest/source of funding: authors have received research grant support from Cryocath technologies and 1 author is Chairman of the Steering Committee for the Arctic Front Trial run by CryoCath technologies.</td>
<td>Number of patients analysed: 64 (57 vs 7)</td>
<td>Oesophageal temperature continued to decrease after termination of the ablation lesion.
<table><tr><th></th><th>Significant luminal oesophageal temperature changes (> 1°C)</th><th>Oesophageal ulceration on endoscopy</th></tr><tr><td>Cryoballoon</td><td>62/67 (93%)</td><td>6/35 (17%)</td></tr><tr><td>Cryofocal</td><td>5/7 (71%)</td><td>0/7</td></tr></table>All patients with ulcerations were asymptomatic and without clinical sequelae. 5 had treatment with Proton Pump Inhibitors. All resolved at 3-month endoscopy.
No occurrences of atrial oesophageal fistula.</td>
<td>Follow-up issues:
35 (52%) cryoballoon and 7 (100%) cryofocal patients had post-procedural endoscopy within 1 week of the procedure. If ulceration was found, patients were prescribed Proton Pump Inhibitors and had follow-up endoscopy at 1 month.
Study design issues:
Luminal oesophageal temperature was monitored but was not used to guide ablation therapy.
Study designed to examine the oesophageal effects of cryoenergy during AF ablation.
Study population issues:
Cryoballoon group all had drug-resistant paroxysmal AF.
Cryofocal group had</td>
</tr>
</table>

Abbreviations used: AF, atrial fibrillation; CT, computed tomography; ECG, electrocardiogram; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; PV, pulmonary vein; RFA, radiofrequency ablation; TTE, transthoracic examination; TOE, transoesophageal echocardiography.			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
			paroxysmal (2), persistent (1) or longstanding persistent (4) drug-resistant AF. **Other issues**: • 23-mm cryoballoon catheter used in 23 (34%) and 28-mm cryoballoon catheter used in 32 (48%). Both balloon sizes needed in 12 (18%) of patients.

Efficacy

Procedural success

A comparative case series of 94 patients treated by balloon cryoablation (n = 30), radiofrequency ablation (n = 29) or robotically assisted radiofrequency ablation (35) reported procedure success (defined as 'no atrial tachyarrhythmias [symptomatic or asymptomatic] lasting ≥ 30 seconds, identified on surface electrocardioagram [ECG], Holter monitoring or 7-day ECG recording') without antiarrhythmic drugs in 66% (23), 66% (19) and 67% (20) of patients respectively at a mean follow-up of 12.64 months (p = 0.625) (denominator not reported)[4]. A case–control study of 40 patients reported procedure success at 6 months (defined as no AF episode or any symptoms suggesting AF recurrence after a 'blanking period' [time period during which transient episodes of arrhythmia were not considered recurrences] of 4 weeks) in 50% (7/14) of patients treated by balloon cryoablation only, in 66% (4/6) of patients treated by balloon cryoablation plus cryocatheter and in 45% (9/20) of patients treated by radiofrequency ablation[6].

A systematic review (19 studies; n = 924 patients) reported acute procedural success (defined as complete isolation of all targeted pulmonary veins) in 99% (95% CI 98 to 99%) of patients (I^2 = 0% [no heterogeneity])[1].

Freedom from atrial fibrillation

The systematic review reported 1-year freedom from atrial fibrillation. The percentage of patients with paroxysmal atrial fibrillation after a 3-month blanking period was 73% (95% CI 69 to 77) (5 studies; n = 519; I^2 = 0%). The percentage of patients with paroxysmal atrial fibrillation who did not have a 3-month blanking period was 60% (95% CI 55 to 66) (3 studies; n = 316; I^2 = 0%). The percentage of patients with persistent atrial fibrillation after a 3-month blanking period was 45% (95% CI 33 to 58) (2 studies; n = 62; I^2 = 0%)[1].

In a case series of 346 patients treated by balloon cryoablation sinus rhythm was maintained without antiarrhythmic drugs in 74% (159, denominator not reported) of patients with paroxysmal atrial fibrillation and 42% (13/31) of patients with persistent atrial fibrillation (timing of assessment not provided)[7].

An event-free survival rate (freedom from atrial fibrillation) of 44% at 365 days was reported in a case series of 141 patients treated by balloon cryoablation[8].

In a non-randomised comparative case series of 177 patients, 124 patients were treated by balloon cryoablation[2]. At 12 months 77% of patients with paroxysmal atrial fibrillation and 48% of patients with persistent atrial fibrillation were free from atrial fibrillation (p = 0.002). In patients with paroxysmal atrial fibrillation treated by radiofrequency ablation (n = 53), 72% were free from atrial fibrillation at 12-month follow-up.

Recurrence of atrial fibrillation

In the case series of 346 patients, in 41 patients (12%) antiarrhythmic drug therapy was continued at 3-month follow-up because patients had ongoing highly symptomatic atrial fibrillation[7].

The case series of 141 patients reported recurrence of atrial fibrillation in 51% (71/139) of patients after one procedure (follow-up 457 days)[8].

Repeat procedure

In the case series of 141 patients, 17% (24/139) of patients had a repeat procedure. Of these, 46% (11/24) had further recurrence of atrial fibrillation (8 patients had recurrence at a mean of 15 days, 3 after a mean of 3 months)[8].

