National Institute for Health and Care Excellence

Draft for consultation

Atrial fibrillation

Ablation

NICE guideline

Intervention evidence review

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Draft for Consultation

This evidence review was developed by the National Guideline Centre

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Contents

1 Ablation

1.1 Review question: What is the clinical and cost effectiveness of different ablative therapies in people with atrial fibrillation?

1.2 Introduction

Atrial fibrillation (AF) is a common arrhythmia associated with poor clinical outcomes including reduced overall survival, and an increased risk of major non-fatal cardiovascular adverse events including stroke and heart failure. Some patients with AF report disabling symptoms that can have a significant impact on quality of life. Rhythm control strategies exist to attempt to increase the likelihood of maintenance of sinus rhythm, and reduce the symptom burden attributable to arrhythmia in patients with symptomatic AF.

Since recognition of the importance of pulmonary venous ectopy in the initiation and maintenance of AF, multiple ablative technologies have been developed to create electrically inert lesions around the pulmonary veins (PVs) and achieve PV isolation (PVI). PVI has been shown to increase maintenance of sinus rhythm, reduced symptom burden, improve quality of life, and improve left ventricular systolic dysfunction in patients with AF, compared to pharmacological rhythm control with anti-arrhythmic drugs.

Although PVI is a common procedure used to achieve rhythm control in patients with AF, multiple different ablative technologies are in routine use across the UK. Costs and procedural details may vary between different ablative technologies and a degree of uncertainty remains about the best ablative technology to use in patients with symptomatic AF. The intention of this chapter is to examine the clinical and cost effectiveness of different ablative technologies used in AF ablation and develop recommendations.

1.3 PICO table

For full details see the review protocol in Appendix A:.

Table 1: PICO characteristics of review question

Population	People aged over 18 with a diagnosis of AF.
Intervention(s)	• surgical ablation – thoracoscopy • surgical ablation - open (not as a concomitant Rx) • Hybrid catheter/surgical (thoracoscopic, not open surgery) • radiofrequency catheter ablation - point by point • radiofrequency catheter ablation – multi-electrode • cryoballoon catheter ablation • laser catheter ablation
Comparison(s)	• To each other (between any of the 7 classes above – no comparison within any of the 7 classes) • Placebo • Usual Care (medical treatment) • No treatment
Outcomes	Critical • health-related quality of life

	• stroke or systemic embolism • mortality • Recurrent symptomatic AF (post-blanking period) • hospitalisation with a primary diagnosis of atrial fibrillation • Redo of procedure (catheter/surgical) • HF/exacerbation of heart failure. • Serious AEs Important • Hospital length of stay
Study design	Randomised controlled trials and SRs of RCTs

1.4 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual.[173]

Methods specific to this review question are described in the review protocol in Appendix A.

1.5 Clinical evidence

1.5.1 Included studies

A search was conducted for randomised trials comparing the effectiveness of different ablation techniques for patients with atrial fibrillation. 53 randomised trials (62 papers) were included in the review.[2, 9, 13, 25, 26, 31, 32, 39, 42, 56, 58, 64, 70, 79, 82, 85-87, 90-93, 95, 96, 99, 104, 117, 121-123, 137, 138, 142, 145, 153, 160, 162, 177, 183, 187, 189, 195, 200-203, 206, 211, 219-221, 231, 235, 242, 245, 253, 256, 259-261, 268, 272] These are summarised in Table 2 to Table 5 below. Evidence from these studies is summarised in the clinical evidence summaries below (Table 6 to Table 23).

As specified in the protocol, studies were divided into 4 different strata defined by AF type: paroxysmal AF, persistent < 1 year AF, persistent > 1 year AF and a mixed stratum (where no specific AF type made up >75% of the sample, or where the proportions were unknown). Within any stratum, if heterogeneity existed for an outcome, sub-grouping was carried out for 1) CHADSVASC <2/CHADSVASC ≥2 and 2)HF / no HF. In all but one outcome, heterogeneity was not resolved by the subgrouping strategies. For those outcomes where heterogeneity was unresolved, a random effects model was used.

For each stratum, included papers covered several different intervention comparisons, which were permutations of the 7 different ablation categories and usual care (see table 1). Usual care comprised medical care (anti-arrhythmic drugs [AAD]) in all included papers. The comparisons were:

Paroxysmal stratum

- RF point by point vs cryoballoon[58, 85]
- [9, 13, 25, 86, 87, 92, 122, 123, 137, 138, 195, 201, 220, 242, 259, 272]
- RF point by point vs laser[70, 245]
- RF point by point vs RF multielectrode[32, 39, 82, 104, 153, 200]
- RF point by point vs hybrid[96, 256]
- RF point by point vs usual care[56, 95, 162, 177, 187, 189, 202, 211, 253, 260, 261, 268]
- RF multielectrode vs cryoballoon[117, 219]
- RF multielectrode vs thoracoscopy[235]

- Laser vs cryoballoon[220]
- Cryoballoon vs usual care[183]

Mixed stratum

- RF point by point vs cryoballoon[90]
- RF point by point vs thoracoscopy[2, 31, 42, 203]
- RF point by point vs RF multielectrode[26]
- RF point by point vs usual care[79, 231,121]
- RF multielectrode vs cryoballoon[145]
- RF multielectrode vs usual care[91, 121]

Persistent <1 year stratum

- RF point by point vs laser[221]
- RF point by point vs usual care[64, 160]

Persistent >1 year stratum

- RF point by point vs usual care[93, 99, 142, 206]

In the majority of studies, patients were naïve to ablation, but comprised people who had failed at least one AAD: thus the studies were largely examining treatment that was second-line to drug therapy. In the studies where the comparator was medical care, the AADs used were generally ensured to be different in type or dosage to the ones previously failed.

There were some studies with different population characteristics to those described above. These were factors, potentially contributing to heterogeneity, that were not addressed by the stratification and sub-grouping strategies in this review. For example, in contrast to most studies, some studies comparing ablation to usual care evaluated patients that had not previously used AADs, thus making these first-line treatment studies[56, 162, 177, 253, 260]. Similarly, in some other studies there were no requirements to have failed AADs[93, 99, 142]. A small number of studies also used patients that had previously failed ablation[31, 42, 201-203]. In these studies, the ablation technique that had previously failed was the technique evaluated in the study, which would tend to reduce the observed efficacy of ablation compared to what might be seen in the normal population. Since we had not planned to stratify or sub-group for these factors, these studies were kept in the same meta-analyses as other studies. It is important to be aware of the potential effect of these factors on outcomes when interpreting the pooled meta-analysis results.

For the outcome of 'serious adverse events', all adverse events described in any eligible paper were screened by the topic expert and only those deemed to be 'serious' were counted. For the outcome of recurrence, the endpoint was the first event between the end of the blanking period (usually 1-3 months) and the end of follow up (so therefore point prevalences at a single time point were excluded). The longest follow up available was use for all outcomes.

1.5.2 Excluded studies

See the excluded studies list in Appendix I.1.

1

1.5.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies comparing ablation techniques in the paroxysmal stratum

Study	Studies (n) and country	Intervention and comparison	Inclusion and exclusion criteria	CHADSVASC category (<2 or ≥2)	Heart failure	First line or after failed AADs	Previous ablation
Andrade, 2020[9]	1(343) Canada	RF point by point versus Cryoballoon	Inclusion: Patients aged >18 years with symptomatic paroxysmal AF refractory to at least 1 Class I or Class III AAD and referred for a first catheter ablation procedure were enrolled. At least 1 electrocardiographic-documented episode of AF was required within 24 months of randomization.	<2 (>70% <2)	No HF (LVEF >59%)	Failed at least 1 AAD	No previous ablations
Bin Waleed, 2019[25]	1(58) China	RF point by point versus Cryoballoon	Inclusion: Symptomatic AF; paroxysmal AF; scheduled for first-time catheter ablation Exclusion: Long-standing and persistent AF; acute cause of AF; HF; vascular diseases such as MI in past 3 months; inflammatory diseases; cancer; renal dysfunction (eGFR <30); LA diam >=55 mm; antiplatelet and NSAIDs within 1 month of enrolment into study	<2 (>75% < 2)	No HF (HF exclusion criterion).	Unclear	No previous ablations
Davtyan, 2018[58]	1(89) Russia	RF point by point versus Cryoballoon	Inclusion: At least 1 documented ECG occurrence of NV symptomatic paroxysmal AF lasting >30 seconds within 90 days of enrolment that was refractory (or intolerance) to at least 1 AAD (including beta blockers); age 18 to 79 inc.; LA diam <50mm; LVEF at least 50% during sinus rhythm Exclusion: History of MI or cardiac surgery within 90 days of enrolment; history of stroke/TIA within 1 year of enrolment; uncontrolled thyroid function; unable to tolerate OACs	<2 (mean of 1.3)	No HF (LVEF had to be >50%)	Failed at least 1 AAD	Not reported
Giannopoulos, 2018[85]	1(30) Greece	RF point by point versus Cryoballoon	Inclusion: Paroxysmal AF; 2 episodes of AF within past 12 months, either self-terminating or cardioverted in <48 hrs; at least 2 had to be symptomatic; at least 1episode should have occurred during treatment with a class I or III AAD Exclusion: Previous left atrial ablation procedure; LA diam >50mm; primary electrical heart disease; atrial thrombus; prosthetic valve; moderate/severe mitral stenosis; severe mitral regurgitation; active infectious disease or malignancy; child pugh class B or C; eGFR <20.	>=2 (median 2)	No HF (LA diam >50mm were excluded)	Failed at least 1 AAD	No prior ablation
Giannopoulos, 2019[86]	1(120) Greece	RF point by point versus Cryoballoon	Inclusion: Paroxysmal AF; 2 symptomatic episodes of AF within past 12 months, either self-terminating in 7 days or cardioverted in <48 hrs; Failure of at least one class I or III AAD; eage 40-80; slated for PVI	<2 (median 1)	No HF (LA diam >50mm were	Failed at least 1 AAD	No prior ablation

Study	Studies (n) and country	Intervention and comparison	Inclusion and exclusion criteria	CHADSVASC category (<2 or ≥2)	Heart failure	First line or after failed AADs	Previous ablation
			Exclusion: Previous left atrial ablation procedure; LA diam >50mm; primary electrical heart disease; atrial thrombus; prosthetic valve; moderate/severe mitral stenosis; severe mitral regurgitation; active infectious disease or malignancy; child pugh class B or C; eGFR <20.		excluded)		
Gunawardene, 2018[87]	1(60) Germany	RF pt to point versus cryoballoon	Inclusion: Documented symptomatic paroxysmal AF within past year; history of prior electrical cardioversion allowed if cardioversion performed within the initial 48 hrs after symptom onset; age >18 <85 yrs; structurally normal heart (LVEF >35%, LA diam <5cm;no valvular disease defined as <2nd degree valvular dysfunction. Exclusion: Patients with previous ablation; intracardiac thrombi; pregnancy; life expectancy <1 year; contraindications to OACs; hyperthyroidism	Unclear	No HF (LA diam <50mm exclusion criterion)	Unclear	No prior ablation
Hunter, 2015[13, 92]	1(158) UK	RF point by point versus Cryoballoon	Inclusion: symptomatic paroxysmal AF refractory to >1 AAD Exclusion: Persistent AF; potentially reversible cause of AF; contraindications to ablation; severe valvular heart disease; prior LA ablation	Unclear	No HF (only 7% with documented HF)	Failed at least 1 AAD	No prior ablation
Kuck, 2016[122] and Kuck, 2016[123] FIRE AND ICE TRIAL	2(762)	RF point by point versus cryoballoon	Inclusion: Symptomatic PAF with at least two episodes and at least one episode documented (30 seconds episode length, documented by ECG within last 12 months); documented treatment failure for effectiveness of at least one anti-arrhythmic drug (AAD Type I or III, including β-blocker and AAD intolerance); ≥18 and ≤75 years of age; Exclusion: life expectancy <1 year; pregnant women or women of childbearing potential; Substance misuse; Active systemic infection; Cryoglobulinaemia; patients with prosthetic valves; any previous LA ablation or surgery; any cardiac surgery or percutaneous coronary intervention (PCI) within three months prior to enrolment; unstable angina pectoris; myocardial infarction within three months prior to enrolment; symptomatic carotid stenosis; chronic obstructive pulmonary disease with detected pulmonary hypertension; any condition contraindicating chronic anticoagulation; stroke or transient ischemic attack within six months prior to enrolment; any significant congenital heart defect corrected or not; New York Heart Association (NYHA) class III or IV congestive heart failure; EF < 35 %; Anteroposterior LA diameter > 55 mm; LA thrombus; Intracardiac thrombus; PV diameter > 26 mm in right sided PVs; Mitral prosthesis; Hyperthrophic cardiomyopathy; 2° (Type II) or 3° atrioventricular block; Brugada syndrome or long QT syndrome; Arrhythmogenic right ventricular dysplasia; Sarcoidosis; PV stent; Myxoma;	<2 (mean <2 in both groups)	No HF (73.9% and 70.3% free from HF)	Failed at least 1 AAD	No prior ablation

