

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of percutaneous occlusion of the left atrial appendage in non-valvular atrial fibrillation for the prevention of thromboembolism

Atrial fibrillation (AF) is the irregular and rapid beating of the upper two chambers of the heart (the atria) which increases the risk of stroke. In people with AF, blood clots often form in the left atrial appendage, which is a small sac off the left atrium. These clots can travel in the blood to the brain, where they may block the blood flow, causing a stroke. In this procedure, a special device is inserted that blocks the mouth of the left atrial appendage in order to prevent migration of the blood clot.

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 December 2009.

Procedure name

- Percutaneous occlusion of the left atrial appendage in non-valvular atrial fibrillation for the prevention of thromboembolism

IP overview: Percutaneous occlusion of the left atrial appendage in non-valvular atrial fibrillation for the prevention of thromboembolism

Specialty societies

- British Cardiovascular Interventional Society
- Society for Cardiothoracic Surgeons of Great Britain & Ireland

Description

Indications and current treatment

Atrial fibrillation (AF) is the irregular and rapid beating of the upper two chambers of the heart (the atria). It may be classified as paroxysmal, persistent or permanent. It is the most common type of arrhythmia.

Patients with AF may be asymptomatic or they may have symptoms including fatigue, chest pain, palpitations, dizziness and shortness of breath. They also have an increased risk of stroke as a result of blood clots forming in the left atrium and then embolising to the brain. Evidence suggests that most thrombi develop in the left atrial appendage (LAA), a small sacculum of the left atrium located between the left upper pulmonary vein and the left ventricle.

The risk of thromboembolic events in patients with AF (of non-rheumatic origin) is assessed by the CHADS₂ score which is based on the presence or absence of congestive heart failure, hypertension, aged over 75, diabetes mellitus and previous stroke or transient ischaemic attack. In patients with low risk of thromboembolism (CHADS score 0 to 1) aspirin may be used. Patients with more than one risk factor are considered to be at a high risk of thromboembolic stroke (CHADS score > 1) and are generally treated with anticoagulation therapy, most commonly warfarin. However, warfarin is associated with haemorrhagic complications, and is contraindicated in some patients. These patients may require alternative therapy to reduce the risk of stroke. Surgical obliteration of the LAA can be through an open or thoracoscopic approach.

What the procedure involves

Percutaneous occlusion of the LAA is usually performed with the patient under general anaesthesia in a cardiac catheterisation laboratory with fluoroscopic and transoesophageal echocardiography (TOE) guidance.

A catheter is advanced through the femoral vein into the right atrium and then into the left atrium via a transseptal puncture. The location of the LAA is confirmed and the size of the LAA orifice may be established by TOE imaging.

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An appropriately sized device is selected and deployed in the mouth of the LAA where it is expanded to fit the space. The implanted device may have anchoring points to ensure it remains in place.

Patients are usually discharged on oral antiplatelet or anticoagulant agents. The position and patency of the occlusion device may be confirmed postoperatively using echocardiographic imaging.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to percutaneous occlusion of the left atrial appendage in non-valvular atrial fibrillation. Searches were conducted of the following databases, covering the period from their commencement to 4 March 2010: 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.

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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 non-valvular atrial fibrillation
Intervention/test	Percutaneous occlusion of the left atrial appendage.
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 approximately 1069 patients from 1 randomised controlled trial (RCT), 6 case series and 2 additional reports of safety events from the RCT.

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.

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Table 2 Summary of key efficacy and safety findings on percutaneous occlusion of the left atrial appendage in non-valvular atrial fibrillation for the prevention of thromboembolism

Abbreviations used: ASD, atrial septal defect; AF, atrial fibrillation; CABG, coronary artery bypass grafting; CHADS ₂ , cardiac failure, hypertension, age, diabetes, stroke (doubled); CrI, credible interval; CV, cardiovascular; ECG, electrocardiogram; INR, international normalised ratio; ITT, intention to treat; LAA, left atrial appendage; MI, myocardial infarction; NIHSS, National Institute for Health Stroke Scale; PFO, patent foramen ovale; PLAATO, percutaneous left atrial appendage transcathether occlusion; RCT, randomised controlled trial; TIA, transient ischaemic attack; TOE, transoesophageal echocardiography																																																																											
Study details		Key efficacy findings		Key safety findings	Comments																																																																						
Holmes DR (2009) ¹ RCT USA, Germany Recruitment period: 2005–2008 Study population: patients with paroxysmal, persistent, or permanent non-valvular AF n = 707 (463 LAA closure vs. 244 warfarin) Mean age: 71.7 years (LAA closure), 72.7 years (warfarin) Sex: 70% male Patient selection criteria: at least 18 years old, CHADS ₂ score of ≥1. Exclusion criteria; contraindications to warfarin, comorbidities other than AF requiring warfarin, LAA thrombus, a PFO with atrial septal aneurysm and right-to-left shunt, mobile aortic atheroma, symptomatic carotid artery disease. Technique: implantation of		Number of patients analysed: 626 (385 LAA closure vs. 241 warfarin) There was successful closure in 88% (408/463) of those randomised. 86% (349) patients stopped warfarin at 45 days (denominator not given) and 92% (355/385) stopped by 6 months. (Failure to stop warfarin was usually because of peri-procedural leak; uncertain of where other 64 patients from the 449 implanted are reported) Incidence of thromboembolic events Intention to treat: The following was based on an ITT population of randomised patients using the last observation carried forward (including those not treated and those who continued on warfarin). <table><tr><th>Outcome</th><th colspan="2">Rate per 100 patient-years (95% CrI)</th><th>Rate ratio</th></tr><tr><td></td><th>Intervention (n = 463)</th><th>Control (n = 244)</th><td></td></tr><tr><td>Ischaemic stroke^a</td><td>2.2 (1.2–3.5)</td><td>1.6 (0.6–3.0)</td><td>1.34 (0.60–4.29)</td></tr><tr><td>CV/unexplained death</td><td>0.7 (0.2–1.5)</td><td>2.7 (1.2–4.4)</td><td>0.26 (0.08–0.77)</td></tr><tr><td>Haemorrhagic stroke^b</td><td>0.1 (0.0–0.5)</td><td>1.6 (0.6–3.1)</td><td>0.09 (0.00–0.45)</td></tr><tr><td>Systemic embolism^c</td><td>0.3 (0.0–0.8)</td><td>0</td><td>n/a</td></tr><tr><td>Primary efficacy (composite)</td><td>3.0 (1.9–4.5)</td><td>4.9 (2.8–1.7)</td><td>0.62 (0.35–1.25)</td></tr><tr><td>All stroke</td><td>2.3 (1.3–3.6)</td><td>3.2 (1.6–</td><td>0.71 (0.35–</td></tr></table>		Outcome	Rate per 100 patient-years (95% CrI)		Rate ratio		Intervention (n = 463)	Control (n = 244)		Ischaemic stroke ^a	2.2 (1.2–3.5)	1.6 (0.6–3.0)	1.34 (0.60–4.29)	CV/unexplained death	0.7 (0.2–1.5)	2.7 (1.2–4.4)	0.26 (0.08–0.77)	Haemorrhagic stroke ^b	0.1 (0.0–0.5)	1.6 (0.6–3.1)	0.09 (0.00–0.45)	Systemic embolism ^c	0.3 (0.0–0.8)	0	n/a	Primary efficacy (composite)	3.0 (1.9–4.5)	4.9 (2.8–1.7)	0.62 (0.35–1.25)	All stroke	2.3 (1.3–3.6)	3.2 (1.6–	0.71 (0.35–	Rate of complications <table><tr><th>Outcome</th><th colspan="2">Rate per 100 patient-years (95% CrI)</th><th>Rate ratio</th></tr><tr><td></td><th>Intervention (n = 463)</th><th>Control (n = 244)</th><td></td></tr><tr><td>All-cause mortality</td><td>3.0 (1.9–4.5)</td><td>4.8 (2.8–7.1)</td><td>0.62 (0.34–1.24)</td></tr><tr><td>Primary safety (ITT)</td><td>7.4 (5.5–9.7)</td><td>4.4 (2.6–6.8)</td><td>1.69 (1.01–3.19)</td></tr><tr><td></td><td>(n = 389)</td><td>(n = 241)</td><td></td></tr><tr><td>Primary safety (per protocol)</td><td>1.5 (0.7–2.8)</td><td>4.4 (2.5–6.7)</td><td>0.35 (0.15–0.80)</td></tr></table> Complications reported <table><tr><th rowspan="2">Outcome</th><th colspan="2">No. of patients (% based on ITT)</th></tr><tr><th>Intervention (n = 463)</th><th>Control (n = 244)</th></tr><tr><td>Series pericardial effusion requiring drainage</td><td>22 (4.8)*</td><td>0</td></tr><tr><td>Pericardial effusion not requiring drainage</td><td>8 (1.7)</td><td>0</td></tr><tr><td>Device embolisation</td><td>3 (0.6)**</td><td>0</td></tr></table>	Outcome	Rate per 100 patient-years (95% CrI)		Rate ratio		Intervention (n = 463)	Control (n = 244)		All-cause mortality	3.0 (1.9–4.5)	4.8 (2.8–7.1)	0.62 (0.34–1.24)	Primary safety (ITT)	7.4 (5.5–9.7)	4.4 (2.6–6.8)	1.69 (1.01–3.19)		(n = 389)	(n = 241)		Primary safety (per protocol)	1.5 (0.7–2.8)	4.4 (2.5–6.7)	0.35 (0.15–0.80)	Outcome	No. of patients (% based on ITT)		Intervention (n = 463)	Control (n = 244)	Series pericardial effusion requiring drainage	22 (4.8)*	0	Pericardial effusion not requiring drainage	8 (1.7)	0	Device embolisation	3 (0.6)**	0	Follow-up issues: - Follow-up visits at 45 days, 6, 9, and 12 months; TOE on 45 day, 6 and 12 month. Neurological assessment at baseline, 12 and 24 months and if an event. - Outcomes were given only in patient-years; used Bayesian analysis. - No apparent loss to follow-up on patients treated in either group (some randomised were not treated – see below). Study design issues: - This was a multi-centre non-inferiority trial (purpose to determine if device is non-inferior to warfarin; known as PROTECT AF trial). - Recruitment not described and no blinding. - Central
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Study details		Key efficacy findings			Key safety findings			Comments									
WATCHMAN (Atritech) followed by warfarin for 45 days to facilitate epithelialisation, then daily clopidogrel + aspirin until 6 months after the procedure with aspirin continuing indefinitely. Mean follow-up: 18 months Conflict of interest/source of funding: funded by manufacturer		5.2) 1.64) ^a all were in patients at subtherapeutic INR levels; 2 (1 in each group) were fatal; of the 15 in the intervention group, 1 occurred after randomisation before implantation, 5 had procedure-related strokes (2 later died at a nursing home), and 9 were after the periprocedural period; all 6 in the control were periprocedural ^b all patients were at therapeutic INR levels; the 1 patient in the intervention group with stroke occurred in the 45 days after implantation while the patient was on warfarin – this patient died; 5 of the 6 events in the control group were fatal ^c this occurred in 2 patients Per-protocol: The following results include patients with successful treatment (defined in treatment group as those treated with the device who discontinued warfarin).			Oesophageal tear 1 (0.2) 0 Procedure-related arrhythmia 1 (0.2) 0 Bleeding requiring minimum 2 units of red blood cells or emergency operation 16 (3.5) 10 (4.1) Death*** 21 (4.5) 18 (7.4) * 15 of these patients were treated by pericardiocentesis and 7 had surgical intervention (none died); the authors stated that effusion rates declined with investigator experience (7.1% [11/154] occurred in the first 3 patients and 4.4% [17/388] in subsequent patients) ** 1 detected during the procedure, 2 discovered on TOE at 45-day follow-up. 1 removed percutaneously by vascular snare and the other 2 underwent surgery (no other details provided) *** Intervention group: 2 from stroke, 4 from unknown or cardiovascular causes and 15 from non-cardiovascular causes (cancer, urosepsis); control group: 6 from stroke, 6 from unknown or other cardiovascular causes and 6 from non-cardiovascular causes (pneumonia).			randomisation in blocks of 6 (4 intervention, 2 control) by statistician. - Warfarin discontinued if TOE confirmed complete closure or residual jet flow < 5 mm wide. 30 patients did not stop warfarin at 6 months; no further details were given. - Use of patient-years potentially misleading as first patient years in intervention group included warfarin. - In the control group, plasma warfarin concentration was in the INR range (2.0–3.0) 66% of the time. - Implantation not attempted in 14 in intervention group and not possible in 41 (first 14: 3 later determined ineligible – cardiac tumour or inadequate anatomy, 6 not implanted in specified timeframe, 4 withdrew consent and 1 died before									
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* Patients where implantation was not attempted, not possible and those still on warfarin were not included. ** Warfarin was not started in 3 patients (no other details provided). Kaplan-Meier analysis Cumulative mortality rates for the intervention and control groups were 3.0% (95%I 1.3–4.6) vs. 3.1% (95% CI 0.8–5.4) at 1 year and 5.9% (95% CI 2.8–8.9) vs. 9.1% (95% CI 4.2–14.1) at 2 years.																	
Separate case reports of safety from this study published before the trial A case report of the patient with device embolisation which was detected minutes after the procedure reported that the device was surgically removed from the aortic valve which needed to be replaced by a prosthetic valve². The postoperative course included pleural effusions requiring drainage, bradycardia and complete heart block which required implantation of a pacemaker 1 year after the procedure².																	