The case series of 346 patients reported that 26 patients with atrial flutter needed an additional right atrial isthmus block. The procedure failed in 35 patients who needed a repeat ablation for recurrent atrial fibrillation at 6 months[7]. In the case–control study of 40 patients, 4 patients treated by balloon cryoablation and 7 patients treated by radiofrequency ablation needed repeat ablation procedures at 6 months[6].

The non-randomised comparative case series of 177 patients treated by balloon cryoablation or radiofrequency ablation reported that 14% (17) and 23% (12) of patients respectively needed to be treated again for recurrent atrial fibrillation (denominators and timing of events not reported)[2].

Quality of life

Among 125 patients in the case series of 141, quality of life improved in 72% (90/125), did not change in 18% (22/125) and worsened in 10% (13/125) of patients after the procedure (follow-up not reported)[8].

Safety

Pericardial effusion

Postoperative pericardial effusion (within 24 hours) was reported in 11% (5/46) of patients treated by balloon cryoablation and in 16% (14/87) of patients treated by radiofrequency ablation in a comparative case series of 133 patients (drainage was needed in 1 patient in each group; all the other effusions resolved spontaneously)[3].

Moderate asymptomatic pericardial effusion was reported in 1 patient treated by radiofrequency ablation at 1-day follow-up in the comparative case series of 94 patients. Electrocardiogram (ECG) showed complete resolution at 1 month[4].

The non-randomised controlled trial of 177 patients treated by balloon cryoablation or radiofrequency ablation reported pericardial effusion in 1 patient (due to guidewire perforating the side branch of the left upper pulmonary vein before any cryoablation was delivered) and 2 patients (unrelated to transseptal puncture requiring drainage) respectively (not otherwise described)[2].

Pericardial tamponade

Periprocedural pericardial tamponade was reported in 2 patients in the case series of 346[7]. This was successfully treated with pericardial drainage and surgery was not needed.

Phrenic nerve palsy

Intraoperative phrenic nerve palsy was reported in 3 patients during balloon cryoablation energy delivery in the right superior pulmonary vein in the comparative case series of 133 patients[3]. Diaphragmatic contraction completely recovered before the end of the procedure in all patients (recovery time 20 ± 9 minutes).

Intraoperative temporary right-sided phrenic nerve palsy (spontaneous recovery after procedure confirmed by fluoroscopy) was reported in 3 patients treated by balloon cryoablation in the case–control study of 40 patients (not reported in radiofrequency ablation group)[6].

In the case series of 346 patients, right phrenic nerve palsy occurred in 8% (26/346) of patients during balloon cryoablation of the right superior pulmonary vein[7]. Of these, 2 resolved during the procedure. Right phrenic function fully recovered in all patients during follow-up of less than 1 year.

4 patients in the case series of 141 patients had persistent right phrenic nerve palsy at discharge. 3 resolved at 3 months – all resolved within 6 months[8].

The non-randomised comparative study of 177 patients reported 2 cases of phrenic nerve palsy in the balloon cryoablation group, resolving in 3 and 14 months[2]. No cases were reported in the radiofrequency ablation group.

Haemoptysis

In the case series of 141 patients, 2 patients had haemoptysis during the first month after pulmonary vein isolation but no pulmonary vein stenosis was observed on CT (computed tomography) scans[8]. The haemoptysis resolved when anticoagulation therapy was temporarily stopped and it did not recur in either patient.

Pseudoaneurysm

Left femoral artery pseudoaneurysm occurred in 4 patients at 1 day follow-up in the comparative case series of 94 patients (1 treated by balloon cryoablation, 2 by radiofrequency ablation, 1 by robotically assisted radiofrequency ablation)[4].

Periprocedural femoral arterial pseudoaneurysm was reported in 2 patients in the case series of 346[7]. This was managed conservatively.

Fistula

In the comparative case series of 133 patients, 1 patient in the radiofrequency ablation group had arteriovenous fistula requiring vascular intervention and 2 more days in hospital[3]. In the comparative case series of 94 patients, 1 patient in the radiofrequency ablation group had an arteriovenous fistula which required vascular intervention and 2 more days in hospital[4].

Periprocedural arteriovenous fistula was reported in 1 patient and was managed conservatively in the case series of 346 patients[7]. 2 patients had arteriovenous fistula in the case series of 141 patients (not otherwise described).

Haematoma

Periprocedural groin haematoma was reported in 5 patients in the case series of 346 (not otherwise described)[7]. 2 patients in the case series of 141 had groin haematoma requiring transfusion[8].

Oesophageal ulceration

A comparative case series of 74 patients reported significant luminal oesophageal temperature changes (more than 1°C) in 93% (62/67) of patients in the balloon cryoablation group and 71% (5/7) of patients in the cryofocal group[9]. Oesophageal ulceration was seen on endoscopy in 17% (6/35) of patients in the balloon cryoablation group and 0% (0/7) of patients in the cryofocal group (all ulceration was resolved at 3-month endoscopy).

Cerebral lesions

Asymptomatic cerebral lesions were reported on MRI in 5.6% (2/36) patients in the cryoablation group, 8.3% (3/36) patients in the irrigated radiofrequency ablation group and 38.9% (14/36) in the non-irrigated multi-electrode catheter group (assessed day after procedure) in the comparative case series of 108 patients. The overall difference was significant among the 3 groups ($p = 0.023$)[5].

Stroke

Stroke or transient ischaemic attack was reported in less than 1% of patients (4/1241) in the systematic review. There of the four cerebrovascular events were observed in the same study and resolved within 24 hours.