Study	Studies (n) and country	Intervention and comparison	Inclusion and exclusion criteria	CHADSVASC category (<2 or ≥2)	Heart failure	First line or after failed AADs	Previous ablation
			Thrombocytosis, thrombocytopenia; Any untreated or uncontrolled hyperthyroidism or hypothyroidism; GFR< 15 ml / min).				
Luik, 2017[137] and Luik, 2015[138] FREEZE AF TRIAL	2(315) Unclear location	RF point by point versus Cryoballoon	Inclusion: Patients with at least 2 episodes of paroxysmal AF (of which at least one was documented) within the 3 months prior to enrolment; aged 18-75; documented inefficacy of at least one AAD. Exclusion: LA > 55mm; LA thrombus; previous LA Surgery or ablation; ejection fraction <40%; NYHA class III or IV; mitral prosthesis; MI in past 3 months; PCI or cardiac surgery in previous 3 months; stroke/TIA in past 6 months; pregnancy; life expectancy of <1 year	Unclear	No HF (LVEF <40 was excluded)	Failed at least 1 AAD	No prior ablation
Perez-Castellano, 2014[195] COR TRIAL	1(50) Spain	RF point by point versus Cryoballoon	Inclusion: symptomatic recurrent paroxysmal AF (>2 episodes in last 2 months) refractory to one or more antiarrhythmic drugs and an anatomic pattern comprising 4 single PVs Exclusion: aged <18 or >75 years; prior AF ablation; prior cardiac surgery; moderate to severe valvular heart disease; AP diameter of left atrium >50mm; hyperthyroidism; intracardiac thrombus; contraindications for anticoagulant therapy; concomitant acute illness; pregnancy.	Unclear	No HF (LA diam >50mm)	Failed at least 1 AAD	No prior ablation
Pokushalov, 2013[201]	1(80) Russia	RFpoint by point versus Cryoballoon	Inclusion: Symptomatic paroxysmal AF; previous failed first RF ablation procedure (recurrences after 3 month blanking period). Exclusion: CHF; LVEF <35%; LA diam >60mm	Unclear	No HF (HF excluded)	Unclear if failed previous AADs	Failed prior (RF) ablation procedure
Schmidt, 2013[220]	1(99) Germany	RF point by point versus cryoballoon AND Laser versus cryoballoon	Inclusion: Drug-refractory paroxysmal AF; indications for catheter ablation Exclusion: LA diam >50mm; LVEF <45%; contraindications for MRI scanning; stage III renal failure; intracardiac thrombus; CHADS >3	>=2 (median 2)	No HF (mean LVEF 59%)	Failed at least 1 AAD	Not reported
Tse, 2005[242]	1(30) Hong Kong	RF point by point versus Cryoballoon	Inclusion: Symptomatic paroxysmal AF selected to undergo catheter ablation procedure Exclusion: CHF; DM; prior stroke or SE; prior CAD and MI; valvular heart disease; malignancy; renal impairment or hepatic dysfunction; active infection/inflammation; ejection fraction <45%; LAD >50mm; previous ablation procedures; AF episodes lasting >48 hours prior to procedure	Unclear	No HF (HF excluded)	Unclear	No prior ablation
Watanabe, 2018[259]	1(52) Japan	RF point by point versus cryoballoon	Inclusion: >18 years; scheduled for PV isolation for AAD refractory AF for first time; paroxysmal AF Exclusion: Renal insufficiency; common left PV trunk	Unclear	No HF (mean LVEF 58-	Failed at least 1 AAD	First ablation received by patients

Study	Studies (n) and country	Intervention and comparison	Inclusion and exclusion criteria	CHADSVASC category (<2 or ≥2)	Heart failure	First line or after failed AADs	Previous ablation
					63%)		
You, 2019[272]	1(210) China	RF point by point versus Cryoballoon	Inclusion: ECG-confirmed PAF that occurred at least twice within 6 months before study enrollment; occurrence of PAF remained despite application of class I and III antiarrhythmic drugs; and <80 years old and agreed to receive catheter ablation treatment for PAF. Exclusion: prior history of receiving catheter ablation for AF;) atrial thrombosis; diagnosis of valvular heart disease (moderate and severe valvular stenosis, severe valvular regurgitation); an LA dimension of >50 mm; prior history of prosthetic heart valve replacement; pregnancy; or existing liver and kidney diseases, malignant tumors or hematological system diseases.	unclear	No HF (HF only in 7.1%).	After failed AADs	Not reported
Jan, 2018[96]	1(50) Slovenia	RF pt to point versus hybrid procedure	Inclusion: paroxysmal AF Exclusion: none reported	<2 mean was 1.2 to 1.5)	No HF (mean LVEF 63-65)	Unclear; Most (58%[hybrid]/69 %[RF]) with prior AAD use and the fact that they were being treated suggests these had failed)	Not reported
Wang, 2014[256]	1(138) China	RF point by point versus thoracoscopy	Inclusion: paroxysmal AF; indication for ablation; preference for minimal invasive surgery Exclusion: unstable angina; shock; cardiac failure; indication for other surgical procedures; hyperthyroidism	Unclear	No HF (HF excluded)	Unclear	Not reported
Dukkipati, 2015[70]	1(353) USA	RF point by point vs laser	Inclusion: 2 or more symptomatic AF episodes of at least 1 min within past 6/12; 1 documented AF episode in past 12 months; refractory or intolerant to aads Exclusion: PV size >35mm; LA thrombus; LA diam >50mm; LVEF <30%; prev ablation; NYHA III or IV; MI in previous 60 days; unstable angina; cardiac surgery in previous 3 months; cabg in previous 6 months; cardiac valve surgery; thromoembolic event in past 3 months; uncontrolled bleeding; active infection; atrail myoma; severe pulmonary disease; or GI bleeding; previous valvular procedure; presence of implantable cardioverter defibrillator; pregnancy, lactating or not using birth control.	Unclear	No HF (only 5% with documented HF)	Refractory or intolerant to AADs	No prior ablation
Ucer, 2018[245] RATISBONA trial	1(50) Germany	RF point by point versus laser	Inclusion: paroxysmal AF; symptomatic AF Exclusion: Asthma; known allergy to adenosine; LA thrombus; LA diam >55mm; LVEF <35%; previous LA ablation for AF; NYHA class IV symptoms; MI in past 60 days; unstable angina; history of cardiac valve surgery; uncontrolled bleeding; active infection; severe pulmonary disease	Unclear	No HF (HF largely excluded)	40%[laser]/30%[RF] on Class I or III AADs suggesting the rest may have been receiving ablation as first	No prior ablation

Study	Studies (n) and country	Intervention and comparison	Inclusion and exclusion criteria	CHADSVASC category (<2 or ≥2)	Heart failure	First line or after failed AADs	Previous ablation
						line; however this is very unclear	
Boersma 2016[32] MYSTIC-PAF	1 (120)	RF point by point versus RF multielectrode	Inclusion:aged 18 to 70 years, with a history of symptomatic paroxysmal AF documented in the past 12 months, and refractory to ≥1 antiarrhythmic drug (AAD) could participate in the trial. Exclusion: significant structural heart disease (including previous cardiac surgery other than coronary artery bypass grafting), NYHA class >2, LVEF <40%, LA diameter >50 mm, ongoing myocardial ischemia, MI within the previous 3 months, valvular disease >grade II, congenital heart disease, previous atrial septal defect or patent foramen ovale closure, hypertrophic cardiomyopathy >15 mm, pulmonary hypertension, previous LA ablation for AF, any ablation within the previous 3 months, cardioversion <7 days before CA	<2	No HF (most low NYHA)	Failed at least 1 AAD	First ablation received by patients
Bulava, 2010[39]	1(102) Czech Republic	RF point by point versus RF multielectrode	Inclusion: At least 3 documented paroxysmal AF occurrences on previous 6 months despite AADs Exclusion: AF as a sole documented rhythm for 6 months or more prior to inclusion; previous ablation; CAD; CHF with NYHA class III and IV; unstable angina or acute MI within past 3 months; LVEF <0.4; LA diameter >50mm; severe mitral regurgitation or stenosis; contraindications to VKAs; known bleeding disorders; presence of LA thrombi; previous cardiac or pulmonary surgery; severe COPD, chronic liver or kidney disease; psychiatric disease; drug or alcohol abuse; pregnancy	Unclear	No HF (LVEF <40% excluded)	Needed to have failed AADs	No prior ablation
Gal, 2014[82]	1(460) Netherlands	RF point by point versus RF multielectrode	Inclusion: Symptomatic AF; accepted for primo PVI Exclusion: none reported	<2 (73.5% <2)	No (mean LA diam 41mm)	Average of 1.58 failed AADs	No prior ablation
Kece, 2019 [104]	1(70) Holland	RF point by point versus RF multielectrode	Inclusion: Scheduled for first-time catheter ablation of paroxysmal drug-refractory AF Exclusion: Previous AF ablation; persistent AF; contraindications for MRI/inability to perform neuropsychological testing	<2 (mean 1.6)	No HF (LVEF >55% for all; LA diameter 39/40mm).	After failed AADs	No previous ablations
McCready, 2014[153]	1(188) UK	RF point by point versus RF multielectrode	Inclusion: Patients with paroxysmal AF; failed at least one AAD; listed for ablation Exclusion: patient objection; prior ablation; LA diam >60mm; mechanical prosthetic vales; hypertrophic cardiomyopathy; contraindications to OACs; pregnancy	<2 (mean 1.19)	No HF (mean LA size 38mm)	Failed at least 1 AAD	No prior ablation
Podd, 2015[200]	1(50)	RF point by point versus	Inclusion: Drug refractory symptomatic paroxysmal AF; class IA	<2 (mean	No HF (HF	Failed at least 1	No prior ablation