Abbreviations used: ASD, atrial septal defect; AF, atrial fibrillation; CABG, coronary artery bypass grafting; CHADS ₂ , cardiac failure, hypertension, age, diabetes, stroke (doubled); CrI, credible interval; CV, cardiovascular; ECG, electrocardiogram; INR, international normalised ratio; ITT, intention to treat; LAA, left atrial appendage; MI, myocardial infarction; NIHSS, National Institute for Health Stroke Scale; PFO, patent foramen ovale; PLAATO, percutaneous left atrial appendage transcatheter occlusion; RCT, randomised controlled trial; TIA, transient ischaemic attack; TOE, transoesophageal echocardiography			
Study details	Key efficacy findings	Key safety findings	Comments
		A case report of a patient who had pericardial effusion requiring urgent pericardiocentesis 2 days after the procedure reported that a set of blood cultures obtained in evaluation grew <i>Staphylococcus aureus</i> 6 days after the patients was hospitalised ³ .	procedure; of the 41: 29 devices not released for reasons including in-situ size stability, 12 had procedure-related complications and are classified as safety endpoints) Study population issues: • Sample size calculations were not explained clearly.

Abbreviations used: ASD, atrial septal defect; AF, atrial fibrillation; CABG, coronary artery bypass grafting; CHADS ₂ , cardiac failure, hypertension, age, diabetes, stroke (doubled); CrI, credible interval; CV, cardiovascular; ECG, electrocardiogram; INR, international normalised ratio; ITT, intention to treat; LAA, left atrial appendage; MI, myocardial infarction; NIHSS, National Institute for Health Stroke Scale; PFO, patent foramen ovale; PLAATO, percutaneous left atrial appendage transcathether occlusion; RCT, randomised controlled trial; TIA, transient ischaemic attack; TOE, transoesophageal echocardiography					
Study details		Key efficacy findings		Key safety findings	Comments
Ostermayer (2005) ⁴		Number of patients analysed: 111		Follow-up issues:	
Case series		Successful closure		Chest X-ray, transthoracic echocardiography and clinical exam at 1 week (Europe), 1 month, 3 months (North America), 6 and 12 months; TOE at 1 month (Europe) and in first 20 patients in North America, in addition to a 6 month scan (TOE also performed if clinical indicated).	
Germany, Italy, USA, Switzerland, Canada			% (n; 95% CI)	Authors report 1 patient lost to follow-up.	
Recruitment period: 2001–2003		Successful closure	97.3% (108/111; 92.3–99.4%)*	Study design issues:	
Study population: patients with non-rheumatic AF and contraindication for anticoagulation therapy and at least 1 additional factor for stroke (mean LAA diameter 22 mm; 50% had AF for > 3 years, 31% 1–3 years, 19% < 1 year)		* Of these patients, 87.0% (94/111) had either a ‘trace leak’ (barely detectable) or no leak after the procedure and 13.0% (14/111) had a ‘mild leak’ (filled one-third of LAA).		This was a feasibility study from 2 prospective multi-centre trials.	
n = 111 (113 procedures)		Incidence of thromboembolic events		All echocardiograms were evaluated in core laboratory.	
Mean age: 71 years		Of the 97 patients who completed 6 months of follow-up, 2.1% (2/97) experienced a <u>major adverse event</u> (defined as major or minor stroke, cardiac or neurological death, MI or requirement for CV surgery). One event is listed in the safety section (resulting in neurological death). The other major event was a stroke which occurred 173 days after the procedure.		Heparin was given to patients to manage clotting time. They were also given aspirin postoperatively (indefinitely). In the	
Sex: 59% male		An additional patient had a stroke which was considered minor 215 days after the procedure.			
Patient selection criteria: history of TIA or stroke or at least 1 (Europe) or 2 (North America) of: congestive heart failure or left ventricular ejection fraction < 40%, history of systolic hypertension > 160 mm Hg, diabetes, ≥ 65 years old, history of MI or known coronary stenosis, moderate or dense spontaneous echocardiographic contrast or		A TOE in both patients who had a stroke showed a stable device and no thrombogenic layer on the surface of the device at 1- and 6-month follow-up. Doppler color flow at 6 months showed a ‘trace leak’ and ‘absent leak’ in these patients, respectively (no other details provided).			
		Three TIAs occurred in 2 patients (no other details provided).			
		The overall stroke rate reported was 2.2% but it is not clear if TIAs were included in this figure and what the denominator was (2 out of 97 patients is 2.1%).			
				</	