Left atrial flutter

Two patients had left atrial flutter within 3 months in the case series of 346 patients[7]. Both complications resolved successfully with a further left atrial ablation. Perimitral valve flutter was successfully ablated in 1 patient in the case series of 141[8].

Bradycardia

Two patients treated by balloon cryoablation in the case–control study of 40 patients had intraoperative bradycardia with a heart rate of less than 50 beats per minute, requiring temporary ventricular pacing[6].

Haematoma

Periprocedural groin haematoma was reported in 5 patients in the case series of 346 (not otherwise described)[7]. 2 patients in the case series of 141 had groin haematoma requiring transfusion[8].

Validity and generalisability of the studies

- A 28-mm and 23-mm cryoballoon is available. Table 2 states which size of cryoballoon was used if it was reported in the literature. Some of the published articles commented that the smaller sized balloon may be associated with a higher incidence of phrenic nerve palsy than the large balloon. However this has not been explicitly reported in table 2.
- There is limited comparative data on this procedure compared with current practice.
- Patient follow-up is relatively short term in the published literature.
- The published literature reports that there is a learning curve associated with this technology.

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

- Thoracoscopic exclusion of the left atrial appendage in atrial fibrillation (with or without other cardiac surgery) for the prevention of thromboembolism. NICE interventional procedures guidance 399 (2011). Available from www.nice.org.uk/guidance/IPG400

- Percutaneous endoscopic catheter laser balloon pulmonary vein isolation for atrial fibrillation. NICE interventional procedures guidance 399 (2011). Available from 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 procedures guidance 349 (2010). Available from www.nice.org.uk/guidance/IPG349
- Percutaneous (non-thoracoscopic) epicardial radiofrequency ablation for atrial fibrillation. NICE interventional procedures guidance 294 (2009). Available from www.nice.org.uk/guidance/IPG294
- Thoracoscopic epicardial radiofrequency ablation for atrial fibrillation. NICE interventional procedures guidance 286 (2009). Available from www.nice.org.uk/guidance/IPG286
- High-intensity focused ultrasound for atrial fibrillation in association with other cardiac surgery. NICE interventional procedures guidance 184 (2006). This guidance is currently under consideration for review. For more information, see www.nice.org.uk/guidance/IPG184
- Percutaneous radiofrequency catheter ablation for atrial fibrillation. NICE interventional procedures guidance 168 (2006). Available from www.nice.org.uk/guidance/IPG168
- Cryoablation for atrial fibrillation in association with other cardiac surgery. NICE interventional procedures guidance 123 (2005). Available from www.nice.org.uk/guidance/IPG123

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

Technology appraisals

- Dronedarone for the treatment of non-permanent atrial fibrillation. NICE technology appraisal guidance 197 (2010). Available from www.nice.org.uk/guidance/TA197

Clinical guidelines

- Atrial fibrillation: the management of atrial fibrillation. NICE clinical guideline 36 (2006). Available from www.nice.org.uk/guidance/CG36

Public health guidance

- None identified.

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 does not represent the view of the society.

Specialist advice was received from Timothy Betts, John Bourke and Richard Schilling (all Heart Rhythm UK).

- Three Specialists Advisers perform this procedure regularly.
- Three Specialist Advisers considered this procedure to be established practice and no longer new. However, one Adviser commented that many clinicians are awaiting efficacy data before considering taking up the technology.
- The Specialist Advisers considered theoretical adverse events to include death, stroke, pulmonary vein stenosis, atrio-oesophageal fistula, permanent phrenic nerve palsy, damage to structures anatomically close to pulmonary veins, and deep vein thrombosis.
- They listed anecdotal adverse events as air embolus and phrenic nerve injury.
- They listed adverse events reported in the literature as transient ischaemic attack, transient phrenic nerve palsy, pulmonary vein stenosis, pericardial effusion, tamponade, groin haematoma at venous entry site and femoral artery pseudoaneurysm.
- Key efficacy outcomes were listed as freedom from atrial fibrillation, the patient not needing antiarrhythmic drugs at 6-month follow-up, reduced need for redo procedures, achieving electrical isolation of 'all pulmonary veins' or 'all 4 pulmonary veins' , and procedure time.
- One Adviser stated that this procedure is for paroxysmal atrial fibrillation that only requires pulmonary vein isolation. Another Adviser commented that it is still unknown whether this procedure is more or less effective than radiofrequency ablation for paroxysmal atrial fibrillation. It is generally accepted that it is not useful for longstanding persistent atrial fibrillation and unclear whether it is useful for recent onset (within the past 3 months) persistent atrial fibrillation.
- The Specialist Advisers said that the training and facilities needed included the ability to perform a catheter atrial fibrillation ablation, standard training in diagnostic electrophysiology and ablation, knowledge of left atrial anatomy, training in transseptal puncture to access the left atrium, and access to emergency surgical support (not necessarily on site).
- The Specialist Advisers said that there was no controversy over dissemination other than anecdotal evidence that some groups were not checking for pulmonary vein isolation after cryoablation.
- The Specialist Advisers said that, if proven to be superior to radiofrequency ablation, balloon cryoablation was likely to be of similar cost to that procedure to the NHS in the short term but it could have a lower cost if fewer repeat procedures were needed.

Patient Commentators' opinions

NICE's Patient and Public Involvement Programme sent 60 questionnaires to 1 trust for distribution to patients who had the procedure (or their carers). NICE received 8 completed questionnaires.