Study	Studies (n) and country	Intervention and comparison	Inclusion and exclusion criteria	CHADSVASC category (<2 or ≥2)	Heart failure	First line or after failed AADs	Previous ablation
	UK	RF multielectrode	indication Exclusion: pregnancy; unstable angina or MI in past 2 months; NYHA class III or IV HF; severe valvar dysfunction; previous left atrial ablation	1.8)	excluded)	AAD	
Jais, 2008[95] A4 STUDY	1(112) Multinational	RF point by point versus medical therapy	Inclusion: symptomatic, documented paroxysmal AF over a span of ✓6 months with at least 2 episodes during the preceding month Exclusion: contraindications to >2 AADs in different classes or to oral anticoagulants, prior AF ablation, an intracardiac thrombus, AF from a potentially reversible cause, pregnancy, or a contraindication to the discontinuation of oral anticoagulation	Unclear	No HF (LA diam 41mm)	Resistant to at least 1 AAD. BUT control group received different AADs to those previously failed.	No prior ablation
Morillo, 2014[162] RAAFT-2 trial	1(127) Multinational	RF point by point versus medical therapy	Inclusion: a history of paroxysmal AF. Patients were enrolled if they were older than 18 and no older than 75 years; were symptomatic with recurrent paroxysmal AF lasting more than 30 seconds (≤4 episodes within the prior 6months); experienced at least 1 episode that was documented by surface ECG, 6months before randomization; and had no previous antiarrhythmic drug treatment. Exclusion: documented left ventricular ejection fraction of lessthan40%;had left atrial diameter larger than 5.5 cm; had moderate to severe left ventricular hypertrophy (wall thickness >1.5 cm), valvular disease, coronary artery disease, or postcardiac surgery within 6 months; had undergone a left heart ablation procedure, either by surgery or by radiofrequency catheter ablation for AF; or had a complete contraindication for the use of heparin, warfarin, or both	<2	No HF (<3% with HF)	FIRST LINE TREATMENT. No previous AADS	No previous ablation.
Nielsen, 2017[177]; Walfridsson, 2015[253] and Cosedis Nielsen, 2012[56] MANTRA-PAF trials	3(294) Denmark	RF point by point versus medical therapy	Inclusion: at least two episodes of symptomatic paroxysmal atrial fibrillation within the preceding 6 months but no episode of atrial fibrillation that was longer than 7 days (without spontaneous termination or cardioversion). Exclusion: age of more than 70 years, previous or ongoing treatment with class IC or class III antiarrhythmic drugs, contraindication to both class IC and class III agents, previous ablation for atrial fibrillation, a left atrial diameter of more than 50 mm, a left ventricular ejection fraction of less than 40%, contraindication to oral anticoagulation therapy, moderate-to-severe mitral valve disease, severe heart failure (New York Heart Association functional class III to IV at the time of enrolment), expected surgery for structural heart disease, and secondary atrial fibrillation (due to cardiac surgery, infection, or hyperthyroidism).	<2	No HF (mostly NYHA grade I)	FIRST LINE THERAPY. No previous treatment with class 1C or class III AADs. Sample were 'candidates for rhythm control therapy' and had not been previously treated.	No previous ablations
Pappone, 2011[189] and	2(198) Italy	RF point by point versus	Inclusion: Age >18 or <70 years, AF history >6 months, and AF burden >2 episodes per month in the last 6 months as assessed	Unclear	No HF	Had received previous AADs.	No information on prior ablation

Study	Studies (n) and country	Intervention and comparison	Inclusion and exclusion criteria	CHADSVASC category (<2 or ≥2)	Heart failure	First line or after failed AADs	Previous ablation
Pappone, 2006[187] APAF		medical therapy	by daily transtelephonic monitoring. Exclusion: Persistent AF, LA diameter >65 mm, LVEF <35%, heart failure symptoms, and New York Heart Association functional class II			Not stated if intolerant or ineffective but the AADs used for control group were distinct to those used previously.	
Pokushalov, 2013b[202]	1(154) Multinational	RF point by point versus medical therapy	Inclusion: patients with a history of symptomatic PAF eligible for AAD therapy or reablation after a previous failed initial radio frequency ablation (RFA) procedure involving only PVI were eligible for this study Exclusion: patients with persistent AF or atrial flutter, inability to tolerate any AAD, amiodarone therapy within 3 months before the ablation procedure, congestive heart failure, left ventricular ejection fraction <35%, or left atrial (LA) diameter >60 mm were excluded	<2	No HF (LVEF 57%)	Intolerance to AADs is an exclusion criterion. Patients stated to be eligible for drugs or repeat ablation.	Previously failed RF ablation.
Wazni, 2005[260]	1(70) Multinational	RF point by point versus medical therapy	Inclusion: monthly symptomatic AF episodes for at least 3 months. Exclusion: age younger than 18 years and older than 75 years, previous history of atrial flutter or AF ablation, previous history of open-heart surgery, previous treatment with antiarrhythmic drugs, and contraindication to long-term anticoagulation treatment.	Unclear	No HF	FIRST LINE TREATMENT. No previous AADS	No previous ablation.
Wilber, 2010[261] and Reynolds, 2010[211]	2(167) Multinational	RF point by point versus medical therapy	Inclusion: at least 3 symptomatic AF episodes (>=1episode verified by electrocardiogram) within the 6 months before randomization, and not responding to at least 1 antiarrhythmic drug (class I, class III, or atrioventricular nodal blocker) Exclusion: patients with AF of more than 30 days in duration, age younger than 18 years, an ejection fraction of less than 40%, previous ablation for AF, documented left atrial thrombus, amiodarone therapy in the previous 6months,NewYork Heart Association class III (marked limitation in activity due to symptoms) or IV (severe limitations), myocardial infarction within the previous 2 months, coronary artery bypass graft procedure in the previous 6 months, thromboembolic event in the previous 12 months, severe pulmonary disease, a prior valvular cardiac surgical procedure, presence of an implanted cardioverter-defibrillator, contraindication to antiarrhythmic or anticoagulation medications, life expectancy of less than 12 months, and left atrial size of at least 50mmin the parasternal long axis view	Unclear	No HF (mostly NYHA class I)	Refractory to at least 1 AAD. Control group received a drug different to that previously failed.	No previous ablation
Xu, 2012[268]	1(123) China	RF point by point versus medical	Inclusion: paroxysmal or persistent AF. Exclusion: none reported	Unclear	Unclear	No information	No information

Study	Studies (n) and country	Intervention and comparison	Inclusion and exclusion criteria	CHADSVASC category (<2 or ≥2)	Heart failure	First line or after failed AADs	Previous ablation
		therapy					
Koch, 2012[117], Schirdewan, 2017 [219] MACPAF trial	1(44) Germany	RF multielectrode versus cryoballoon	Inclusion: Symptomatic paroxysmal AF; prior ineffective AAd treatment; no previous ablation; no unstable structural heart disease; lifespan at least 2 years; contraindications for MRI. Exclusion: None (see inclusion criteria)	>=2 (median is 2)	No HF (only 2.3% with documented HF)	Failed at least one AAD	No prior ablation
Sugihara, 2018[235]	1(73) UK	RF multielectrode versus thoracoscopy	Inclusion: Age >18; symptomatic paroxysmal AF suitable for ablation Exclusion: Prior cardiac or thoracic surgery; inability to undergo GA for AF ablation; pregnancy; cardiac rhythm disorders other than AF; presence of pre-existing permanent pacemakers or implantable loop recorders that did not allow for continuous monitoring of AF occurence, or were not MRI safe.	>=2 (most around 2)	Unclear	Unclear	16% had had prior AF ablation
Packer, 2013[183] STOP AF TRIAL	1(245) USA	Cryoballoon versus medical therapy	Inclusion: patients with >2 episodes of PAF in 2 months prior to randomisation; at least 1 membrane active drug failure Exclusion: LA>50mm; LVEF <40%; NYHA clas III or IV; CAD; Stroke or TIA in previous 6 months; previous LA ablation/surgery for AF; prosthetic heart valves; amiodarone therapy in previous 3 months; >2 cardioversions within 2 years; implantable rhythm device	<2	No HF (NYHA class III or IV excluded)	Refractory to at least 1 AAD. Control group received drugs that they had not used before.	No previous ablation

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2 **Table 3: Summary of studies comparing ablation techniques in the mixed stratum (no specific AF type present in >75% of sample)**

Study	Studies (n) and country	Intervention and comparison	Details of how stratum is mixed	Inclusion and exclusion criteria	CHADSVASC category (<2 or ≥2)	Heart failure	First line or after failed AADs	Previous ablation
Hererra Siklody, 2012[90]	1(60) France and Germany	RF pt to point versus cryoballoon	Mixed (paroxysmal 70% in cryoballoon group and 56.7% in RF pt to pt group; the rest were persistent <1 year)	Inclusion: symptomatic, drug refractory paroxysmal or persistent AF Exclusion: long persistent AF (>12 months); LA diam >55mm; intracardiac thrombi; MI or cardiac surgery in previous 3 months; previous ablation	Unclear	No HF (LA diam 40-41mm)	Failed at least 1ADD	No prior ablation
Adiyaman, 2018[2]	1(52) Netherlands	RFpoint by point versus thoracoscopy	Mixed (proportions not given) between	Inclusion: symptomatic paroxysmal or early persistent (<3 months) with failure of at least 1 classl or III AADs; >=18 years; at	<2(74%)	No (exclusion of LA diam >50mm)	Drug refractory sample.	No prior ablation

Study	Studies (n) and country	Intervention and comparison	Details of how stratum is mixed	Inclusion and exclusion criteria	CHADSVASC category (<2 or ≥2)	Heart failure	First line or after failed AADs	Previous ablation
			paroxysmal and early persistent. Analysis not stratified for type	least 1 symptomatic episode of AF required in prior 6 months Exclusion: Structural heart disease; permanent or persistent AF >3 months; LVEF <30%; LA diam >50mm; amiodarone use in prior 6 months; history of CVD; pregnancy; life expectancy <1 year; previous LA ablation				
Boersma, 2012[31] and Castella, 2019[42]. FAST TRIAL	2(129) Netherlands	RF point by point versus thoracoscopy	Mixed (paroxysmal [67%] and short term persistent [33%].	Inclusion: Documented, symptomatic paroxysmal and/or persistent AF for at least 12 months that was refractory to or intolerant of at least 1 AAD, age between 30 and 70 years, and mentally able and willing to give informed consent. Exclusion: Patients excluded if they had longstanding AF >1 year, cardiac CA or a surgical cardiac procedure in the last 3 months, previous stroke or transient ischemic attack, LA thrombus, LA size >65 mm, left ventricular ejection fraction <45%, mitral or aortic valve regurgitation above grade 2, moderate to severe mitral or aortic stenosis, active infection or sepsis, pregnancy, unstable angina, myocardial infarction within the previous 3 months, AF secondary to electrolyte imbalance, thyroid disease, other reversible or noncardiovascular causes for AF, history of blood-clotting abnormalities, known sensitivity to heparin or warfarin, life expectancy of <12 months, involvement in another clinical study involving an investigational drug or device, pleural adhesions, prior thoracotomy, prior cardiac surgery, and elevated hemidiaphragm	Unclear	No HF (mean LVEF 56%)	Failed or intolerant to at least 1 AAD	Prior failed catheter ablation in 60.3% of RF pt to pt group and 73.8% of thoracoscopy group.
Pokushalov 2013[203]	1(64) Russia	RF point by point versus thoracoscopy	Mixed	Inclusion: history of symptomatic PAF/PersAF after a previous failed first RF ablation procedure were eligible for this study. Exclusion congestive heart failure, LA thrombus, LV ejection fraction <35%, left	<2	No HF (LVEF >55%)	Failed at least 1 AAD	Yes. This study was only for those with a previous failed RF ablation