Abbreviations used: ASD, atrial septal defect; AF, atrial fibrillation; CABG, coronary artery bypass grafting; CHADS ₂ , cardiac failure, hypertension, age, diabetes, stroke (doubled); CrI, credible interval; CV, cardiovascular; ECG, electrocardiogram; INR, international normalised ratio; ITT, intention to treat; LAA, left atrial appendage; MI, myocardial infarction; NIHSS, National Institute for Health Stroke Scale; PFO, patent foramen ovale; PLAATO, percutaneous left atrial appendage transcatheter occlusion; RCT, randomised controlled trial; TIA, transient ischaemic attack; TOE, transoesophageal echocardiography			
Study details	Key efficacy findings	Key safety findings	Comments
blood flow velocity $\leq$ 20 cm/s in the LAA. Exclusion criteria: thrombus formation in left atrium or LAA and complex aortic plaque, valve stenosis or regurgitation, left atrial diameter > 6.5 cm, acute MI or unstable angina, recent stroke (< 2 months), symptomatic carotid disease Technique: implantation of PLAATO under local or general anaesthetic. Mean follow-up: 9.8 months (74 completed 1 year) Conflict of interest/source of funding: supported by manufacturer		was started. ^b Resolved with aspirin and clopidogrel. ^c In 2 patients this occurred because of catheter manipulation while attempting to access LAA after trans-septal puncture, which the authors reported occurred in the first treated patients at a new site so it was likely attributed to lack of experience. There were 5.4% (6/111) deaths which the authors claimed were not device or procedure-related. Causes included cardiac or neurological death (4), secondary complications after gastrointestinal bleeding (1) and incarcerated hernia (1).	North American centres, clopidogrel and sub-acute endocarditis prophylaxis were also given postoperatively (for 4–6 weeks and 6 months, respectively). Administration of these in European centres was left to investigator's discretion. - The authors claim that the deaths were not related to the device or procedure, but this is questionable, particularly for the cardiac or neurological deaths. Other issues: - This study was included in the original overview. - PLAATO device is no longer being manufactured.

Abbreviations used: ASD, atrial septal defect; AF, atrial fibrillation; CABG, coronary artery bypass grafting; CHADS ₂ , cardiac failure, hypertension, age, diabetes, stroke (doubled); CrI, credible interval; CV, cardiovascular; ECG, electrocardiogram; INR, international normalised ratio; ITT, intention to treat; LAA, left atrial appendage; MI, myocardial infarction; NIHSS, National Institute for Health Stroke Scale; PFO, patent foramen ovale; PLAATO, percutaneous left atrial appendage transcathether occlusion; RCT, randomised controlled trial; TIA, transient ischaemic attack; TOE, transoesophageal echocardiography																																				
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Sick PB (2007)⁵ Case series USA Recruitment period: not reported Study population: patients with documented chronic or paroxysmal non-valvular AF who were eligible for warfarin therapy (CHADS₂ score 1.8, average LAA diameter 19.66 mm) n = 75 Mean age: 68.5 years Sex: 64% male Patient selection criteria: over 18 years with life expectancy of at least 2 years, with minimum CHADS₂ score 1 Exclusion criteria: congenital heart disease, symptomatic carotid disease or valvular disease, aortic arch atheroma, prosthetic valve, intracardiac thrombus, left ventricular ejection < 35%, multiple pacemaker lead, implanted cardioverter-defibrillator, hypercoagulable state or pregnancy.	Number of patients analysed: 75 Incidence of thromboembolic events No strokes occurred at mean follow-up of 24 months despite most patients (> 90%) having discontinued anticoagulation There were two TIAs: - 1 at 6 months; a smooth layer of thrombus was visible on the device - 1 in a patient with a history of TIA at 4 months. There was no thrombus visible on the device. (no other details provided of the patients with TIA) Successful placement 88% (66/75) had successful placement of device; in the remaining patients, trans-septal sheath could not be placed because of scar in right groin (1), core wire malfunction (1) and an unsuitable anatomy for device placement (7). Successful occlusion (at 45 days) The closure was successful in 93% (54/58) of patients at 45-day follow-up; 5 patients were late for follow-up and their results were not reported, 3 were lost to follow-up. Successful occlusion (at 6 months) Of the 60 patients who were followed-up at 6 months, 91.7% (55/60) had discontinued warfarin therapy.	Complications <table><thead><tr><th>Event</th><th>1st generation device (n = 16)</th><th>2nd generation device (n = 59)</th></tr></thead><tbody><tr><td>Device embolisation (retrieved percutaneously)</td><td>2^a</td><td>0</td></tr><tr><td>Air embolisation</td><td>1^b</td><td>0</td></tr><tr><td>Delivery wire fracture requiring surgical removal^c</td><td>1</td><td>0</td></tr><tr><td>Wire failure with no consequences</td><td>1</td><td>0</td></tr><tr><td>Flat thrombus on device noted at 6 and 12 months resolved with anticoagulation</td><td>0</td><td>4^d</td></tr><tr><td>Femoral pseudoaneurysm</td><td>1</td><td>1</td></tr><tr><td>Cardiac tamponade/pericardial effusion^e</td><td>1</td><td>1</td></tr><tr><td>Minor pericardial effusion with no treatment</td><td>0</td><td>3</td></tr><tr><td>Minor bleeding with haematomas in groin requiring transfusion</td><td colspan="2">2^f</td></tr><tr><td>Death not related to device^g</td><td>2</td><td>0</td></tr></tbody></table> ^a 1 patient had internal bleeding because of retrieval but	Event	1 st generation device (n = 16)	2 nd generation device (n = 59)	Device embolisation (retrieved percutaneously)	2 ^a	0	Air embolisation	1 ^b	0	Delivery wire fracture requiring surgical removal ^c	1	0	Wire failure with no consequences	1	0	Flat thrombus on device noted at 6 and 12 months resolved with anticoagulation	0	4 ^d	Femoral pseudoaneurysm	1	1	Cardiac tamponade/pericardial effusion ^e	1	1	Minor pericardial effusion with no treatment	0	3	Minor bleeding with haematomas in groin requiring transfusion	2 ^f		Death not related to device ^g	2	0	Follow-up issues: • Follow-up with TOE at 45 days and 6 months; follow-up every year with TOE for up to 5 years in case of clinical necessity. • 3 were lost to follow-up at 45 days; 5 had late follow-up. • 2 were not followed up at 6 months; 4 had late follow-up. Study design issues: • This study was a pilot/feasibility trial at 3 European cardiac centre and 4 American centres. • A revised device with reinforced delivery cable and a series of barbs to attach the device better was given to patients after first 16 were given older device. • The article states that 53 patients were treated with this device but a table states that this figure was 59 patients.
Event	1 st generation device (n = 16)	2 nd generation device (n = 59)																																		
Device embolisation (retrieved percutaneously)	2 ^a	0																																		
Air embolisation	1 ^b	0																																		
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Abbreviations used: ASD, atrial septal defect; AF, atrial fibrillation; CABG, coronary artery bypass grafting; CHADS ₂ , cardiac failure, hypertension, age, diabetes, stroke (doubled); CrI, credible interval; CV, cardiovascular; ECG, electrocardiogram; INR, international normalised ratio; ITT, intention to treat; LAA, left atrial appendage; MI, myocardial infarction; NIHSS, National Institute for Health Stroke Scale; PFO, patent foramen ovale; PLAATO, percutaneous left atrial appendage transcatheter occlusion; RCT, randomised controlled trial; TIA, transient ischaemic attack; TOE, transoesophageal echocardiography			
Study details	Key efficacy findings	Key safety findings	Comments
Technique: Implantation with WATCHMAN system with administration of heparin during implantation; warfarin (for 45 days) and aspirin (indefinitely). Mean follow-up: 24 months (13 for 4+ years, 20 for 3+ years and 29 for 2+ years) Conflict of interest/source of funding: not reported		was discharged with no sequelae. ^b This patient was discharged from hospital without adverse consequences, but the device was not implanted (it is unclear if this patient was one of the 9 patients reported in the efficacy section who did not have successful implantation of the device). ^c Authors state that this problem was avoided with second generation devices (uncertain if this is the same patient reported in efficacy section with core wire malfunction) ^d This was from the table of the study. The text in the study describes 3 patients with thrombus formation on atrial surface of device without neurological symptoms. This discrepancy is not clear. The study states that after 6 months of warfarin, all thrombi had resolved; however, it also states that 1 patient was noncompliant (not clear if thrombi in this patient was also resolved). ^e 1 was related to an overly vigorous 'tug' to determine if device was stable ^f This outcome was not included in a table in the study and it is not clear which generation of device these patients were treated with ^g From ascending aortic dissection and multi-organ failure after bowel surgery.	Other issues: - There appear to be some inconsistencies between figures given in the tables and in the text of the study. - Authors state that they now give aspirin and clopidogrel between 45 days and 6 months to facilitate the endothelialisation process.