The Patient Commentators' views on the procedure were consistent with the published evidence and the opinions of the Specialist Advisers.

Issues for consideration by IPAC

- Percutaneous balloon cryoablation may be most appropriate for patients with paroxysmal atrial fibrillation as opposed to persistent atrial fibrillation.
- A 28-mm and 23-mm cryoballoon is available. Table 2 states which size of cryoballoon was used if it was reported in the literature. Some of the published articles commented that the smaller sized balloon may be associated with a higher incidence of phrenic nerve palsy than the large balloon. However this has not been explicitly reported in table 2.
- More recent publications describe two strategies; a dual balloon and a single balloon strategy. The efficacy and safety of these strategies may differ, however this is not discussed in any further detail in this overview.
- Ongoing trials are:
  - NCT01038115. Comparing pulmonary vein isolation with the cryoballoon, radiofrequency energy, or both in the treatment of atrial fibrillation (AF) (Cryo Vs RFA). Currently recruiting patients with an estimated primary study completion date of September 2012. UK.
  - NCT00774566. PV-isolation with the cryoballoon versus RF: a randomised controlled prospective non-inferiority trial (FreezeAF). Currently recruiting patients with an estimated study completion date of July 2012. Germany.
  - NCT00523978. A clinical study of the Arctic Front cryoablation balloon for the treatment of paroxysmal atrial fibrillation (Stop-AF). Estimated recruitment: 243 patients. Completed: June 2009. USA (awaiting publication).
  - NCT00821015. Effect of balloon cryoablation on left atrial function (CRYO-LA). Currently recruiting participants with an estimated study completion date of December 2011. USA.
  - NCT00969735. Cryoenergy or radiofrequency for pulmonary vein isolation (COR). Recruitment status unknown (last updated 2009). Spain.
  - NCT01061931. Trial terminated with no reason provided. Mesh ablator versus cryoballoon pulmonary vein ablation of symptomatic paroxysmal atrial fibrillation (MACPAF).
  - NCT01490814. Cryoablation or radiofrequency ablation for pulmonary vein isolation in patients with paroxysmal atrial fibrillation (FIRE and ICE). Currently recruiting participants with an estimated study completion date of August 2014. Germany and Spain.

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7. Neumann T, Vogt J, Schumacher B, et al. (2008) Circumferential pulmonary vein isolation with the cryoballoon technique results from a prospective 3-center study. Journal of the American College of Cardiology Jul 22;52(4):273–8.

8. Van Belle Y, Janse P, Theuns D, et al. (2008) One year follow-up after cryoballoon isolation of the pulmonary veins in patients with paroxysmal atrial fibrillation. Europace Nov; 10(11): 1271–6

9. Ahmed H, Neuzil P, D'Avila A et al (2009) The esophageal effects of cryoenergy during cryoablation for atrial fibrillation. Heart Rhythm Jul; 6(7): 962–9

Appendix A: Additional papers on percutaneous balloon cryoablation for atrial fibrillation

The following table outlines the studies that are considered potentially relevant to the 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.

Due to the high volume of relevant papers identified, a threshold for inclusion in Appendix A was set. Only relevant papers reporting on more than 30 patients have been included, unless they report on important safety events not described in Table 2.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Bhagwandien, R., VAN, Belle Y., De, Groot N., et a. (2011) Hemoptysis after pulmonary vein isolation with a cryoballoon: An analysis of the potential etiology. Journal of Cardiovascular Electrophysiology 22 (9) 1067-69.	n = 359 Follow-up = 3 months	Haemoptysis can occur after cryoballoon ablation for several reasons, especially when a stringent anticoagulation regimen is adhered to, and when occlusion is associated with very low freezing temperatures.	Outcomes reported in Table 2.
Bhagwandien, R., Knops, P., VAN, Belle Y., Szili-Torok, Tet al. (2011) Haemoptysis after pulmonary vein isolation with a cryoballoon: An increased risk is associated with extreme low freezing temperatures. European Heart Journal Conference: European Society of Cardiology, ESC Congress 2011 Paris France. Conference Start: 20110827 Conference End: 20110831. Conference Publication: (var.pagings) 801-802.	n = 142 Follow-up = 3 months	Pulmonary vein isolation using a cryoballoon was associated with haemoptysis in 4% of the patients. Freezing with extreme low temperatures was related to the occurrence of haemoptysis.	Conference abstract. New outcomes reported.
Chan, N.-Y., Choy, C.-C., Lau, C.-Let al(2010) Persistent iatrogenic atrial septal defect after	n = 13 Follow-up = maximum 9 months	This is a study on the incidence of persistent iatrogenic atrial septal defect (iASD) after	Conference abstract. Safety outcome not reported in Table 2.