Study	Studies (n) and country	Intervention and comparison	Details of how stratum is mixed	Inclusion and exclusion criteria	CHADSVASC category (<2 or ≥2)	Heart failure	First line or after failed AADs	Previous ablation
				atrial diameter >65 mm, prior thoracotomy, prior cardiac surgery, and elevated hemidiaphragm were excluded from the study.				
Bittner, 2011[26]	1(80) Multinational	RF point by point versus RF multielectrode	Mixed(55% paroxysmal and 45% persistent).Analysis not stratified for type	Inclusion: Symptomatic paroxysmal or persistent AF with failure of at least 1 AAD, referred for first AF ablation procedure and in whom PV isolation had been planned Exclusion: Longstanding persistent AF; moderate or severe mitral valve stenosis or regurgitation, CHF with NYHA class III or IV; LVEF<40%; severe COPD; prior cardiac surgery other than coronary revascularisation; prior ablation; other supraventricular tachycardia; LA thrombus; contraindications to OACs; pregnancy	Unclear	No HF (HF excluded)	Failure of at least 1 AAD	No prior ablation
Forleo, 2009[79]	1(70) Italy	RF point by point versus medical therapy	Mixed (paroxysmal 41%)	Inclusion: type II DM patients with symptomatic paroxysmal AF for >6 months refractory to 1-3 AADs Exclusion: age <18 or >75 years; LVEF <30%; LA diam >55mm; <12 months life expectancy; prior cardiac surgery or ablation	Unclear	No HF (LA diameter <55mm)	Refractory to 1-3 AADs. Given maximal tolerated dose of a drug based on a flexible regimen – hence likely for control group to have received a different drug to any previously failed.	No prior ablations
Stabile, 2006[231] CATCAAF	1(137) Italy	RF point by point versus medical therapy	Mixed (paroxysmal 67%)	Inclusion: patients with paroxysmal or persistent AF who were intolerant of antiarrhythmic drugs or in whom two or more antiarrhythmic drug regimens had failed. Exclusion: (1) age ,18 or >80 years; (2) permanent AF (AF was the sole rhythm for the last 12 months); (3) AF secondary to a	Unclear	No HF	Sample intolerant of at least 1 AAD. Amiodarone given to control group but if	Not stated if prior ablation

Study	Studies (n) and country	Intervention and comparison	Details of how stratum is mixed	Inclusion and exclusion criteria	CHADSVASC category (<2 or ≥2)	Heart failure	First line or after failed AADs	Previous ablation
				transient or correctable abnormality, including electrolyte imbalance, trauma, recent surgery, infection, toxic ingestion, and endocrinopathy; (4) persistence of AF episodes triggered by another uniform arrhythmia (i.e. atrial flutter or atrial tachycardia) despite previous supraventricular tachycardia ablation; (5) intra-atrial thrombus, tumour, or other abnormality precluding catheter insertion; (6) Wolff–Parkinson–White syndrome; (7) heart failure with NYHA class III or IV or EF <35%; (7) unstable angina or acute myocardial infarction within 3 months; (8) cardiac revascularization or other cardiac surgery within 6 months or with prior atrial surgery; (9) renal failure requiring dialysis, or hepatic failure;(10) an implanted device (pacemaker or cardioverter-defibrillator); (11) left atrial diameter >60 mm			intolerant a class 1C antiarrythmic given instead.	
Krittayaphong, 2003[121]	1(30) Thailand	RF point by point versus medical therapy	Mixed (only 70% paroxysmal)	Inclusion: male and female aged 15-75 years; symptomatic paroxysmal or persistent AF > 6 months; refractory to at least 1 antiarrythmic medication including class 1A or class IC agents, digitalis, beta-blockers or Ca channel blockers; never had amiodarone Exclusion: transient AF or treatable cause of AF; bleeding disorders; thyroid disorders; previous stroke; severe underlying illness limiting life expectancy to <1 year; psychiatric disorders; valvular heart disease	Unclear	No HF (LVEF>60%)	Refractory to at least 1 AAD. Control group given amiodarone, which they had not had before.	Previous ablation not reported
Malmborg, 2013[145] AF-COR TRIAL	1(110) Sweden	RF multielectrode versus cryoballoon	Mixed (69.1% paroxysmal and 30.9% persistent). Analysis not stratified for type	Inclusion: Symptomatic 12 lead ECG-verfied AF; failed at least 1 AAD; Vaughan William Class I or III; scheduled for AF ablation. Exclusion: long standing persistent or permanent AF; previous ablation; CHF with NYHA class IV; LVEF <30%; LA diam >6cm.	<2 (but not clear)	No HF (unlikely as LVEF <30% excluded)	Must have failed at least 1 AAD	No prior ablation
Hummel,	1(210)	RF	Mixed (persistent	Inclusion:18-70 years; symptomatic	<2	No HF (LVEF	Failed at	No previous

Study	Studies (n) and country	Intervention and comparison	Details of how stratum is mixed	Inclusion and exclusion criteria	CHADSVASC category (<2 or ≥2)	Heart failure	First line or after failed AADs	Previous ablation
2014[91]		multielectrode versus medical therapy	<1 year and >1 year; proportions not reported)	persistent AF lasting 7 days to 1 year or 1-4 years (unclear on proportions so categorised as mixed); failed >1 class I or III AAD; continuous AF / flutter on 48 hr holter monitor; failed DCCV Exclusion: prior AF ablation; treated ventricular tachyarrythmia; active infection; history of CVA; pregnancy; active LA thrombus; contrast media allergy; reversible cause of AF; blood clotting abnormalities; sensitivity to heparin/warfarin; severe pulmonary disease; LVEF <40%; NYHA III or IV; severe comorbidity preventing FU; significant structural heart disease		>40%)	least 1 AAD. Control group received a different dose of the previously failed drug, or a new drug	ablation

Table 4: Summary of studies comparing ablation techniques in the persistent <1 year stratum

Study	Studies (n) and country	Intervention and comparison	Inclusion and exclusion criteria	CHADSVASC category (<2 or ≥2)	Heart failure	First line or after failed AADs	Previous ablation
Schmidt, 2017[221]	1(152) Multinational	RF point by point versus laser	Inclusion: symptomatic persistent AF refractory to at least 1 AAD including beta blockers class 1-111; episode duration of >7 days and <1 year; 18-80 years old; LVEF <50mm; LVEF >45% Exclusion: Previous PVI; ineligible for OACs; intracardiac thrombus; moderate or severe mitral valve disease	Unclear	No HF (mean LVEF 61%)	Failed at least 1 AAD	No prior ablation
Di Biase 2016[64] AATAC	1(203) Multinational	RF point by point versus medical therapy	Inclusion: Patients ≥18 years of age with persistent AF, dual-chamber implantable cardioverter defibrillator or cardiac resynchronization therapy defibrillator, New York Heart Association functional class II to III, and LV ejection fraction (LVEF) ≤40% within the past 6 months Exclusion: if AF was caused by a reversible etiology, and if they had valvular or coronary heart disease requiring surgical intervention, early postoperative AF (within 3 months of surgery), or a life expectancy ≤2 years. Other exclusions included prolonged QT interval, hypothyroidism, history of severe pulmonary disease, and liver failure. Patients receiving a regular dose of AMIO (≥200 mg/d) were also excluded.	Unclear	HF	Had received previous AADs such as beta blockers, but not stated if intolerant or ineffective.	No information on prior ablation
Mont, 2014[160]	1(146)	RF point by point versus	Inclusion: patients with symptomatic persistent AF7 (>7or,<7days requiring electrical or pharmacological	Unclear	No HF (most NYHA class I)	Refractory to at least 1	No previous ablations

Study	Studies (n) and country	Intervention and comparison	Inclusion and exclusion criteria	CHADSVASC category (<2 or ≥2)	Heart failure	First line or after failed AADs	Previous ablation
SARA trial	Spain	medical therapy	cardioversion) refractory to at least one class I or class III antiarrhythmic drug were recruited. Exclusion: Age,18 or.70 years, long-standing persistent AF(.1 year of continuous AF), first episode ofAF, hyper- or hypothyroidism, hypertrophic cardiomyopathy, implanted pacemaker or defibrillator, moderate or severe mitral disease or mitral prosthesis, left ventricular ejection fraction <30%, left atrial diameter .50 mm, prior ablation procedure, contraindication for oral anticoagulation, left atrial thrombus, active infection or sepsis, pregnancy, unstable angina, acute myocardial infarction during previous 3 months, life expectation,12 months, current participation in another clinical trial, mental disease or inability to give informed consent, or disease contraindicating ablation or ADT.			AAD. Drug regimen for control group stated to be flexible but not stated that AADs would be different to those used previously.	

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2 **Table 5: Summary of studies comparing ablation techniques in the persistent >1 year stratum**

Study	Studies (n) and country	Intervention and comparison	Inclusion and exclusion criteria	CHADSVASC category (<2 or ≥2)	Heart failure	First line or after failed AADs	Previous ablation
Hunter, 2014[93] CAMTAF	1(55) UK	RF point by point versus medical therapy	Inclusion: persistent AF, symptomatic HF (New York Heart Association [NYHA] class II–IV), and LV systolic dysfunction (ejection fraction [EF] <50%). Patients had to have adequate ventricular rate control as defined in the stricter guidelines in place at the time of the study design (since inadequate rate control would arguably have mandated some sort of intervention), with a heart rate <80 bpm at rest and <110 bpm on moderate exertion as assessed on ambulatory monitoring and exercise testing. Male and female patients aged ≥18 years were considered. There was no requirement for AF to be symptomatic, or for patients to have failed antiarrhythmic drug therapy or DC cardioversion Exclusion: HF that had a suspected reversible cause, previous left atrial ablation, any contraindication to catheter ablation, AF that was paroxysmal, symptoms that were clearly attributable to AF rather than HF (ie, palpitations or dizziness) that might arguably mandate a rhythm control strategy, any event during the past 6 months that might continue to effect on LV function (including implantation of	unclear	HF	No need to have failed AADs – AADs 'optimised' for 3 months prior to study	No previous ablations

Study	Studies (n) and country	Intervention and comparison	Inclusion and exclusion criteria	CHADSVASC category (<2 or ≥2)	Heart failure	First line or after failed AADs	Previous ablation
			a pacemaker or cardiac resynchronization therapy device, cardiac surgery, myocardial infarction, or coronary revascularization), or a realistic expectation of these occurring within the next year.				
Jones, 2013[99]	1(52) UK	RF point by point versus medical therapy	Inclusion: the enrolment criteria were 18 to 80 years of age, persistent AF (>7 days), symptomatic HF (New York Heart Association functional class II to IV) on optimal HF therapy, and left ventricular ejection fraction (EF) >35%. Exclusion: cardiovascular implantable electronic device insertion or cerebrovascular event within 6 months; coronary revascularization or atrioventricular nodal ablation within 3 months; reversible causes of AF or HF including thyroid dysfunction, alcohol, primary valvular disease, or recent major surgery; prior heart transplant or on urgent transplant waiting list; pregnancy; active malignancy; severe renal impairment; single chamber pacemaker and atrioventricular block; and contraindications to general anesthesia or oral anticoagulation	Unclear	HF	Prior failure of rate control drugs NOT a pre-requisite for inclusion.	Not stated if previous ablations allowed
McDonald, 2011[142]	1(41) UK	RF point by point versus medical therapy	Inclusion: aged 18-80 years, with New York Heart Association functional class II-IV symptoms despite optimal heart failure treatment for at least 3 months, ejection fraction <35% measured by radionuclide ventriculography, persistent AF and no contraindication to cardiovascular MRI were eligible. Exclusion: Paroxysmal AF; QRS duration >150 ms (or QRS 120e150 with evidence of mechanical cardiac dysynchrony15); any contraindication to oral anti-coagulant drugs; primary valvular disease or acute myocarditis as the cause of heart failure; coronary revascularisation within the preceding 6 months; pregnancy and expected cardiac transplantation within 6 months.	Unclear	HF	Not allowed to have contraindications to AADs. All patients had been receiving 'optimised' medications for 3 months	No information on previous ablations
Prabhu, 2017[206] CAMERA-MRI	1(66) Australia	RF point by point versus medical therapy	Inclusion: 1) 18 to 85 years of age; 2) had New York Heart Association (NYHA) functional class >II; 3) had persistent AF; 4) had an LVEF <45% on baseline cardiac magnetic resonance (CMR); 5) had significant coronary artery disease excluded via conventional or computed tomography–guided angiography or functional imaging; and 6) had no other identifiable cause explaining the left ventricular dysfunction Exclusion: 1) if they were unable or unwilling to consent or commit to follow-up requirements; 2) if they had any	>2	HF	Most had used previous AADs but not stated if intolerant/refractory. Not stated if AADs given to control group were different	No information on prior ablation

Study	Studies (n) and country	Intervention and comparison	Inclusion and exclusion criteria	CHADSVASC category (<2 or ≥2)	Heart failure	First line or after failed AADs	Previous ablation
			contraindication to AF ablation; 3) if they had any contraindication to cardiac magnetic resonance imaging (MRI); or 4) if they had paroxysmal AF.			to those given previously.	