Abbreviations used: ASD, atrial septal defect; AF, atrial fibrillation; CABG, coronary artery bypass grafting; CHADS ₂ , cardiac failure, hypertension, age, diabetes, stroke (doubled); CrI, credible interval; CV, cardiovascular; ECG, electrocardiogram; INR, international normalised ratio; ITT, intention to treat; LAA, left atrial appendage; MI, myocardial infarction; NIHSS, National Institute for Health Stroke Scale; PFO, patent foramen ovale; PLAATO, percutaneous left atrial appendage transcatheter occlusion; RCT, randomised controlled trial; TIA, transient ischaemic attack; TOE, transoesophageal echocardiography													
Study details	Key efficacy findings	Key safety findings	Comments										
Park (2009)⁸ Case series (registry) Germany Recruitment period: not reported Study population: patients with AF with contraindication or rejection of anticoagulation therapy (65 permanent, 8 paroxysmal) n = 73 Mean age: 72.7 years Sex: 50.7% male Patient selection criteria: thomboembolic event despite sufficient anticoagulation, major gastrointestinal bleeding, major bleeding of other source, unstable international normalised ratio, increase bleeding risk after anticoagulation Exclusion criteria: congenital heart disease, persistent foramen ovale (particularly if combined with atrial septal aneurysm. Technique: Implantation with PLAATO followed by daily	Number of patients analysed: 71 Incidence of thromboembolic events There were no cases of major adverse cerebrovascular or cardiovascular events in 24 months of follow-up. One patient had a minor stroke which resolved within 24 hours with heparin therapy (time of occurrence not reported).	<table><tr><th colspan="2">Complications</th></tr><tr><th>Event</th><th>No. of patients</th></tr><tr><td>Death from device embolisation</td><td>1</td></tr><tr><td>Unstable implant requiring open heart surgery</td><td>1</td></tr><tr><td>Pericardial effusion from LAA tip perforation not requiring pericardial puncture</td><td>1</td></tr></table> (the first patient had cardiac arrest 30 minutes after the procedure because the device which embolised occluded the left ventricular outflow tract; time of other events not reported) Mortality In addition to the periprocedural death, 10 more patients died during follow-up from lung cancer (1), colon cancer (1), stomach perforation (1), acute right-heart failure due to pulmonary embolism (1) and cardiac arrest (2) (known dilated cardiomyopathy or nonobstructive hypertrophic cardiomyopahty, respectively; both had implanted internal defibrillators), four died a natural death at home (as determined by the family practitioners' death certificate; 3 had coronary artery disease and 2 had previous CABG). None of these patients died because of a stroke.	Complications		Event	No. of patients	Death from device embolisation	1	Unstable implant requiring open heart surgery	1	Pericardial effusion from LAA tip perforation not requiring pericardial puncture	1	Follow-up issues: - Clinical evaluation with TOE 3–6 months after implantation, but only 52 patients agree to have TOE. - All patients (except the 2 with serious safety events) were followed up for 24 months, mostly by telephone. Study design issues: - This is a report of all consecutive patients treated at one centre Study population issues: - In 6 patients, baseline TOE revealed LAA thrombus so the procedure was delayed for 10 days while patients were treated with low-molecular-weight heparin. 9 patients required the implant to be removed and replace with a different size
Complications													
Event	No. of patients												
Death from device embolisation	1												
Unstable implant requiring open heart surgery	1												
Pericardial effusion from LAA tip perforation not requiring pericardial puncture	1												

IP overview: Percutaneous occlusion of the left atrial appendage in non-valvular atrial fibrillation for the prevention of thromboembolism

Abbreviations used: ASD, atrial septal defect; AF, atrial fibrillation; CABG, coronary artery bypass grafting; CHADS ₂ , cardiac failure, hypertension, age, diabetes, stroke (doubled); CrI, credible interval; CV, cardiovascular; ECG, electrocardiogram; INR, international normalised ratio; ITT, intention to treat; LAA, left atrial appendage; MI, myocardial infarction; NIHSS, National Institute for Health Stroke Scale; PFO, patent foramen ovale; PLAATO, percutaneous left atrial appendage transcatheter occlusion; RCT, randomised controlled trial; TIA, transient ischaemic attack; TOE, transoesophageal echocardiography			
Study details	Key efficacy findings	Key safety findings	Comments
aspirin and clopidogrel for 6 months. Follow-up: 24 months Conflict of interest/source of funding: no conflicts			implant. Other issues: The authors estimated that 7 strokes were to be expected in this group of patients.

Abbreviations used: ASD, atrial septal defect; AF, atrial fibrillation; CABG, coronary artery bypass grafting; CHADS ₂ , cardiac failure, hypertension, age, diabetes, stroke (doubled); CrI, credible interval; CV, cardiovascular; ECG, electrocardiogram; INR, international normalised ratio; ITT, intention to treat; LAA, left atrial appendage; MI, myocardial infarction; NIHSS, National Institute for Health Stroke Scale; PFO, patent foramen ovale; PLAATO, percutaneous left atrial appendage transcathether occlusion; RCT, randomised controlled trial; TIA, transient ischaemic attack; TOE, transoesophageal echocardiography													
Study details	Key efficacy findings	Key safety findings	Comments										
Block (2009)⁹ Case series USA and Canada Recruitment period: up to 2003 (start date not written) Study population: patients with non-rheumatic, (either permanent or paroxysmal) AF n = 64 Mean age: 73 years Sex: 60.9% male Patient selection criteria: patients at high-risk for developing thromboembolic events or stroke and not candidates for long-term warfarin, CHADS₂ score ≥ 2 Exclusion criteria: left ventricular thrombus, mobile or planar clot in left atrium or LAA, stroke within 2 months, prior intracranial haemorrhage or cardiac surgical procedure for LAA, moderate or worse mitral stenosis or mitral regurgitation, left atrial diameter < 6.5cm, prosthetic heart valve or inferior vena cava filter, endocarditis, other infection, acute MI, unstable angina, percutaneous	Number of patients analysed: 61 <i>Incidence of major adverse events</i> (defined as new major or minor stroke, cardiac or neurological death, myocardial infarction or requirement for cardiovascular surgery related to the procedure). 30-day freedom from major adverse events was 98.4% (63/64). One patient required cardiovascular surgery and died (reason for surgery not described). Throughout the study, there were 8 strokes: - 5 were major (the signs of the stroke were present for more than 7 days or had an increased NIHSS more than 4) each occurring 216, 979, 1004, 1043 and 1586 days after the procedure (approximately 7, 33, 34, 35 and 53 months). - 3 were minor (resolved within 7 days or increased NIHSS by < 3) each occurring at 255, 274 and 689 days after the procedure (approximately 8.5, 9 and 23 months) The treatment of these patients and final outcome (i.e. survival of these specific patients) was not clearly described in the study. (It was not stated by the paper whether or not these were haemorrhagic or thromboembolic strokes.)	<i>Complications</i> There were no device failures or malfunctions. <table><tr><th>Event</th><th>No. of patients</th></tr><tr><td>Cardiac tamponade requiring surgery*</td><td>1</td></tr><tr><td>Cerebral haemorrhage/death</td><td>1</td></tr><tr><td>Myocardial infarction</td><td>1</td></tr><tr><td>Congestive heart failure</td><td>12**</td></tr></table> *this was the only event said to be attributable to the implant **occurred 35 times in these patients and related to exacerbation of pre-existing condition <i>Mortality</i> There were 17 deaths during the study period. None were said to be device or procedure related and all related to comorbidities such as renal failure, congestive heart failure	Event	No. of patients	Cardiac tamponade requiring surgery*	1	Cerebral haemorrhage/death	1	Myocardial infarction	1	Congestive heart failure	12**	Follow-up issues: • At 1-, 3-, and 6-month follow-up and then annually for 5 years (included 12-lead ECG, NIHSS score, blood count, chest X-ray; 1st 20 patients had TOE at 1 and 6 month and others had transthoracic echocardiogram). • 1 patient was lost to follow-up at 1 year. Study design issues: • This was a multi-centre study. • A clinical events committee of invasive and noninvasive cardiologists and neurologists in clinical practice adjudicated complications in a blinded fashion to be categorise the severity of the event. Study population issues: 51.6% (33/64) were
Event	No. of patients												
Cardiac tamponade requiring surgery*	1												
Cerebral haemorrhage/death	1												
Myocardial infarction	1												
Congestive heart failure	12**												