pulmonary vein isolation by cryoballoon-an under-recognized complication. European Heart Journal Conference: European Society of Cardiology, ESC Congress 2010 Stockholm Sweden. Conference Start: 20100828 Conference End: 20100901. Conference Publication: (var.pagings) 551.		transseptal puncture with a large 12-F sheath used for pulmonary vein isolation (PVI) by cryoballoon. Of all pulmonary veins, 85% (44/52) were successfully isolated. With a median follow-up of 14 months, Nine (69%) patients were free of atrial fibrillation recurrence. At 6 months, 5 (38%) patients had persistent iASD with left to right shunt, but not right to left shunt. The mean size of iASD was 5.5+/-2.4mm. At 9 months, 1 patient had closure of the iASD. No patient died or suffered clinically from cerebral or cardiac embolism. Conclusions: There is a high incidence of persistent iASD after PVI by cryoballoon at 9 month follow-up. Regular surveillance for this under-recognised complication is needed. Down-sizing of the large transseptal sheath and cryoballoon catheter is highly preferable to reduce this complication	
Defaye, P., Kane, A., Jacon, P., and Mondesert, B (2010) Cryoballoon for pulmonary vein isolation: Is it better tolerated than radiofrequency? Retrospective study comparing the use of analgesia and sedation in both ablation techniques. Archives of cardiovascular diseases 103 (6-7) 388-393.	n = 60 Follow-up not reported	In this study, patients who underwent cryoballoon ablation required a lower dose of morphine compared with those who underwent radiofrequency ablation. Catheter cryoballoon ablation appears better tolerated than radiofrequency ablation for the treatment of paroxysmal atrial fibrillation.	Larger studies included in Table 2. Focus of the study was the use of analgesia and sedation.
Guiot, A., Godin, B., Savoure, A et al.(2010) Treatment of atrial fibrillation by pulmonary vein isolation using cryotherapy balloon technique: Feasibility,	n = 34 Follow-up = maximum 4 months	Thirty-one patients were free of atrial fibrillation at hospital discharge (83.8 %). No pulmonary vein narrowing, atrio-oesophageal fistula or thromboembolic event	Conference abstract. New outcome not reported in Table 2.

complications, and shortterm outcome. Archives of Cardiovascular Diseases Supplements Conference: 20th European Days - Annual Meeting of the French Society of Cardiology Paris France. Conference Start: 20100113 Conference End: 20100116. Conference Publication: (var.pagings) 68		occurred. Three phrenic nerve palsies (8.1%) were observed after cryoapplication at the right superior pulmonary vein. The most frequent complications were pericardial effusions (n = 8) and groin haematoma (n = 3) or ecchymosis (n = 6), all spontaneously reversible.	

Guiot, A., Savoure, A., Godin, B. et al. (2011) Gastroparesia as an unusual complication of cryoballoon pulmonary vein isolation. European Heart Journal Conference: European Society of Cardiology, ESC Congress 2011 Paris France. Conference Start: 20110827 Conference End: 20110831. Conference Publication: (var.pagings) 801	n = 62 Follow-up = not reported	Gastroparesia was observed in 7 patients (11%), 2 of them suffered from a gastric bezoar (3%) and 5 from a severe gastroparesia (8%). None of them was symptomatic. None of them had prior history of gastroparesia. One had a prior history of diabetes mellitus but with no nervous complication. Among these 7 patients, 3 have also experienced phrenic nerve palsy during isolation of the right superior pulmonary vein, supporting the hypothesis of nerve injuries due to cryoenergy delivery. Conclusions: When assessed by systematic upper gastrointestinal endoscopy, a significant risk of gastroparesia (11%) is observed after cryoballoon ablation of atrial fibrillation, which is likely related to procedural peri-oesophageal vagal nerve damage	Conference abstract therefore not included in Table 2, however new safety outcome described that is not reported in Table 2.
Halbfass, P., Dorwarth, U., Horack, M., et al Cryoballoon ablation for patients with atrial fibrillation: Long-term results of the German Ablation Registry. Europace Conference: 17th World Congress in Cardiac Electrophysiology and Cardiac Techniques, Cardiostim 2010 Nice France. Conference Start: 20100616 Conference End: 20100619. Conference Publication: (var.pagings) i17-2010.	N = 776 Follow-up = 1 year	Acute success was 96. 8%. Freedom from AF 52% (166/316) of patients. In total, one stroke occurred during hospitalisation (0.1%) and 11 patients (1.4%) suffered a relevant postprocedural complication until hospital discharge (2 major bleedings, 7 vascular complications at the access site, 1 relevant pericardial effusion and 1 third degree AV-block). None of these complications was fatal. Sixteen minor bleedings occurred (2.2%).	Conference publication. Outcomes reported in Table 2.
Herrera, Siklody C., Deneke, T., Hocini, M., (2011) Incidence of asymptomatic intracranial embolic	n = 74 Follow-up = not reported	The multi-electrode phased radiofrequency pulmonary vein ablation catheter is associated with a significantly	Larger studies included in Table 2.

events after pulmonary vein isolation: Comparison of different atrial fibrillation ablation technologies in a multicenter study. Journal of the American College of Cardiology 58 (7) 681-88.		higher incidence of subclinical intracranial embolic events. Further study of the causes and significance of these emboli is required to determine the safety of the pulmonary vein ablation catheter.	
Hofmann, R., Honig, S., Leisch, F., and Steinwender, C. (2010) Pulmonary vein isolation with Mesh Ablator versus cryoballoon catheters: 6-month outcomes. Journal of Interventional Cardiac Electrophysiology 29 (3) 179-185.	n = 79 Follow-up = 6 months	After 6 months, the clinical success rate was 44% (19/43) in the MESH versus 69% (25/36) in the CRYO group ($p < 0.05$).	Outcomes reported in Table 2.
Holdova, K., Plevkova, L., Bari, K. et al (2011) Esophageal temperature measurement during balloon cryoablation for paroxysmal atrial fibrillation. European Journal of Cardiovascular Nursing Conference: 11th Annual Spring Meeting on Cardiovascular Nursing Brussels Belgium. Conference Start: 20110401 Conference End: 20110402. Conference Publication: (var.pagings) S13-2011.	n = 45 Follow-up = not reported	Regardless of balloon size, the effects of cryothermal energy on the oesophagus are most pronounced during RIPV ablation. Similar to heat sink in radiofrequency ablation, the temperature change continues to drop after the ablation is terminated, creating a cold sink phenomenon. Despite the observed temperature changes, there were no occurrences of atrial-oesophageal fistulas or other evidence of oesophageal damage	Conference abstract.
Koch, L., Schuett, H., Zacharzowsky, U. et al.(2009) Incidence of atrial tachycardias after cryoballoon pulmonary vein ablation in patients with paroxysmal or persistent atrial fibrillation. European Heart Journal Conference: European Society of Cardiology, ESC Congress 2009	n = 47 Follow-up = 3 months	New-onset isthmus-dependent atrial flutter in 12.8% and left atrial tachycardia in 2.1% of patients after antral cryoballoon pulmonary vein ablation. Therefore, prophylactic isthmus ablation in combination with cryoballoon pulmonary vein ablation may be advisable.	Conference abstract. New safety outcome not reported in T2.