See Appendix D:for full evidence tables.

1.5.4 Quality assessment of clinical studies included in the evidence review

PAROXYSMAL AF STRATUM

Table 6: Clinical evidence summary: RF point by point versus cryoballoon (paroxysmal stratum)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Cryoballoon [PAROXYSMAL]	Risk difference with RF point by point (95% CI)
Health related quality of life: SF12 mental 0-100, higher better	466 (1) 12 months	LOW[a] Due to risk of bias			The mean sf12 mental in the intervention groups was 0.5 lower (2.19 lower to 1.19 higher) [MID deemed to be 4.7 points (based on 0.5 x median sd (9.4) in comparator group)]
Health related quality of life: SF12 physical 0-100, higher better	466 (1) 12 months	LOW[a] Due to risk of bias			The mean sf12 physical in the intervention groups was 0.8 higher (0.8 lower to 2.4 higher) [MID deemed to be 4.6 points (based on 0.5 x median sd (9.2) in comparator group)]
Health related quality of life: EQ-5D-3L 0-1, higher better	511 (1) 12 months	LOW[a] Due to risk of bias			The mean eq-5d-3l in the intervention groups was 0 higher (0.02 lower to 0.02 higher) [MID deemed to be 0.065 points (based on 0.5 x median sd (0.13) in comparator group)]
Stroke or thromboembolic complications	1610 (6)	VERY LOW[a,b] Due to risk of bias,	RD -0.00 (-0.01 to 0.01)	Moderate	
				5 per 1000	2 fewer per 1000

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Cryoballoon [PAROXYSMAL]	Risk difference with RF point by point (95% CI)
	1 -3 years	imprecision			(from 10 fewer to 10 more)
asymptomatic cerebral lesions on MRI	66 (1) 1-2 days	VERY LOW[a,b,c] Due to risk of bias, imprecision, indirectness	RR 1.33 (0.52 to 3.42)	Moderate	
				182 per 1000	60 more per 1000 (from 87 fewer to 440 more)
Mortality	1230 (6) 1 – 3 years	VERY LOW[a,b] Due to risk of bias, imprecision	RD -0.01 (-0.01 to 0.00)	Moderate	
				2 per 1000	2 fewer per 1000 (from 3 fewer to 0 more)
Recurrent symptomatic AF (post blanking period)	1498 (7) 6 months – 3 years	VERY LOW[a,d] Due to risk of bias, indirectness	RR 1.00 (0.87 to 1.15)	Moderate	
				333 per 1000	0 fewer per 1000 (from 43 fewer to 50 more)
hospitalisation with a primary diagnosis of AF	750 (1) 30 months	VERY LOW[a,b,e] Due to risk of bias, imprecision, indirectness	RR 1.51 (1.2 to 1.89)	Moderate	
				238 per 1000	121 more per 1000 (from 48 more to 212 more)
Redo of procedure	1801 (8) 1 – 3 years	VERY LOW[a,b,f] Due to risk of bias, inconsistency, imprecision	Random effects RR 0.95 (0.71 to 1.27)	Moderate	
				264 per 1000	13 fewer per 1000 (from 77 fewer to 71 more)
HF incidence or exacerbation	0 (0)		Not estimable		
Serious AEs	2171 (11) 3 months – 3 years	VERY LOW[a,b] Due to risk of bias, imprecision	RD -0.01 (-0.03 to 0.01)	Moderate	
				21 per 1000	3 fewer per 1000 (from 13 fewer to 4 more)
Hospital length of stay	0 (0)		Not estimable		

CI: Confidence interval; RR: Risk ratio; OR: Odds ratio;

[a] Risk of bias was graded as very serious because the majority of studies did not report allocation concealment and blinding of patients, carers and assessors was not possible / not carried out

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Cryoballoon [PAROXYSMAL]	Risk difference with RF point by point (95% CI)

[b] Imprecision was graded as very serious if the confidence intervals crossed both default 'minimum important differences' (MIDs), and as serious imprecision if the confidence intervals crossed one of the MIDs. If risk differences were used because of zero events in both arms, then imprecision was decided on the basis of the optimum information size (power<0.8=very serious, power 0.8-0.89=serious)

[c] Indirectness was graded as serious because asymptomatic cerebral lesions were different, but related, to the intended outcome of symptomatic stroke/thromboembolic complications

[d] Indirectness was graded as serious because the majority of studies did not evaluate recurrence of symptomatic AF as specified in the protocol – instead most studies evaluated any AF (symptomatic or asymptomatic).

[e] Indirectness was graded as serious because hospitalisation was not specifically for AF

[f] Inconsistency was graded as serious if I2 was >50% but <75%, and very serious if >75%

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2 **Table 7: Clinical evidence summary: RF point by point versus hybrid (paroxysmal stratum)**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Hybrid [PAROXYSMAL]	Risk difference with RF point by point (95% CI)
Health related quality of life	0 (0)		Not estimable		
Stroke or thromboembolic complications	50 (1) 30.5 months	VERY LOW[a,c] Due to risk of bias, imprecision	RD 0.00 (-0.07 to 0.07)	Moderate	
				0 per 1000	0 more per 1000 (from 70 fewer to 70 more)
Mortality	50 (1) 30.5 months	VERY LOW[a,c] Due to risk of bias, imprecision	RD 0.00 (-0.07 to 0.07)	Moderate	
				0 per 1000	0 more per 1000 (from 70 fewer to 70 more)
Recurrent symptomatic AF (post blanking period)	50 (1)	VERY LOW[a,b] Due to risk of bias,	RR 1.57 (0.91 to 2.72)	Moderate	
				417 per 1000	238 more per 1000

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Hybrid [PAROXYSMAL]	Risk difference with RF point by point (95% CI)
	30.5 months	indirectness, imprecision[c]			(from 38 fewer to 717 more)
hospitalisation with a primary diagnosis of AF	0 (0)		Not estimable		
Redo of procedure	50 (1) 30.5 months	VERY LOW[a,c] Due to risk of bias, imprecision	RR 2.08 (0.73 to 5.87)	Moderate	
				167 per 1000	180 more per 1000 (from 45 fewer to 813 more)
HF incidence or exacerbation	0 (0)		Not estimable		
Serious AEs	50 (1) 30.5 months	VERY LOW[a,c] Due to risk of bias, imprecision	Peto OR 0.11 (0.01 to 1.15)	Moderate	
				125 per 1000	110 fewer per 1000 (from 124 fewer to 16 more)
Hospital length of stay	0 (0)		Not estimable		

CI: Confidence interval; RR: Risk ratio; OR: Odds ratio;

[a] Risk of bias was graded as very serious because the majority of studies did not report allocation concealment and blinding of patients, carers and assessors was not possible / not carried out

[b] Indirectness was graded as serious because the majority of studies did not evaluate recurrence of symptomatic AF as specified in the protocol – instead most studies evaluated any AF (symptomatic or asymptomatic).

[c]Imprecision was graded as very serious if the confidence intervals crossed both default 'minimum important differences' (MIDs), and as serious imprecision if the confidence intervals crossed one of the MIDs. If risk differences were used because of zero events in both arms, then imprecision was decided on the basis of the optimum information size (power<0.8=very serious, power 0.8-0.89=serious)

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1 **Table 8: Clinical evidence summary: RF point by point versus laser (paroxysmal stratum)**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Laser [PAROXYSMAL]	Risk difference with RF point by point (95% CI)
Health-related quality of life	0 (0)		Not estimable		
Stroke or thromboembolic complications	342 (1) 12 months	VERY LOW[a,b] Due to risk of bias, imprecision	RR 0.49 (0.05 to 5.4)	Moderate	
				12 per 1000	6 fewer per 1000 (from 11 fewer to 53 more)
asymptomatic cerebral lesions on MRI	66 (1) 1-2 days	VERY LOW[a,b,c] Due to risk of bias, imprecision, indirectness	RR 1 (0.43 to 2.35)	Moderate	
				242 per 1000	0 fewer per 1000 (from 138 fewer to 327 more)
Mortality	342 (1) 12 months	VERY LOW[a,b] Due to risk of bias, imprecision	Peto OR 0.13 (0 to 6.74)	Moderate	
				6 per 1000	5 fewer per 1000 (from 6 fewer to 33 more)
Recurrent symptomatic AF (post blanking period)	333 (1) 12 months	VERY LOW[a,b] Due to risk of bias, imprecision	RR 0.99 (0.74 to 1.31)	Moderate	
				365 per 1000	4 fewer per 1000 (from 95 fewer to 113 more)
hospitalisation with a primary diagnosis of AF	0 (0)		Not estimable		
Redo of procedure	0 (0)		Not estimable		
HF incidence or exacerbation	0 (0)		Not estimable		
Serious AEs	458 (3) 1-2 days to 12 months	VERY LOW[a,b] Due to risk of bias, imprecision	RD -0.01 (-0.05 to 0.02)	Moderate	
				40 per 1000	14 fewer per 1000 (from 51 fewer to 20 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Laser [PAROXYSMAL]	Risk difference with RF point by point (95% CI)
Hospital length of stay	0 (0)		Not estimable		

CI: Confidence interval; RR: Risk ratio; OR: Odds ratio;

[a] Risk of bias was graded as very serious because the majority of studies did not report allocation concealment and blinding of patients, carers and assessors was not possible / not carried out

[b] Imprecision was graded as very serious if the confidence intervals crossed both default 'minimum important differences' (MIDs), and as serious imprecision if the confidence intervals crossed one of the MIDs. If risk differences were used because of zero events in both arms, then imprecision was decided on the basis of the optimum information size (power<0.8=very serious, power 0.8-0.89=serious)

[c] Indirectness was graded as serious because the outcome was not exactly as specified in the protocol. The protocol outcome is stroke/systemic thromboembolism, and whilst asymptomatic cerebral lesions fit into the category they are not an outcome that would normally be regarded as clinically relevant.