IP overview: Percutaneous occlusion of the left atrial appendage in non-valvular atrial fibrillation for the prevention of thromboembolism

Abbreviations used: ASD, atrial septal defect; AF, atrial fibrillation; CABG, coronary artery bypass grafting; CHADS ₂ , cardiac failure, hypertension, age, diabetes, stroke (doubled); CrI, credible interval; CV, cardiovascular; ECG, electrocardiogram; INR, international normalised ratio; ITT, intention to treat; LAA, left atrial appendage; MI, myocardial infarction; NIHSS, National Institute for Health Stroke Scale; PFO, patent foramen ovale; PLAATO, percutaneous left atrial appendage transcatheter occlusion; RCT, randomised controlled trial; TIA, transient ischaemic attack; TOE, transoesophageal echocardiography			
Study details	Key efficacy findings	Key safety findings	Comments
coronary intervention or CABG within 1 month, complex aortic plaque, symptomatic atherosclerotic carotid artery disease, requirement of warfarin for other disease, contraindication to aspirin or other medications prescribed, known hypercoagulability, other medical conditions such as oesophageal varices, life expectancy < 2 years, or inability to lie flat for procedure pregnancy. Technique: Implantation with PLAATO followed by daily clopidogrel for 4–6 weeks and daily aspirin indefinitely. Mean follow-up: 3.75 years (up to 5 years) Conflict of interest/source of funding: the research was supported by ev3 Inc.			diagnosed with AF for more than 3 years at baseline.

Abbreviations used: ASD, atrial septal defect; AF, atrial fibrillation; CABG, coronary artery bypass grafting; CHADS ₂ , cardiac failure, hypertension, age, diabetes, stroke (doubled); CrI, credible interval; CV, cardiovascular; ECG, electrocardiogram; INR, international normalised ratio; ITT, intention to treat; LAA, left atrial appendage; MI, myocardial infarction; NIHSS, National Institute for Health Stroke Scale; PFO, patent foramen ovale; PLAATO, percutaneous left atrial appendage transcatheter occlusion; RCT, randomised controlled trial; TIA, transient ischaemic attack; TOE, transoesophageal echocardiography			
Study details	Key efficacy findings	Key safety findings	Comments
Ussia GP (2009)⁶ Case series Italy Recruitment period: 2004–2007 Study population: patients with non-valvular AF with contraindications to anticoagulant therapy with a high risk of stroke (60% had previous stroke/TIA) n = 20 Age: 69 years Sex: 65% male Patient selection criteria: contraindication to oral coagulant, left ventricular ejection fraction > 20%, no left atrial thrombi, LAA diameter > 22 mm, CHADS₂ ≥ 2 or 1 plus spontaneous echocardiographic contrast. Exclusion criteria: contraindication to TOE, trans-septal puncture, prosthetic valves, mitral or aortic disease, caval filters or masses, intracardiac masses or thrombi, complex aortic plaque, recent MI or unstable	Number of patients analysed: 18 (2 were found not to be suitable for the procedure) <i>Incidence of thromboembolic events</i> There were no adverse embolic events in the mean 40-month follow-up period. <i>Procedural success</i> 90% (18/20) of patients had procedure success (this was defined as successful device deployment with no residual leaks as determined by transoesophageal echocardiogram). Occlusion was not possible in 2 patients because of the presence of a multi-lobed LAA. <i>Mild leaks</i> After the device was positioned, 3 patients had mild leaks (these were defined as filling one-third of the LAA; subsequent treatment of these leaks was not reported).	<i>Complications</i> The device needed to be refitted in 2 patients: - unsatisfactory compression diameter and reinsertion of a larger device - device expansion caused severe systemic hypotension with signs of pericardial effusion after device expansion. This was due to incorrect positioning of the device which was collapsed, retracted a few mm and then re-expanded. When haemodynamic stabilisation was achieved, the PFO in this patient was subsequently closed. One patient died from gastric cancer 36 months after the procedure.	Follow-up issues: • Transthoracic echocardiogram at 1, 3 and every 6 months; TOE at 6 months. Phone interview at 24 months. • There was no reported loss to follow-up. Study design issues: • 37 patients were screened, 20 fit selection criteria but occlusion was not possible in 2 patients because of the presence of multi-lobed LAA. • Primary endpoints were reduction of stroke rate and cardioembolic events. Study population issues: • 2 patients also had closure of the PFO during the same session after occlusion of the LAA. • PLAATO device is no longer being manufactured.

Abbreviations used: ASD, atrial septal defect; AF, atrial fibrillation; CABG, coronary artery bypass grafting; CHADS ₂ , cardiac failure, hypertension, age, diabetes, stroke (doubled); CrI, credible interval; CV, cardiovascular; ECG, electrocardiogram; INR, international normalised ratio; ITT, intention to treat; LAA, left atrial appendage; MI, myocardial infarction; NIHSS, National Institute for Health Stroke Scale; PFO, patent foramen ovale; PLAATO, percutaneous left atrial appendage transcatheter occlusion; RCT, randomised controlled trial; TIA, transient ischaemic attack; TOE, transoesophageal echocardiography			
Study details	Key efficacy findings	Key safety findings	Comments
angina or planned surgical intervention Technique: implantation of PLAATO followed by administration of aspirin in the long term and 250 mg ticlopidine for 6 months (also had day before procedure) Mean follow-up: 40 months Conflict of interest/source of funding: none			

Abbreviations used: ASD, atrial septal defect; AF, atrial fibrillation; CABG, coronary artery bypass grafting; CHADS ₂ , cardiac failure, hypertension, age, diabetes, stroke (doubled); CrI, credible interval; CV, cardiovascular; ECG, electrocardiogram; INR, international normalised ratio; ITT, intention to treat; LAA, left atrial appendage; MI, myocardial infarction; NIHSS, National Institute for Health Stroke Scale; PFO, patent foramen ovale; PLAATO, percutaneous left atrial appendage transcatheter occlusion; RCT, randomised controlled trial; TIA, transient ischaemic attack; TOE, transoesophageal echocardiography			
Study details	Key efficacy findings	Key safety findings	Comments
Meier (2003)⁷ Case series USA, Switzerland Recruitment period: not reported Study population: patients with AF assessed to be free of mobile thrombi by TOE n = 16 Mean age: 66 years Sex: 81% male Patient selection criteria: not reported Technique: implantation of Amplatzer septal occluder with local anaesthesia (2 general) with no TOE or X-ray guidance, antibiotic prophylaxis, heparin and anticoagulant given during the procedure, aspirin and clopidogrel postoperatively until device positioning confirmed by TOE. Mean follow-up: 4 months Conflict of interest/source of funding: not reported	Number of patients analysed: 16 Thromboembolic events There were no thromboembolic episodes stemming from the LAA in an average follow-up of 4 months. Echocardiographic follow up had found the device to be in a stable position with complete occlusion achieved, and absence of thrombus all but one case. All patients were discharged the day following the intervention.	Complications Device embolisation into the left atrium occurred in 1 patient a few minutes after implantation. The device selected was discovered to be too large and only partially unfolded in the LAA. The patient remained asymptomatic, but the device was removed surgically while performing an operation to close the ASD and obliterate both the right and left atrial appendages.	Follow-up issues: - Patients were assessed with TOE a few months after the operation (no other details reported). Study design issues: - This was a 4 centre study. - One centre continued to treat patients with warfarin for 6 weeks after the procedure. Study population issues: - It was reported that patients with a PFO or ASD did not receive a septal puncture. Other issues: - This study was included in the original overview.