Barcelona Spain. Conference Start: 20090829 Conference End: 20090902. Conference Publication: (var.pagings) 119			
. Kuck, K. H. and Furnkranz, A. (2010) Cryoballoon ablation of atrial fibrillation Journal of Cardiovascular Electrophysiology 21 (12) 1427-1431.	n = not reported Follow-up = not reported	In the future, development of an even bigger (32 mm) cryoballoon may further increase procedural safety by reducing the risk of phrenic nerve palsy or pulmonary vein stenosis	Outcomes reported in Table 2.
Langbein, A., Koller, M. L., Schade, A (2010) Incidence and determinants of pulmonary vein stenosis following cryoballoon pulmonary vein isolation. Heart Rhythm Conference: 31st Annual Scientific Sessions of the Heart Rhythm Society, Heart Rhythm 2010 Denver, CO United States. Conference Start: 20100512 Conference End: 20100515 Sponsor: St Jude Medical. Conference Publication: (var.pagings) S111-	n = 403 Follow-up = 6 months	The overall incidence of pulmonary vein stenosis was 1.4% (6 patients out of 443 ablation procedures). The degree of stenosis was mild (< 50%) in 2, moderate (50–70%) in 4 and severe (> 70%) in none of the cases. We did not observe any symptoms of pulmonary vein stenosis or signs of pulmonary hypertension in all of these patients. Conclusions: Cryoballoon ablation is a safe technology for PVI without risk of severe pulmonary vein stenosis. Only a very low incidence of asymptomatic mild and moderate pulmonary vein stenosis was observed in this study. Occurrence of pulmonary vein stenosis can completely be avoided by ablating only in antral positions without mechanical compression of the balloon.	Conference abstract. Outcomes not reported in Table 2.
Malmborg, H., Lonnerholm, S., and Blomstrom-Lundqvist, C (2008) Acute and clinical effects of cryoballoon pulmonary vein isolation in patients with symptomatic paroxysmal and persistent atrial	n = 40 Follow-up = mean 8.9 months	At follow-up (mean 8.9 +/- 4.6 months), 52.5% of patients were free from arrhythmia-related symptoms and another 17.5% had reduction of arrhythmia-related symptoms. Two cases each of phrenic nerve	Outcomes and larger studies reported in Table 2.

fibrillation. Europace 10 (11) 1277-1280.		paralysis and dysphagia occurred.	
Mikhaylov, E., Van Belle Y., Janse, P et al (2009) Characteristics of atrial tachycardias after pulmonary vein isolation: Comparison between cryoballoon and circumferential radiofrequency ablation. European Heart Journal Conference: European Society of Cardiology, ESC Congress 2009 Barcelona Spain. Conference Start: 20090829 Conference End: 20090902. Conference Publication: (var.pagings) 813-2009.	n = 302 Follow-up = 586 days	There were 16 (8.8%) patients after cryoballoon ablation and 13 (10.7%) patients after radiofrequency PVI with regular atrial tachycardias on at least one of the follow-up recordings during a mean follow-up period of 586+/-290 days (p = non significant).	Conference abstract. New safety outcome not reported in Table 2.
Moreira, W., Manusama, R., Timmermans, C. (2008) . Long-term follow-up after cryothermic ostial pulmonary vein isolation in paroxysmal atrial fibrillation. Journal of the American College of Cardiology 51 (8) 850-55.	n = 70 Follow-up = mean 33 months	Pulmonary vein cryoisolation is effective in 82% of patients with recent-onset paroxysmal atrial fibrillation during a mean follow-up of 33 +/- 15 (range 15 to 60) months.	Larger studies reported in Table 2. Adverse events not related to device.
Neumann T, Kuniss M, Conradi G, et al. (2011) MEDAFI-Trial (Micro-embolization during ablation of atrial fibrillation): comparison of pulmonary vein isolation using cryoballoon technique vs. radiofrequency energy. Europace Jan;13(1):37-44.	N = 89 Follow-up = minimum 4 months	A considerable portion of patients with AF but without any neurological symptoms had chronic cerebral lesions before PVI. Additional acute lesions could be added after the procedure. Both ablation techniques showed additional cerebral acute lesions with no neurological symptoms after PVI.	Larger studies reported in Table 2.