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2 **Table 9: Clinical evidence summary: RF point by point versus RF multielectrode (paroxysmal stratum)**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with RF multielectrode [PAROXYSMAL]	Risk difference with RF point by point (95% CI)
Health-related quality of life	167 (2) 12 months	MODERATE[a] Due to risk of bias			The mean quality of life in the intervention groups was 0.06 lower (SMD) (0.36 lower to 0.24 higher) [MID was 0.5 sds, as this was a standardised MD]
Stroke or thromboembolic complications	810 (4) 12 months – 5 years	LOW[b] Due to imprecision	RD 0.00 (-0.02 to 0.01)	Moderate	
				5 per 1000	5 fewer per 1000 (from 20 fewer to 10 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with RF multielectrode [PAROXYSMAL]	Risk difference with RF point by point (95% CI)
Asymptomatic cerebral lesions	70 (1) 1-2 days	VERY LOW[a,b] Due to risk of bias, imprecision	RD 0.00 (-0.02 to 0.01)	Moderate	
				229 per 1000	172 fewer per 1000 (from 215 fewer to 21 more)
Mortality	510 (2) 12 months – 5 years	VERY LOW[a,b] Due to risk of bias, imprecision	RD 0.00 (-0.01 to 0.01)	Moderate	
				0 per 1000	0 more per 1000 (from 10 fewer to 10 more)
Recurrent symptomatic AF (post blanking period)	452 (4) 200 days to 12 months	VERY LOW[a,b] Due to risk of bias, imprecision	RR 1.03 (0.75to 1.41)	Moderate	
				249 per 1000	7 more per 1000 (from 62 fewer to 102 more)
Survival from recurrent symptomatic AF	460 (1) 5 years	VERY LOW[a,b] Due to risk of bias, imprecision	HR 1.27 (0.99 to 1.64)		
hospitalisation with a primary diagnosis of AF	0 (0)		Not estimable		
Redo of procedure	233 (2) 12 months	LOW[b] Due to imprecision	RD -0.01 (-0.11 to 0.09)	Moderate	
				205 per 1000	10 fewer per 1000 (from 110 fewer to 90 more)
HF incidence or exacerbation	0 (0)		Not estimable		
Serious AEs	880 (5) 12 months – 5 years	VERY LOW[a,b,c] Due to risk of bias, imprecision,	RD 0.01 (-0.01 to 0.03)	Moderate	
				13 per 1000	11 more per 1000 (from 9 fewer to 29 more)
Hospital length of stay	1 (117) 12 months	VERY LOW[a,b] Due to risk of bias, imprecision			The mean length of stay in the intervention groups was 0 higher (0.26 lower to 0.26 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with RF multielectrode [PAROXYSMAL]	Risk difference with RF point by point (95% CI)
					[MID deemed to be 0 points (based on 0.5 x median sd (0) in comparator group); Sd was 0, presumably because *all* in comparator group stayed for 1 day.]

CI: Confidence interval; RR: Risk ratio; OR: Odds ratio; SMD=standardised mean difference

[a] Risk of bias was graded as very serious because the majority of studies did not report allocation concealment and blinding of patients, carers and assessors was not possible / not carried out

[b] Imprecision was graded as very serious if the confidence intervals crossed both default 'minimum important differences' (MIDs), and as serious imprecision if the confidence intervals crossed one of the MIDs. If risk differences were used because of zero events in both arms, then imprecision was decided on the basis of the optimum information size (power<0.8=very serious, power 0.8-0.89=serious). For the continuous outcome of Hospital length of stay, imprecision was very serious because the 95% Cis crossed both MIDs, which were set at 0 (sd in comparator group was 0 presumably because all had the same value for the outcome).

[c] Inconsistency was graded as serious if I2 was between 50% and 74% and very serious if I2 was 75% or higher

Table 10: Clinical evidence summary: RF point by point versus medical care (paroxysmal stratum)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Medical care [PAROXYSMAL]	Risk difference with RF point by point (95% CI)
Health-related quality of life SF36 Physical (higher better)	843 (5) 6 months – 5 years	VERY LOW[a,b,c] due to risk of bias, inconsistency, imprecision			The mean quality of life sf36 phys in the intervention groups was 0.24 standard deviations higher (0.02 lower to 0.51 higher) [MID deemed to be 0.5 sds as standardised mean difference

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Medical care [PAROXYSMAL]	Risk difference with RF point by point (95% CI)
					used]
Health-related quality of life SF36 mental (higher better)	843 (5) 6 months – 5 years	VERY LOW[a,b,c] due to risk of bias, inconsistency, imprecision			The mean quality of life sf36 mental in the intervention groups was 0.41 standard deviations higher (0.08 to 0.74 higher) [MID deemed to be 0.5 sds as standardised mean difference used]
Health-related quality of life EQ5D index (higher better)	294 (1) 5 years	LOW[a,c] due to risk of bias, imprecision			The mean quality of life eq5d index in the intervention groups was 0.04 higher (0 to 0.08 higher) [MID deemed to be 0.08 points (based on 0.5 x median sd in comparator group)]
Health-related quality of life EQ5D VAS (higher better)	294 (1) 5 years	MODERATE,[a] due to risk of bias			The mean quality of life eq5d vas in the intervention groups was 0.3 lower (3.76 lower to 3.16 higher)
Stroke or thromboembolic complications	686 (4) 12 months – 5 years	VERY LOW[a,c] due to risk of bias, imprecision	RD 0.01 (-0.01 to 0.02)	Moderate	
				3 per 1000	6 more per 1000 (from 10 fewer to 20 more)
Mortality	693 (4) 9 months – 5 years	VERY LOW[a,c] due to risk of bias, imprecision	RD -0.01 (-0.03 to 0.01)	Moderate	
				17 per 1000	6 fewer per 1000 (from 18 fewer to 6 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Medical care [PAROXYSMAL]	Risk difference with RF point by point (95% CI)
Recurrent symptomatic AF (post blanking period)	615 (5) 9 months – 2 years	VERY LOW[a,c,d] due to risk of bias, inconsistency, indirectness	Random effects RR 0.38 (0.25 to 0.58)	Moderate	
				764 per 1000	474 fewer per 1000 (from 321 fewer to 573 fewer)
hospitalisation with a primary diagnosis of AF	361 (2) 12 months – 5 years	VERY LOW[a,e] due to risk of bias, indirectness	RR 0.18 (0.06 to 0.5)	Moderate	
				278 per 1000	228 fewer per 1000 (from 139 fewer to 261 fewer)
Redo of procedure	0 (0)		Not estimable		
HF incidence or exacerbation	198 (1) 4 years	VERY LOW[a,c] due to risk of bias, imprecision	RD 0.00 (-0.02 to 0.02)	Moderate	
				0 per 1000	0 more per 1000 (from 20 fewer to 20 more)
Serious AEs	997 (6) 9 months – 4 years	VERY LOW[a,c] due to risk of bias, inconsistency, imprecision	RR 1.04 0.64 to 1.69)	Moderate	
				42 per 1000	3 more per 1000 (from 21 fewer to 21 more)
Hospital length of stay	0 (0)		Not estimable		

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[a] Risk of bias was graded as very serious if the majority of studies did not report allocation concealment and blinding of patients, carers and assessors was not possible / not carried out. Risk of bias was graded as serious if allocation concealment was reported as having been adequately done, but blinding of patients, carers and assessors was not possible / not carried out.

[b] Inconsistency was graded as serious if I2 was between 50% and 74% and very serious if I2 was 75% or higher.

[c] Imprecision was graded as very serious if the confidence intervals crossed both default 'minimum important differences' (MIDs), and as serious imprecision if the confidence intervals crossed one of the MIDs. If risk differences were used because of zero events in both arms, then imprecision was decided on the basis of the optimum information size (power<0.8=very serious, power 0.8-0.89=serious). For the SF36 physical and mental continuous outcomes, imprecision resulted from the 95% CIs crossing the single MID of +0.5 SDs (standardised MD used because one study used a different scale to

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Medical care [PAROXYSMAL]	Risk difference with RF point by point (95% CI)
the others despite labelling the outcome as SF36), and for the EQ5D, imprecision resulted from the upper 95% CI touching the single MID of +0.08. [d] Indirectness was graded as serious because the majority of studies did not evaluate recurrence of symptomatic AF as specified in the protocol – instead most studies evaluated any AF (symptomatic or asymptomatic). [e]Indirectness was graded as serious because hospitalisation was not specifically for AF in either study					

Table 11: Clinical evidence summary: RF multielectrode versus cryoballoon (paroxysmal stratum)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Cryoballoon [PAROXYSMAL]	Risk difference with RF multielectrode (95% CI)
Health-related quality of life	0 (0)		Not estimable		
Stroke or thromboembolic complications	32 (1) 6 months	VERY LOW[a,b] Due to risk of bias, imprecision	RD 0.00 (-0.11 to 0.11)	Moderate 0 per 1000	 0 more per 1000 (from 110 fewer to 110 more)
Mortality	32 (1) 6 months	VERY LOW[a,b] Due to risk of bias, imprecision	RD 0.00 (-0.11 to 0.11)	Moderate 0 per 1000	 0 more per 1000 (from 110 fewer to 110 more)
Recurrent symptomatic AF (post blanking period)	32 (1) 6 months	VERY LOW[a,b] Due to risk of bias, imprecision	RR 1.13 (0.69-1.86)	Moderate 591 per 1000	 77 more per 1000 (from 183 fewer to 508

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Cryoballoon [PAROXYSMAL]	Risk difference with RF multielectrode (95% CI)
					more)
hospitalisation with a primary diagnosis of AF	0 (0)		Not estimable		
Redo of procedure	0 (0)		Not estimable		
HF incidence or exacerbation	0 (0)		Not estimable		
Serious AEs	32 (1) 6 months	VERY LOW[a,b] Due to risk of bias, imprecision	RR 1.13 (0.18 to 7.09)	Moderate	
				118 per 1000	15 more per 1000 (from 97 fewer to 719 more)
Hospital length of stay	0 (0)		Not estimable		

CI: Confidence interval; RR: Risk ratio;

[a] Risk of bias was graded as very serious because the majority of studies did not report allocation concealment and blinding of patients, carers and assessors was not possible / not carried out

[b] Imprecision was graded as very serious if the confidence intervals crossed both default 'minimum important differences' (MIDs), and as serious imprecision if the confidence intervals crossed one of the MIDs. If risk differences were used because of zero events in both arms, then imprecision was decided on the basis of the optimum information size (power<0.8=very serious, power 0.8-0.89=serious)

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2 **Table 12: Clinical evidence summary: RF multielectrode versus thoracoscopy (paroxysmal stratum)**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Thoracoscopy[PAROXYSMAL]	Risk difference with RF multielectrode (95% CI)
Health-related quality of life	0		Not		

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Thoracoscopy[PAROXYSMAL]	Risk difference with RF multielectrode (95% CI)
	(0)		estimable		
Stroke or thromboembolic complications	0 (0)		Not estimable		
Mortality	69 (1) 12 months	VERY LOW[a,b] Due to risk of bias, imprecision	Peto OR 0.03 (0 to 2.39)	Moderate	
				50 per 1000	48 fewer per 1000 (from 50 fewer to 62 more)
Recurrent symptomatic AF (post blanking period)	69 (1) 12 months	LOW[a] Due to risk of bias	Peto OR 5.7 (1.58 to 20.59)	Moderate	
				0 per 1000	290 more per 1000 (from 140 more to 430 more)
hospitalisation with a primary diagnosis of AF	0 (0)		Not estimable		
Redo of procedure	69 (1) 12 months	LOW[a] Due to risk of bias	Peto OR 5.53 (1.48 to 20.7)	Moderate	
				0 per 1000	270 more per 1000 (from 130 more to 400 more)
HF incidence or exacerbation	0 (0)		Not estimable		
Serious AEs	69 (1) 12 months	LOW[a] Due to risk of bias	Peto OR 0.02 (0 to 0.15)	Moderate	
				300 per 1000	292 fewer per 1000 (from 240 fewer to 300 fewer)
Hospital length of stay	0 (0)		Not estimable		