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Efficacy

An RCT of 707 patients reported 2.2 ischaemic strokes per 100 patient-years among patients treated with percutaneous LAA closure vs. 1.6 events among patients treated with warfarin over a mean follow-up of 18 months (rate ratio 1.34, credible interval [CrI] 0.60–4.29; intention-to-treat analysis)¹. Of the 14 strokes that occurred in patients treated with the LAA occluder, 1 occurred before the procedure, 5 were procedure-related and 9 occurred after the peri-procedure timeframe. Two strokes (1 in each group) were fatal and 2 patients with ischaemic stroke in the intervention group died later in a nursing home.

Haemorrhagic stroke was reported to have occurred in 0.1 per 100 patient-years in the intervention group compared with 1.6 per 100 patient-years in the control group. One occurred in a patient in the intervention group within 45 days of the procedure (the patient was still on warfarin). Five of the 6 patients with haemorrhagic strokes in the control group resulted in death.

Systemic embolism was reported to have occurred in 2 patients in the intervention group (0.3 per 100 patient-years). None occurred in the control group).

The RCT reported all-cause mortality to be 3.0 per 100 patient-years in patients who received an implant compared with 4.8 per 100 patient-years in patients treated with warfarin. There were 21 deaths in the intervention group (2 from stroke, 4 from unknown or cardiovascular causes and 15 from non-cardiovascular causes such as cancer and urosepsis) compared with 18 in the control group (6 from stroke, 6 from unknown or other cardiovascular causes and 6 from non-cardiovascular causes such as pneumonia).

A case series of 111 patients reported stroke in 2 patients. One stroke, which was considered to be major, occurred 173 days after the procedure and the other which was considered to be minor occurred 215 days after the procedure. TOE at 1- and 6-months revealed a stable device in both patients and no thrombogenic layer on the surface of the device. Three transient ischaemic attacks occurred in 2 patients (no other details given)⁴.

A case series of 75 patients reported that no strokes had occurred at a mean follow-up of 24 months in the 66 patients who had successful device placement, despite most patients having discontinued anticoagulation (patients were given warfarin for 45 days after the operation to facilitate epithelialisation)⁵.

A case series of 73 patients reported no major cerebrovascular or cardiovascular events in 24 months of follow-up. One patient had a minor stroke which was resolved with heparin within 24 hours (time of occurrence not reported)⁸.

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A case series of 64 patients reported that 5 incidences of a major stroke approximately 7, 33, 34, 35 and 53 months after the procedure. There were 3 incidences of a minor stroke (resolved within 7 days) approximately 8.5, 9 and 23 months after the procedure (sequelae of these patients not clearly described)⁹.

A case series of 20 patients reported no embolic events in the 18 patients treated with this procedure at a mean follow-up of 40 months (2 patients were not treated because of the presence of a multi-lobed LAA)⁶.

A case series of 16 patients treated with LAA occlusion reported that there were no thromboembolic episodes stemming from the LAA in any patient at a mean follow-up of 4 months⁷.

Safety

Death

The case series of 111 patients reported 1 patient who had cardiac tamponade requiring pericardiocentesis, median sternotomy and ligation of the LAA 4 hours after the procedure. The patient later developed right leg deep vein thrombosis and died 27 days after the procedure. The authors suggested that this may have been due to a cerebral haemorrhage after anticoagulation was started⁴.

The case series of 73 patients reported that one patient suffered a cardiac arrest 30 minutes after the procedure because the device embolised, occluding the left ventricular outflow tract⁸.

The case series of 64 patients reported cerebral haemorrhage and death in one patient (time of occurrence not reported)⁹.

Device embolisation

The RCT reported device embolisation in 0.6% (3/463) of patients: 1 detected during the procedure and 2 discovered on transoesophageal echocardiography 45 days after the procedure¹ (one was removed percutaneously with a vascular snare and the other two underwent surgery; no other details provided). A separate case report from this trial reported device embolisation in 1 patient, which required surgical removal from the aortic valve, and replacement with a prosthetic valve². It is likely that this is the same patient that was reported by the RCT to have embolisation during the procedure.

The case series of 75 patients reported device embolisation which was retrieved percutaneously in 2 patients. One patient suffered from internal bleeding because of the retrieval but was later discharged with no sequelae. The same study

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reported wire fracture with no consequence in 1 patient and delivery wire fracture requiring surgical removal in another⁵.

The case series of 16 patients reported device embolisation in the left atrium a few minutes after implantation in 1 patient. This was attributed to an incorrect device size; both the left and right atrial appendages were obliterated surgically during an operation that included removal of the device and closure of an atrial septal defect (time of event not reported)⁷.

Other

The RCT reported pericardial effusion successfully treated surgically or with pericardiocentesis in 5% (22/463), pericardial effusion not requiring drainage in 2% (8/463), oesophageal tear in 0.2% (1/463) and procedure-related arrhythmia in 0.2% (1/463) (time of occurrence not reported for all outcomes).

A separate case report on a patient included in this trial reported the development of *Staphylococcus aureus* in blood cultures taken from a patient treated by pericardiocentesis after pericardial effusion³.

The case series of 111 patients reported pericardial effusion treated successfully with pericardiocentesis in 3.6% (4/111) of patients. Left atrial thrombus at the time of the procedure (no other details provided), perforation of right femoral artery when trying to access the right femoral vein (both preventing the implantation of the device), laminar growth on the superior edge of the occluder 6 months after the procedure requiring aspirin and clopidogrel (no other details provided), dyspnoea requiring reintubation, left-sided haemothorax, right leg deep vein thrombosis and brachial plexus palsy in 1 patient each were also reported.

The same case series of 111 patients reported deaths in 5.4% (6/111) of patients, which the authors reported were not device or procedure-related (4 cardiac or neurological death, 1 from secondary complications after gastrointestinal bleeding and 1 from incarcerated hernia).

The case series of 75 patients reported air embolisation in 1 patient during the procedure. This patient was not implanted with the device but was released without adverse consequences⁵. The same study (in which 66 devices were placed successfully) reported femoral pseudoaneurysm in 3% (2/66), cardiac tamponade/pericardial effusion in 3% (2/66), minor pericardial effusion with no treatment in 5% (3/66) and a flat thrombus on the device which was resolved with anticoagulation in 6% (4/66) of patients 6 and 12 months after implantation⁵.

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The case series of 73 patients reported that one implant required open-heart surgery because the device was unstable. Another patient in this study had pericardial effusion because of perforation of the appendage, but a pericardial puncture was not necessary⁸.

The case series of 64 patients reported cardiac tamponade requiring surgery in 1 patient (time of occurrence not reported). Another patient in this study was reported to have had a myocardial infarction but no other details were provided⁹.

Validity and generalisability of the studies

- The previous overview included 2 case series and data on safety from an abstract (case series included in this overview^{1, 5}) including a total of 127 patients (plus 39 in the abstract) with at least 74 patients who completed 12 months of follow-up. This overview includes 1 RCT, 2 case reports of safety from patients included in the RCT, and 6 case series including 1069 patients with at least 14 patients who completed 4 years of follow-up, and a number of patients who completed 5 year follow-up (the study which reported up to 5-year follow-up did not report how many patients were followed up for this length of time⁹).
- LAA occlusion may offer an alternative treatment for patients at risk of thromboembolic stroke who for various reasons are unable to take anticoagulation. The RCT published since the previous overview specifically excludes patients who have a contraindication to anticoagulants (although warfarin was used for up to 6 months in some patients).
- An RCT on the occlusion of the LAA during coronary artery bypass grafting was excluded because it was not performed percutaneously (also, the authors occluded the appendage with sutures or staples).

Existing assessments of this procedure

The guideline on 'Management of patients with stroke or TIA: assessment, investigation, immediate management and secondary prevention' published in December 2008 by the Scottish Intercollegiate Guidelines Network recommended that:

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Left atrial appendage occlusion should only be considered as part of a randomised controlled clinical trial.

In April 2009, the US Food and Drug Administration gave the WATCHMAN device 'Approval' with the following conditions:

- 1. Indications to be changed to [use as a non-inferior treatment to long-term warfarin therapy in patients with non-valvular atrial fibrillation to reduce the risk of ischemic stroke, cardiovascular or unexplained death, and systemic embolization]*
- 2. Postapproval registry of approximately 2000 newly enrolled patients, followed to at least 2 years to evaluate acute procedural and longer term outcomes, similar to those from the pivotal study, with FDA to make the final recommendations with respect to study size. In addition, that the patients enrolled in the premarket trial (PROTECT AF), both arms, be followed for 5 years.*
- 3. Physician certification program [to involve a certification program for implanting physicians, including a minimum of three guided successful implantations, proficiency in trans-septal catheterization and an on-line training program for trans-esophageal echocardiography (TEE) operators]*
- 4. Labeling to specify that device implantation should only be performed at institutions where cardiac surgeon and facilities for cardiac surgery are accessible (urgently available).*

Related NICE guidance

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

Interventional procedures

- Percutaneous (non-thoracoscopic) epicardial catheter radiofrequency ablation for atrial fibrillation. NICE interventional procedures guidance 294. Available from www.nice.org.uk/IPG294.
- Percutaneous radiofrequency catheter ablation for atrial fibrillation. NICE interventional procedures guidance 168. Available from www.nice.org.uk/IPG168.
- Thoracoscopic epicardial radiofrequency ablation for atrial fibrillation. NICE interventional procedures guidance 286. Available from www.nice.org.uk/IPG286.