Packer DL, Irwin JM, Champagne J, et al. (2010) Cryoballoon ablation of pulmonary veins for paroxysmal atrial fibrillation: first results of the North American Arctic Front STOP-AF pivotal trial. J Am Coll Cardiol;55:E3015–E3016.	n = 245 Follow-up = 12 months	No results reported in the abstract. Results reported in systematic review (Andrade 2011): Acute procedural success: 98.2% (95% CI 94.7-99.6); 1 year freedom from recurrent atrial fibrillation: In patients with paroxysmal AF after a 3 month blanking period: 69.9% (95% CI 62.2-76.9); In patients with paroxysmal AF without a 3 month blanking period: 60.1% (95% CI 52.2-67.7)	Is included in the systematic review (Andrade 2011) in Table 2.
Pison, L., La, Meir M., Maessen, J., and Crijns, H. (2010) Extracardiac ice formation during cryoballoon technique for atrial fibrillation. Heart Rhythm 7 (10) 1518.	n = 1 Follow-up = not reported	Thirty-two seconds after starting cryothermal energy application using the cryoballoon, ice crystals started to appear on the epicardial surface of the left interior pulmonary vein antrum; 119 seconds later, those crystals had formed an ice plaque.	New safety outcome not reported in Table 2.
Schmidt, M., Dorwarth, U., Wankerl, M (2011) Double balloon strategy in persistent atrial fibrillation: A pilot study. European Heart Journal Conference: European Society of Cardiology, ESC Congress 2011 Paris France. Conference Start: 20110827 Conference End: 20110831. Conference Publication: (var.pagings) 625.	n = 42 Follow-up = 6 months	The 'double balloon strategy' combining cryoballoon induced ostial pulmonary vein isolation followed by antral cryoablation for treatment of persistent atrial fibrillation was feasible and was associated with a favourable mid-term outcome.	Conference abstract. Outcomes reported in Table 2. Focus on double balloon strategy.
Schumacher, B. M., Schade, A., Langbein, A, et al (2010) Efficacy and safety of cryoballoon PVI in patients with paroxysmal atrial fibrillation. Results from a single center experience in 600 patients. Heart Rhythm Conference: 31st Annual	n = 600 Follow-up = 12 months	Major complications after cryoballoon ablation were phrenic nerve palsy in 46 patients (7.7%), cardiac tamponade in 1 patient (0.16%), ischemic stroke in 2 patients (0.3%). After a blanking period of 3 months, maintenance of normal sinus rhythm off drugs was found in 72% of all	Conference abstract. Outcomes reported in Table 2 but large case series.

Scientific Sessions of the Heart Rhythm Society, Heart Rhythm 2010 Denver, CO United States. Conference Start: 20100512 Conference End: 20100515 Sponsor: St Jude Medical. Conference Publication: (var.pagings) S398-S399.		patients. Phrenic nerve palsy recovered spontaneously in 33/46 patients (72%) prior to the 3 months follow-up visit. In none of the patients a significant pulmonary vein stenosis (> 50% loss of diameter) or an atrio-oesophageal fistula was found.	
Schmidt, M., Daccarett, M., Marschang, H et al. (2010) Intracardiac echocardiography improves procedural efficiency during cryoballoon ablation for atrial fibrillation: a pilot study. Journal of Cardiovascular Electrophysiology 21 (11) 1202-07.	n = 43 Follow-up = not reported	Acute procedural success and atrial fibrillation recurrence rate at 6 months were similar in both groups (atrial fibrillation recurrence: Intracardiac echocardiography-guided = 27% vs pluoroscopy = 33%; p = non-significant). Patients without ICE guidance had significantly longer procedure (143 +/- 27 minutes vs 130 +/- 19 minutes; p = 0.05) and fluoroscopy times (42 +/- 13 minutes vs 26 +/- 10, p = 0.01).	Larger studies included in Table 2.
Sorgente, A., Chierchia, G. B., de, Asmundis Cet al. (2011) Pulmonary vein ostium shape and orientation as possible predictors of occlusion in patients with drug-refractory paroxysmal atrial fibrillation undergoing cryoballoon ablation. Europace 13 (2) 205-12.	n = 52 Follow-up = not reported	Pulmonary vein ostium shape and orientation evaluated by multislice cardiac computed tomography proved to be useful in predicting the degree of occlusion obtained during cryoballoon ablation.	Larger studies included in Table 2.

Trim, G., Brabant, J., Henry, A. et al. (2011) Initial experience of arctic front cryoablation for atrial fibrillation.Heart Lung and Circulation Conference: Cardiac Society of Australia and New Zealand Annual Scientific Meeting and the International Society for Heart Research Australasian Section Annual Scientific Meeting 2011 Perth, WA Australia. Conference Start: 20110811 Conference End: 20110814. Conference Publication: (var.pagings) S98	n = 60 Follow-up = not reported	Arctic Front cryoablation is a safe and effective method of achieving PVI in patients with paroxysmal atrial fibrillation. There was a trend towards higher acute procedural success with shorter procedure and fluoroscopy times following the first 10 cases suggestive of a relatively short learning curve for performing Arctic Front PVI for operators experienced in radiofrequency ablation of atrial fibrillation.	Conference abstract. Outcomes reported in Table 2.
. Van Belle Y., Janse, P., Rivero-Ayerza, M. J (2007). Pulmonary vein isolation using an occluding cryoballoon for circumferential ablation: feasibility, complications, and short-term outcome European Heart Journal 28 (18) 2231-37	n = 57 Follow-up = maximum 6 months	Balloon cryoablation of the pulmonary veins with additional segmental isolation if necessary, is a good approach for patients presenting with paroxysmal atrial fibrillation, showing a significant reduction in atrial fibrillation burden after a single procedure. The major complication seems to be phrenic nerve paralysis after ablation of the right superior pulmonary vein, but this is potentially reversible over several months.	Larger studies included in Table 2. Possible duplicate reporting with Table 2 study.