CI: Confidence interval; OR: Odds ratio;

[a] Risk of bias was graded as very serious because the majority of studies did not report allocation concealment and blinding of patients, carers and

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Thoracoscopy[PAROXYSMAL]	Risk difference with RF multielectrode (95% CI)
assessors was not possible / not carried out [b] Imprecision was graded as very serious if the confidence intervals crossed both default 'minimum important differences' (MIDs), and as serious imprecision if the confidence intervals crossed one of the MIDs. If risk differences were used because of zero events in both arms, then imprecision was decided on the basis of the optimum information size (power<0.8=very serious, power 0.8-0.89=serious)					

Table 13: Clinical evidence summary: laser versus cryoballoon (paroxysmal stratum)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Laser versus cryoballoon [PAROXYSMAL] (95% CI)
Health-related quality of life	0 (0)		Not estimable		
Stroke or thromboembolic complications	0 (0)		Not estimable		
asymptomatic cerebral lesions on MRI	66 (1) 1-2 days	VERY LOW[a,b,c] Due to risk of bias, indirectness, imprecision	RR 1.33 (0.52 to 3.42)	Moderate 182 per 1000	60 more per 1000 (from 87 fewer to 440 more)
Mortality	0 (0)		Not estimable		
Recurrent symptomatic AF (post blanking period)	0 (0)		Not estimable		

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Laser versus cryoballoon [PAROXYSMAL] (95% CI)
hospitalisation with a primary diagnosis of AF	0 (0)		Not estimable		
Redo	0 (0)		Not estimable		
HF incidence or exacerbation	0 (0)		Not estimable		
serious adverse events	66 (1) 1-2 days	VERY LOW[a,c] Due to risk of bias, imprecision	RD 0.00 (-0.06 to 0.06)	Moderate	
				0 per 1000	0 more per 1000 (from 60 fewer to 60 more)
Hospital length of stay	0 (0)		Not estimable		

[a] Risk of bias was graded as very serious because the majority of studies did not report allocation concealment and blinding of patients, carers and assessors was not possible / not carried out

[b] Indirectness was graded as serious because the outcome was not exactly as specified in the protocol. The protocol outcome is stroke/systemic thromboembolism, and whilst asymptomatic cerebral lesions fit into the category they are not the clinical outcome that would normally be regarded as clinically important.

[c] Imprecision was graded as very serious if the confidence intervals crossed both default 'minimum important differences' (MIDs), and as serious imprecision if the confidence intervals crossed one of the MIDs. If risk differences were used because of zero events in both arms, then imprecision was decided on the basis of the optimum information size (power<0.8=very serious, power 0.8-0.89=serious)

Table 14: Clinical evidence summary: cryoballoon versus medical care (paroxysmal stratum)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Medical care [PAROXYSMAL]	Risk difference with Cryoballoon (95% CI)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Medical care [PAROXYSMAL]	Risk difference with Cryoballoon (95% CI)
Health-related quality of life	0 (0)		Not estimable		
Stroke or thromboembolic complications	245 (1) 12 months	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 4.67 (0.95 to 22.89)	Moderate	
				0 per 1000	40 more per 1000 (from 10 fewer to 80 more)
Mortality	245 (1) 12 months	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 4.5 (0.07 to 286.16)	Moderate	
				0 per 1000	10 more per 1000 (from 20 fewer to 30 more)
Recurrent symptomatic AF (post blanking period)	0 (0)		Not estimable		
hospitalisation with a primary diagnosis of AF	0 (0)		Not estimable		
Redo	0 (0)		Not estimable		
HF incidence or exacerbation	0 (0)		Not estimable		
serious adverse events	0 (0)		Not estimable		
Hospital length of stay	0 (0)		Not estimable		

[a] Risk of bias was graded as very serious if the majority of studies did not report allocation concealment and blinding of patients, carers and assessors was not possible / not carried out. Risk of bias was graded as serious if allocation concealment was reported as having been adequately done, but blinding of patients, carers and assessors was not possible / not carried out.

[b] Imprecision was graded as very serious if the confidence intervals crossed both default 'minimum important differences' (MIDs), and as serious imprecision if the confidence intervals crossed one of the MIDs. If risk differences were used because of zero events in both arms, then imprecision was

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Medical care [PAROXYSMAL]	Risk difference with Cryoballoon (95% CI)
decided on the basis of the optimum information size (power<0.8=very serious, power 0.8-0.89=serious)					

MIXED STRATUM (<75% in any category [paroxysmal, persistent <1 year and persistent >1 year])

Table 15: Clinical evidence summary: RF point by point versus cryoballoon (mixed stratum)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Cryoballoon [MIXED]	Risk difference with RF point by point (95% CI)
Health related quality of life	0 (0)		Not estimable		
Stroke or thromboembolic complications	0 (0)		Not estimable		
Mortality	0 (0)		Not estimable		
Recurrent symptomatic AF (post blanking period)	60 (1) 12 months	VERY LOW[a,b] Due to risk of bias, imprecision	RR 0.55 (0.23 to 1.28)	Moderate	
				367 per 1000	165 fewer per 1000 (from 283 fewer to 103 more)
hospitalisation with a primary diagnosis of AF	0 (0)		Not estimable		
Redo of procedure	60 (1) 12 months	VERY LOW[a,b] Due to risk of bias, imprecision	RR 0.6 (0.25 to 1.44)	Moderate	
				333 per 1000	133 fewer per 1000 (from 250 fewer to 147 more)
HF incidence or exacerbation	0 (0)		Not estimable		
Serious AEs	60 (1) 12 months	VERY LOW[a,b] Due to risk of bias, imprecision	Peto OR 0.14 0 to 6.82)	Moderate	
				33 per 1000	28 fewer per 1000 (from 33 fewer to 156 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Cryoballoon [MIXED]	Risk difference with RF point by point (95% CI)
Hospital length of stay	0 (0)		Not estimable		

CI: Confidence interval; RR: Risk ratio;

[a] Risk of bias was graded as very serious because the majority of studies did not report allocation concealment and blinding of patients, carers and assessors was not possible / not carried out

[b] Imprecision was graded as very serious if the confidence intervals crossed both default 'minimum important differences' (MIDs), and as serious imprecision if the confidence intervals crossed one of the MIDs. If risk differences were used because of zero events in both arms, then imprecision was decided on the basis of the optimum information size (power<0.8=very serious, power 0.8-0.89=serious)

Table 16: Clinical evidence summary: RF point by point versus thoracoscopy (mixed stratum)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Thoracoscopy [MIXED]	Risk difference with RF point by point (95% CI)
Health related quality of life	0 (0)		Not estimable		
Stroke or thromboembolic complications	188 (2) 1 – 7 years	VERY LOW[a,b,c] Due to risk of bias, imprecision, inconsistency	Random RR 0.48 (0.06 to 3.88)	Moderate	
				150 per 1000	65 fewer per 1000 (from 116 fewer to 61 more)
Mortality	175 (2) 2 - 7 years	VERY LOW[a,b] Due to risk of bias, imprecision	RR 0.98 (0.31 to 3.09)	Moderate	
				52 per 1000	1 fewer per 1000 (from 36 fewer to 109 more)
Recurrent symptomatic AF (post blanking period)	238 (3)	VERY LOW[a,d] Due to risk of bias,	RR 1.77 (1.4 to 2.23)	Moderate	
				304 per 1000	234 more per 1000

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Thoracoscopy [MIXED]	Risk difference with RF point by point (95% CI)
	1- 7 years	indirectness			(from 122 more to 374 more)
Survival from recurrent AF	80 (1) 2 years	VERY LOW[a,d] Due to risk of bias, indirectness	HR 0.56 (0.26 to 1.21)		
hospitalisation with a primary diagnosis of AF	0 (0)		Not estimable		
Redo of procedure	188 (2) 1-7 years	LOW[a] Due to risk of bias	RR 4.11 (2.13 to 7.93)	Moderate	
				81per 1000	252 more per 1000 (from 92 more to 561 more)
HF incidence or exacerbation	0 (0)		Not estimable		
Serious AEs	237(3) 1-7 years	LOW[a] Due to risk of bias	RR 0.24 (0.12 to 0.48)	Moderate	
				312 per 1000	237fewer per 1000 (from 162 fewer to 275 fewer)
Hospital length of stay	1 (64) 1 year	VERY LOW[a,b] Due to risk of bias, imprecision	-		MD: 2.8 less days in intervention group than control (from 3.31 lower to 2.29 higher)

CI: Confidence interval; RR: Risk ratio;

[a] Risk of bias was graded as very serious because the majority of studies did not report allocation concealment and blinding of patients, carers and assessors was not possible / not carried out

[b] Imprecision was graded as very serious if the confidence intervals crossed both default 'minimum important differences' (MIDs), and as serious imprecision if the confidence intervals crossed one of the MIDs. If risk differences were used because of zero events in both arms, then imprecision was decided on the basis of the optimum information size (power<0.8=very serious, power 0.8-0.89=serious)

[c] Inconsistency was graded as serious if I2 was between 50% and 74% and very serious if I2 was 75% or higher

[d] Indirectness was graded as serious because the majority of studies did not evaluate recurrence of symptomatic AF as specified in the protocol – instead most studies evaluated any AF (symptomatic or asymptomatic).

Table 17: Clinical evidence summary: RF point by point versus RF multielectrode (mixed stratum)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with RF multielectrode [MIXED]	Risk difference with RF point by point (95% CI)
Health-related quality of life	0 (0)		Not estimable		
Stroke or thromboembolic complications	80 (1) 244 days	VERY LOW[a,c] Due to risk of bias, imprecision	RD 0.00 (-0.05 to 0.05)	Moderate	
				0 per 1000	0 more per 1000 (from 50 fewer to 50 more)
Mortality	80 (1) 254 days	VERY LOW[a,c] Due to risk of bias, imprecision	RD 0.00 (-0.05 to 0.05)	Moderate	
				0 per 1000	0 more per 1000 (from 50 fewer to 50 more)
Recurrent symptomatic AF (post blanking period)	80 (1) 254 days	VERY LOW[a,b,c] Due to risk of bias, indirectness, imprecision	RR 1.18 (0.6 to 2.32)	Moderate	
				275 per 1000	49 more per 1000 (from 110 fewer to 363 more)
hospitalisation with a primary diagnosis of AF	0 (0)		Not estimable		
Redo of procedure	80 (1) 254 days	VERY LOW[a,c] Due to risk of bias, imprecision	RR 0.8 (0.23 to 2.76)	Moderate	
				125 per 1000	25 fewer per 1000 (from 96 fewer to 220 more)
HF incidence or exacerbation	0 (0)		Not estimable		
Serious AEs	80 (1) 254 days	VERY LOW[a,c] Due to risk of bias, imprecision	Peto OR 7.58 (0.47 to 123.37)	Moderate	
				0 per 1000	50 more per 1000 (from 30 fewer to 130

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with RF multielectrode [MIXED]	Risk difference with RF point by point (95% CI)
					more)
Hospital length of stay	0 (0)		Not estimable		

CI: Confidence interval; RR: Risk ratio;

[a] Risk of bias was graded as very serious because the majority of studies did not report allocation concealment and blinding of patients, carers and assessors was not possible / not carried out

[b] Indirectness was graded as serious because the majority of studies did not evaluate recurrence of symptomatic AF as specified in the protocol – instead most studies evaluated any AF (symptomatic or asymptomatic).