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- Radiofrequency ablation for atrial fibrillation in association with other cardiac surgery. NICE interventional procedures guidance 121. Available from www.nice.org.uk/IPG121.
- Microwave ablation for atrial fibrillation in association with other cardiac surgery. NICE interventional procedures guidance 122. Available from www.nice.org.uk/IPG122.
- Cryoablation for atrial fibrillation in association with other cardiac surgery. NICE interventional procedures guidance 123. Available from www.nice.org.uk/IPG123.
- High intensity focused ultrasound ablation for atrial fibrillation as an associated procedure with other cardiac surgery. NICE interventional procedures guidance 184. Available from www.nice.org.uk/IPG184.

Clinical guidelines

- The management of atrial fibrillation. NICE clinical guideline 36. Available from www.nice.org.uk/CG36.

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.

Dr Stephen Brecker, Dr Jonathan Townend, British Cardiovascular Intervention Society, Mr Malcolm Dalrymple-Hay, Mr Steven Hunter, Mr Jonathan Hyde, Society of Cardiothoracic Surgeons of Great Britain and Ireland.

- The Specialist Advisers reported that the comparator is anticoagulation, aspirin, aspirin plus clopidogrel, no treatment or surgical LAA occlusion.
- One Adviser commented that they have started using the Amplatzer cardiac plug which has not has published clinical results.
- The Specialist Advisers highlighted that this procedure is indicated for patients who cannot tolerate warfarin or have contraindications to warfarin.
- Didactic and simulator training is required to before performing the procedure, followed by formal mentoring.
- Key efficacy outcomes are freedom from stroke, adverse cardiac and neurological events.

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- In addition to the events reported in the literature, Specialist Advisers stated theoretical adverse events include inability to recover an incorrectly positioned device by endovascular means, so requiring emergency surgery; persistent atrial septal defect, femoral vein injury and perforation requiring percutaneous or cardiac surgical drainage.

Patient Commentators' opinions

NICE's Patient and Public Involvement Programme was unable to obtain patient commentary for this procedure.

Issues for consideration by IPAC

- The original overview stated that 3 devices could be used for this procedure. Two of these devices (the WATCHMAN and PLAATO) were designed specifically for this procedure. PLAATO is no longer being manufactured because of financial difficulties. The third device (Amplatzer septal occluder) was not specifically designed for this indication. There is a new device specifically designed for this procedure (the Amplatzer Cardiac Plug) but there was no evidence on this procedure at the time of writing this overview.

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References

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3. Khumri TM, Thibodeau JB, Main ML. (2008) Transesophageal echocardiographic diagnosis of left atrial appendage occluder device infection. *European Journal of Echocardiography* 9:565–6.
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9. Block PC, Burstein S, Casale PN et al. (2009) Percutaneous left atrial appendage occlusion for patients with atrial fibrillation suboptimal for

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warfarin therapy: 5-year results of the PLAATO study. Journal of the American college of cardiology: Cardiovascular interventions: 594–600.

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Appendix A: Additional papers on percutaneous occlusion of the left atrial appendage in non-valvular atrial fibrillation for the prevention of thromboembolism

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.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Block PC. (2009) Percutaneous left atrial appendage closure in a patient with atrial fibrillation. Nature Clinical Practice Cardiovascular Medicine 3:456–9.	Case report n = 1 Follow-up = 2 years	Case report of a patient with successful occlusion 2 years after implantation of PLAATO.	Larger studies in table 2.
Brinkman V, Kalbfleisch S, Auseon A et al. (2009) Real time three-dimensional transoesophageal echocardiography-guided placement of left atrial appendage occlusion device 26:855–8.	Case report n = 1 Follow-up = 6 months	At 6 months, there appeared to be endothelialisation or fibrosis on the surface of the occlusion device.	Larger studies in table 2.
El-Chami MF, Grow P, Eilen D et al. (2007) Clinical outcomes three years after PLAATO implantation. Catheterisation and cardiovascular interventions 69:704–707.	Case series n = 11 Follow-up = 36 months	Of patients who received PLAATO, 1 had a stroke 3 years after the operation. No systemic embolic events and no long-term complications. One patient died 1 year after implantation but it was not thought to be because of the device.	Larger studies in table 2.
Hanna IR, Kolm P, Martin R et al. (2004) Left atrial structure and function after percutaneous left atrial appendage transcatheter occlusion (PLAATO): six-month echocardiographic follow-up. Journal of the American College of Cardiology 43:1868–72.	Case series n = 11 Follow-up = 6 months	PLAATO devices remained stable in sites at 6-month follow-up. No significant difference in pulmonary vein diameter and peak systolic and diastolic flow velocities from baseline.	Patient included in study in table 2 ² .
Ho IC, Neuzil P, Mraz T et al. (2007) Use of intracardiac echocardiography to guide implantation of a left atrial appendage occlusion device (PLAATO). Heart Rhythm 4:567–71.	Case series n = 10 Follow-up = 12 months	Intracardiac echocardiography confirmed stable implantation of PLAATO device	Study on alternative imaging for the procedure; larger studies in table 2.

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Jorgensen J, Palmer S, Kalogeropoulos A et al. (2007) Implantation of left atrial appendage occlusion devices and complex appendage anatomy: the importance of transesophageal echocardiography. <i>Echocardiography</i> 24:159–61.	Case report n = 1	TOE showed WATCHMAN device which otherwise appeared to be properly positioned was malpositioned.	Larger studies in table 2.
Kukuta K, Klopotoski M, Konka M et al. (2009) Left atrial appendage occlusion using the PLAATO system in high-risk patients with atrial fibrillation. <i>Postępy w Kardiologii Interwencyjnej</i> 5: 51–7.	Case series n = 6 Follow-up = 54 months	No cases of death, ischaemic stroke, or intracranial or gastrointestinal bleeding. No periprocedural complications.	Larger studies in table 2.
Mráz T, Neuzil P, Mandysova E et al. (2007) Role of echocardiography in percutaneous occlusion of the left atrial appendage. <i>Echocardiography</i> 24:401–4.	Case series n = 30 Follow-up = 1 month	Occlusion was successful in all patients. One patient had an irregular LAA shape and despite trying alternate device sizes, a mild-moderate leak was left but this decreased at 1 month follow-up. All other patients were still in place at 1-month follow-up.	Outcomes not on occurrence of thromboembolic events.
Nakai T, Lesh M, Ostermayer S et al. (2003) An endovascular approach to cardioembolic stroke prevention in atrial fibrillation patients. <i>Pacing & Clinical Electrophysiology</i> 26:1604–6.	Case report n = 1 Follow-up = 6 months	Successful implantation of PLAATO; no device migration or thrombus at 1- or 6-month follow-up.	Larger studies in table 2.
Omran H, Hardung D, Schmidt H et al. (2003) Mechanical occlusion of the left atrial appendage. <i>Journal of Cardiovascular Electrophysiology</i> 14:S56–9.	Case series n = 9 Mean follow-up = 5 months	Patients treated with PLAATO. No neurological complications on follow-up. One case of minor plexus paresis resolving in 4 weeks and 1 case of pericardial effusion 48 hours after procedure. No thrombi on TOE	Larger studies in table 2.
Omran H, Schmidt H, Hardung D et al. (2005) Post mortem analysis of a left atrial appendage	Case report n = 1 Follow-up = 1 year	Investigation of a patient who died 1 year after PLAATO implantation showed the device had	Larger studies in table 2.