Vogt, J., Heintze, J., Gutleben, K. J., et al (2011) A dual balloon strategy improves long term outcome in cryoballoon pulmonary vein isolation. European Heart Journal Conference: European Society of Cardiology, ESC Congress 2011 Paris France. Conference Start: 20110827 Conference End: 20110831. Conference Publication: (var.pagings) 630	n = 506 Follow-up = 6 months maximum	Comparing long-term outcome of a single large versus a dual balloon size strategy we found significant less recurrences of atrial fibrillation (22 versus 45%, p = 0.00003) when dual balloon strategy had been applied. While comparison between single small and single large was favouring the small balloon (p = 0.005). No significant difference between single small and two balloons was found (p = 0.25).	Conference abstract. Outcomes reported in Table 2. Focus on dual balloon strategy.
Weig, H. J., Weretka, S., Parade, U. et al (2010) Cryo-specific complications using the single big cryoballoon technique for pulmonary vein isolation in patients with paroxysmal atrial fibrillation. European Heart Journal Conference: European Society of Cardiology, ESC Congress 2010 Stockholm Sweden. Conference Start: 20100828 Conference End: 20100901. Conference Publication: (var.pagings) 556	n = 82 Follow-up = mean 5.1 months	In 3 patients with a minimum temperature of −56°C and −59°C at a rather small left inferior and right inferior pulmonary vein, respectively, a CT documented frozen lung complication occurred, leading to coughing and haemoptysis for a maximum of one week. This complication forced us to stop post interventional anticoagulation.	Conference abstract reporting new safety outcome.

Appendix B: Related NICE guidance for percutaneous balloon cryoablation for atrial fibrillation

Guidance	Recommendations
Interventional procedures	**Percutaneous radiofrequency ablation for atrial fibrillation. NICE interventional procedures 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 (available from www.nice.org.uk/IPG168publicinfo). 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 UK Central Cardiac Audit Database (UKCCAD), and clinicians are encouraged to enter all patients undergoing percutaneous radiofrequency ablation for atrial fibrillation onto this database (www.ccad.org.uk).
Interventional procedures	**Percutaneous endoscopic catheter laser balloon pulmonary vein isolation for atrial fibrillation. NICE interventional procedures guidance 399 (2011).** 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 (available from www.nice.org.uk/guidance/IPG399/publicinfo). 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 (www.ccad.org.uk). 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.
Interventional procedures	**Thoracoscopic epicardial radiofrequency ablation for atrial fibrillation. NICE interventional procedures 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 (available from www.nice.org.uk/guidance/IPG286/publicinfo). 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 (www.ccad.org.uk). 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.
Interventional procedures	**High-intensity focused ultrasound for atrial fibrillation in association with other cardiac surgery. NICE interventional procedures 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 ('Understanding NICE guidance') is recommended (available from www.nice.org.uk/guidance/IPG184/PublicInfo/pdf/English). 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.
Interventional procedures	**Radiofrequency ablation for atrial fibrillation in association with other cardiac surgery. NICE interventional procedures 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.

Appendix C: Literature search for percutaneous balloon cryoablation for atrial fibrillation

Database	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	01/02/2012	Issue 1 of 12, Jan 2012
Database of Abstracts of Reviews of Effects – DARE (CRD website)	01/02/2012	n/a
HTA database (CRD website)	01/02/2012	n/a
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	01/02/2012	Issue 1 of 12, Jan 2012
MEDLINE (Ovid)	01/02/2012	1946 to January Week 3 2012
MEDLINE In-Process (Ovid)	01/02/2012	January 31, 2012
EMBASE (Ovid)	01/02/2012	1980 – 2012 Week 04
CINAHL (NLH Search 2.0/EBSCOhost)	01/02/2012	1981 - date

Trial sources searched on 01/06/2011

- Current Controlled Trials *meta*Register of Controlled Trials – *m*RCT
- Clinicaltrials.gov
- National Institute for Health Research Clinical Research Network Coordinating Centre (NIHR CRN CC) Portfolio Database

Websites searched
- National Institute for Health and Clinical Excellence (NICE)
- Food and Drug Administration (FDA) - MAUDE database
- French Health Authority (FHA)
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- Conference search
- General internet search

MEDLINE search strategy

Strategy used:

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1 Atrial Fibrillation/
2 ((atrial or auricular or atrium) adj3 fibrill$).tw.
3 af.tw.

4 or/1-3
5 Cryosurgery/
6 (cryosurg* or cryoablat* or cryogen* or cryotherm*).tw.
7 Freezing/
8 (freez* adj3 tissue$).tw.
9 or/5-8
10 exp balloon dilation/
11 catheter ablation/
12 ((balloon or catheter* or antral) adj3 (dilat* or ablat* or catheter*)).tw.
13 or/10-12
14 9 and 13
15 (cryoballoon* or cryo-balloon*).tw.
16 (arctic adj1 front).tw.
17 or/15-16
18 4 and 9
19 4 and 14
20 4 and 7
21 or/18-20
22 Animals/ not Humans/
23 21 not 22
24 limit 23 to ed=20110601-20111031