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occlusion device (PLAATO) in a patient with permanent atrial fibrillation. Journal of Interventional Cardiac Electrophysiology 14:17–20.		occluded the device completely.	
Park JW, Gerk U, Franke RP et al. (2009) Post-mortem analysis of a left atrial appendage occlusion device (PLAATO) in a patient with permanent atrial fibrillation. Cardiology 112:205–8.	Case report n = 1 Follow-up = 2.5 years	Patient died (likely of sudden cardiac arrest) 2.5 years after successful PLAATO implantation. Post mortem examination showed stable device and no sign of thromboembolism.	Larger studies in table 2.
Schwartzman D, Katz WE, Smith AJ et al. (2007) Malpositioning of a left atrial appendage occlusion device? A case with implications for percutaneous transcatheter left atrial appendage occlusion device therapy. Heart Rhythm 4:648–50.	Case report n = 1 Follow-up = 45 days	Report of patient who received WATCHMAN device. TOE imaging at 45 days, 6 months and 1 year showed para-device leak but repeat CT imaging at 45 days showed that device had not properly occluded the appendage. Patient remained on warfarin.	Larger studies in table 2.
Stöllberger C, Finsterer J, Avanzini M et al. (2009) Risk of stroke and thrombus formation from delay incontinence of a PLAATO device in Friedreich ataxia. Clinical cardiology 32: E83–4.	Case report n = 1	Report of device leakage 2 years after implantation.	Larger studies in table 2.
Sievert H, Lesh MD, Trepels T et al. (2002) Percutaneous left atrial appendage transcatheter occlusion to prevent stroke in high-risk patients with atrial fibrillation: early clinical experience. Circulation 105:1887–9.	Case series n = 15 Follow-up = 1 month	Implantation of PLAATO was successful in all patients. No complications or embolic events during follow-up.	Patient already included in study in table 2 ² .
Ussia GP, Mangiafico S, Privitera A et al. (2006) Percutaneous left atrial appendage transcatheter occlusion in patients with chronic nonvalvular atrial fibrillation: early institutional experience. Journal of	Case series n=7 Follow-up=7 months	PLAATO successfully implanted without complication or thromboembolic or cardiac event at follow-up.	Larger studies in table 2.

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Cardiovascular Medicine 7:569–72.			
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Appendix B: Related NICE guidance for percutaneous occlusion of the left atrial appendage in non-valvular atrial fibrillation for the prevention of thromboembolism

Guidance	Recommendations
Interventional procedures	Percutaneous occlusion of the left atrial appendage for atrial fibrillation. NICE interventional procedures guidance 181 (2006). 1.1 Current evidence on the safety and efficacy of percutaneous occlusion of the left atrial appendage (LAA) for atrial fibrillation does not appear adequate for this procedure to be used without special arrangements for consent and for audit or research. 1.2 Clinicians wishing to undertake percutaneous occlusion of the LAA for atrial fibrillation 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 the public is recommended (available from www.nice.org.uk/IPG181publicinfo). • Audit and review clinical outcomes of all patients undergoing percutaneous occlusion of the LAA for atrial fibrillation. 1.3 This procedure should only be performed in specialist units where there are arrangements for cardiac surgery in the event of complications. 1.4 Patient selection is important. This procedure should only be performed in patients for whom normal medical treatment is unsuitable. 1.5 The Department of Health runs the Central Cardiac Audit Database (CCAD); clinicians are encouraged to enter all patients undergoing percutaneous occlusion of the LAA onto this database (www.ccad.org.uk). 1.6 Publication of safety and efficacy outcomes will be useful. The Institute may review the procedure upon publication of further evidence. Percutaneous (non-thoracoscopic) epicardial catheter radiofrequency ablation for atrial fibrillation. NICE interventional procedures guidance 294 (2009). 1.1 Current evidence on the safety and efficacy of percutaneous (non-thoracoscopic) epicardial catheter radiofrequency ablation for atrial fibrillation (AF) is inadequate in quantity. Therefore this procedure should only be used with special arrangements for clinical governance and consent. 1.2 Clinicians wishing to undertake percutaneous (non-thoracoscopic) epicardial catheter radiofrequency ablation for AF should take the

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	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/IPG294publicinfo). 1.3 Patient selection and treatment should be carried out only by a team specialising in the treatment of cardiac arrhythmias that includes experts in electrophysiology and ablation. 1.4 The procedure should only be carried out by interventional cardiologists with specific training in electrophysiology, and in accessing the pericardial space and performing complex ablation procedures. 1.5 The procedure should only be carried out in units with arrangements for emergency cardiac surgical support in case of complications. 1.6 The NHS Information Centre for health and social care runs the UK Central Cardiac Audit Database, and clinicians should enter details about all patients undergoing percutaneous (non thoracoscopic) epicardial catheter radiofrequency ablation for AF onto this database (www.ccad.org.uk). 1.7 Clinicians are encouraged to enter patients into research studies that aim to provide more information about patient selection, the use of this procedure as an adjunct to other procedures, freedom from AF in the long term and relief of associated symptoms, and the safety profile of the procedure. NICE may review the procedure on publication of further evidence. Percutaneous radiofrequency catheter 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
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	undergoing percutaneous radiofrequency ablation for atrial fibrillation onto this database (www.ccad.org.uk). 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/IPG286publicinfo). 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. 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
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	multidisciplinary team. Cardiac surgeons wishing to use this procedure should have specific training in the use of radiofrequency equipment. Microwave ablation for atrial fibrillation in association with other cardiac surgery. NICE interventional procedures guidance 122 (2005). 1.1 Current evidence on the safety and efficacy of microwave ablation for atrial fibrillation in association with other cardiac surgery appears adequate to support the use of this procedure provided that the normal arrangements are in place for consent, audit and clinical governance. 1.2 Patient selection and follow-up should be carried out by a multidisciplinary team. Cardiac surgeons wishing to use this procedure should have specific training in the use of microwave energy equipment. Cryoablation for atrial fibrillation in association with other cardiac surgery. NICE interventional procedures guidance 123 (2005). 1.1 Current evidence on the safety and efficacy of cryoablation for atrial fibrillation in association with other cardiac surgery appears adequate to support the use of this procedure provided that the normal arrangements are in place for consent, audit and clinical governance. 1.2 Patient selection and follow-up should be carried out by a multidisciplinary team. Cardiac surgeons wishing to use this procedure should have specific training in the use of cryoablation equipment. High intensity focused ultrasound ablation for atrial fibrillation as an associated procedure 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 the public is recommended (available from www.nice.org.uk/IPG184publicinfo). • 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.
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Clinical guidelines	The management of atrial fibrillation. NICE clinical guideline 36 (2006) 1.4.2.2 In patients with permanent AF where antithrombotic therapy is given to prevent strokes and/or thromboembolism (see section 1.8.6): • adjusted-dose warfarin should be given as the most effective treatment • adjusted-dose warfarin should reach a target INR of 2.5 (range 2.0 to 3.0) • where warfarin is not appropriate, aspirin should be given at 75 to 300 mg/day • where warfarin is appropriate, aspirin should not be coadministered with warfarin purely as thromboprophylaxis, as it provides no additional benefit.
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Appendix C: Literature search for percutaneous occlusion of the left atrial appendage in atrial fibrillation

Database	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	04/03/2010	February 2010
Database of Abstracts of Reviews of Effects – DARE (CRD website)	04/03/2010	-
HTA database (CRD website)	04/03/2010	-
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	04/03/2010	February 2010
MEDLINE (Ovid)	04/03/2010	1950 to February Week 4 2010
MEDLINE In-Process (Ovid)	04/03/2010	March 3, 2010
EMBASE (Ovid)	04/03/2010	1980 to 2010 Week 8
CINAHL (NLH Search 2.0/EBSCOhost)	04/03/2010	-
Zetoc (for update searches only)	04/03/2010	-

Trial sources searched

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

Websites searched on 15/12/2009:

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

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

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1 Balloon Occlusion/
 2 Balloon Dilatation/
 3 ((Balloon* or transcathet* or percutan*) adj5 (occlus* or dilatat*)).tw.
 4 (left atrial append* adj3 occlus*).tw.
 5 Embolization, Therapeutic/
 6 (Emboli?at* adj3 therap*).tw.
 7 or/1-6
 8 Atrial Appendage/
 9 left atrial append*.tw.
 10 LAA.tw.
 11 (Atr* adj3 append*).tw.
 12 or/8-11 (2957)
 13 Atrial Fibrillation/
 14 AF.tw.
 15 (Atr* adj3 Fibrill*).tw.
 16 or/13-15
 17 7 and 16 and 12
 18 PLATTO.tw.
 19 WATCHMAN.tw.
 20 Atr* append* closur* device*.tw.
 21 or/18-20
 22 21 or 17
 23 Animals/ not Humans/
 24 22 not 23
 25 200511\$.ed.
 26 200512\$.ed.
 27 2006\$.ed.
 28 2007\$.ed.
 29 2008\$.ed.
 30 2009\$.ed.
 31 or/25-30
 32 24 and 31
 33 from 32 keep 1-51

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