[c] Imprecision was graded as very serious if the confidence intervals crossed both default 'minimum important differences' (MIDs), and as serious imprecision if the confidence intervals crossed one of the MIDs. If risk differences were used because of zero events in both arms, then imprecision was decided on the basis of the optimum information size (power<0.8=very serious, power 0.8-0.89=serious)

1 **Table 18: Clinical evidence summary: RF point by point versus medical care (mixed stratum)**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Medical care [mixed]	Risk difference with RF point by point (95% CI)
Health-related quality of life	0 (0)		Not estimable		
Stroke or thromboembolic complications	237 (3) 1 year	VERY LOW[a,b] due to risk of bias, imprecision	RD 0.01 (-0.03 to 0.04)	Moderate	
				8 per 1000	9 more per 1000 (from 30 fewer to 40 more)
Mortality	137 (1) 1 year	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.51 (0.05 to 5.47)	Moderate	
				29 per 1000	14 fewer per 1000 (from 28 fewer to 130 more)
Recurrent symptomatic AF (post blanking	207	LOW[a,c]	RR 0.4	Moderate	

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Medical care [mixed]	Risk difference with RF point by point (95% CI)
period)	(2) 1 year	due to risk of bias, indirectness	(0.3 to 0.54)	742 per 1000	445 fewer per 1000 (from 341 fewer to 519 fewer)
hospitalisation with a primary diagnosis of AF	70 (1) 1 year	VERY LOW[a,b,d] due to risk of bias, imprecision, indirectness	RR 0.25 (0.08 to 0.81)	Moderate	
				343 per 1000	257 fewer per 1000 (from 65 fewer to 316 fewer)
Redo of procedure	0 (0)		Not estimable		
HF incidence or exacerbation	0 (0)		Not estimable		
Serious AEs	237 (2) 1 year	VERY LOW[a,b,d] due to risk of bias, imprecision, inconsistency	RR 0.69 (0.22 to 2.21)	Moderate	
				86 per 1000	27 fewer per 1000 (from 67 fewer to 104 more)
Hospital length of stay	0 (0)	See comment	Not estimable	See comment	See comment

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[a] Risk of bias was graded as very serious if the majority of studies did not report allocation concealment and blinding of patients, carers and assessors was not possible / not carried out. Risk of bias was graded as serious if allocation concealment was reported as having been adequately done, but blinding of patients, carers and assessors was not possible / not carried out.

[b] Imprecision was graded as very serious if the confidence intervals crossed both default 'minimum important differences' (MIDs), and as serious imprecision if the confidence intervals crossed one of the MIDs. If risk differences were used because of zero events in both arms, then imprecision was decided on the basis of the optimum information size (power<0.8=very serious, power 0.8-0.89=serious)

[c] Indirectness was graded as serious because the majority of studies did not evaluate recurrence of symptomatic AF as specified in the protocol – instead most studies evaluated any AF (symptomatic or asymptomatic).

[d] Indirectness was graded as serious because hospitalisation was not specifically for AF

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2 **Table 19: Clinical evidence summary: RF multielectrode versus cryoballoon (mixed stratum)**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Cryoballoon [MIXED]	Risk difference with RF multielectrode (95% CI)
Health-related quality of life	0 (0)		Not estimable		
Stroke or thromboembolic complications	0 (0)		Not estimable		
Mortality	0 (0)		Not estimable		
Recurrent symptomatic AF (post blanking period)	106 (1) 1 year	VERY LOW[a,b] Due to risk of bias, imprecision	RR 1.22 (0.89 to 1.68)	Moderate	
				540 per 1000	119 more per 1000 (from 59 fewer to 367 more)
hospitalisation with a primary diagnosis of AF	0 (0)		Not estimable		
Redo of procedure	106 (1) 1 year	VERY LOW[a,b] Due to risk of bias, imprecision	RR 1.28 (0.53 to 3.1)	Moderate	
				140 per 1000	39 more per 1000 (from 66 fewer to 294 more)
HF incidence or exacerbation	0 (0)		Not estimable		
Serious AEs	106 (1) 1 year	VERY LOW[a,b] Due to risk of bias, imprecision	RR 0.45 (0.04 to 4.78)	Moderate	
				40 per 1000	22 fewer per 1000 (from 38 fewer to 151 more)
Hospital length of stay	0 (0)		Not estimable		

CI: Confidence interval; RR: Risk ratio;

[a] Risk of bias was graded as very serious because the majority of studies did not report allocation concealment and blinding of patients, carers and assessors was not possible / not carried out

[b] Imprecision was graded as very serious if the confidence intervals crossed both default 'minimum important differences' (MIDs), and as serious imprecision

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Cryoballoon [MIXED]	Risk difference with RF multielectrode (95% CI)
if the confidence intervals crossed one of the MIDs. If risk differences were used because of zero events in both arms, then imprecision was decided on the basis of the optimum information size (power<0.8=very serious, power 0.8-0.89=serious)					

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2 **Table 20: Clinical evidence summary: RF multielectrode versus medical care (mixed stratum)**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Medical care [MIXED]	Risk difference with RF multielectrode (95% CI)
Health-related quality of life	0 (0)		Not estimable		
Stroke or thromboembolic complications	210 (1) 30 days	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 4.72 (0.73 to 30.45)	Moderate	
				0 per 1000	40 more per 1000 (from 0 fewer to 70 more)
mortality	210 (1) 30 days	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 4.58 (0.07 to 284.55)	Moderate	
				0 per 1000	10 more per 1000 (from 20 fewer to 30 more)
Recurrent symptomatic AF (post blanking period)	0 (0)		Not estimable		
hospitalisation with a primary diagnosis of AF	0 (0)		Not estimable		
Redo of procedure	0 (0)		Not estimable		
HF incidence or exacerbation	0 (0)		Not estimable		
Chronic serious AEs	210	VERY LOW[a,b]	RR 1.39	Moderate	

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Medical care [MIXED]	Risk difference with RF multielectrode (95% CI)
	(1) 30 days	due to risk of bias, imprecision	(0.38 to 5.08)	42 per 1000	16 more per 1000 (from 26 fewer to 171 more)
Hospital length of stay	0 (0)		Not estimable		

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[a] Risk of bias was graded as very serious if the majority of studies did not report allocation concealment and blinding of patients, carers and assessors was not possible / not carried out. Risk of bias was graded as serious if allocation concealment was reported as having been adequately done, but blinding of patients, carers and assessors was not possible / not carried out.

[b] Imprecision was graded as very serious if the confidence intervals crossed both default 'minimum important differences' (MIDs), and as serious imprecision if the confidence intervals crossed one of the MIDs. If risk differences were used because of zero events in both arms, then imprecision was decided on the basis of the optimum information size (power<0.8=very serious, power 0.8-0.89=serious)

[c] Indirectness was graded as serious because the majority of studies did not evaluate recurrence of symptomatic AF as specified in the protocol – instead most studies evaluated any AF (symptomatic or asymptomatic).

CI: Confidence interval; RR: Risk ratio; OR: Odds ratio;

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PERSISTENT AF <1 YEAR STRATUM

Table 21: Clinical evidence summary: RF point by point versus laser (persistent <1 year)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Laser [PERSISTENT]	Risk difference with RF point by point (95% CI)
Health-related quality of life	0 (0)		Not estimable		
Stroke or thromboembolic complications	134 (1) 1 year	VERY LOW[a,b] Due to risk of bias, imprecision	Peto OR 0.14 (0.01 to 1.32)	Moderate	
				44 per 1000	38 fewer per 1000 (from 44 fewer to 13 more)
Mortality	134 (1) 1 year	VERY LOW[a,b] Due to risk of bias, imprecision	RD 0.00 (-0.03 to 0.03)	Moderate	
				0 per 1000	0 fewer per 1000 (from 30 fewer to 30 more)
Recurrent symptomatic AF (post blanking period)	134 (1) 1 year	VERY LOW[a,b,c] Due to risk of bias, imprecision, indirectness	RR 1.06 (0.62 to 1.81)	Moderate	
				288 per 1000	17 more per 1000 (from 109 fewer to 233 more)
hospitalisation with a primary diagnosis of AF	0 (0)		Not estimable		
Redo of procedure	134 (1) 1 year	VERY LOW[a,b] Due to risk of bias, imprecision	RR 1.16 (0.48 to 2.82)	Moderate	
				118 per 1000	19 more per 1000 (from 61 fewer to 215 more)
HF incidence or exacerbation	0 (0)		Not estimable		
Serious AEs	134	VERY LOW[a,b]	RR 1.55	Moderate	

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Laser [PERSISTENT]	Risk difference with RF point by point (95% CI)
	(1) 1 year	Due to risk of bias, imprecision	(0.27 to 8.95)	29 per 1000	16 more per 1000 (from 21 fewer to 231 more)
Hospital length of stay	0 (0)		Not estimable		

CI: Confidence interval; RR: Risk ratio; OR: Odds ratio;

[a] Risk of bias was graded as very serious because the majority of studies did not report allocation concealment and blinding of patients, carers and assessors was not possible / not carried out

[b] Imprecision was graded as very serious if the confidence intervals crossed both default 'minimum important differences' (MIDs), and as serious imprecision if the confidence intervals crossed one of the MIDs. If risk differences were used because of zero events in both arms, then imprecision was decided on the basis of the optimum information size (power<0.8=very serious, power 0.8-0.89=serious)

[c]Indirectness was graded as serious because the majority of studies did not evaluate recurrence of symptomatic AF as specified in the protocol – instead most studies evaluated any AF (symptomatic or asymptomatic).

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2 **Table 22: Clinical evidence summary: RF point by point versus medical care (persistent <1 year)**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Laser [PERSISTENT]	Risk difference with RF point by point (95% CI)
Health related quality of life (AF QoL) Higher better	146 (1) 1 year	LOW[a] due to risk of bias			The mean change in SF36 Physical in the intervention groups was 3.8 higher (5.8 lower to 13.40 higher) [MID unknown as no sd given]
Health related quality of life (Minnesota	177	VERY LOW[a,b]			The mean change in

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Laser [PERSISTENT]	Risk difference with RF point by point (95% CI)
living with HF questionnaire); range 0-102, lower better	(1) 2 years	due to risk of bias, imprecision			MLHFQ in the intervention groups was 5 lower (10.3 lower to 0.3 higher) [MID deemed to be 8.5 points (based on 0.5 x median sd in comparator group)
Stroke or thromboembolic complications	146 (1) 1 year	VERY LOW[a,b] due to risk of bias, imprecision	RD 0.00 (-0.03 to 0.03)	Moderate 0 per 1000	0 fewer per 1000 (from 30 fewer to 30 more)
Mortality	349 (2) 1- 2 years	VERY LOW[a,b,e] due to risk of bias, imprecision, inconsistency	Random RD -0.05 (-0.23 to 0.14)	Moderate 121 per 1000	50 fewer per 1000 (from 230 fewer to 140 more)
Recurrent symptomatic AF (post blanking period)	349 (2) 1- 2 years	LOW[a,c] due to risk of bias, indirectness	RR 0.50 (0.4 to 0.63)	Moderate 686 per 1000	343 fewer per 1000 (from 254 fewer to 412 fewer)
hospitalisation with a primary diagnosis of AF	349 (2) 1- 2 years	LOW[a,d] due to risk of bias, indirectness	RR 0.53 (0.38 to 0.74)	Moderate 318 per 1000	149 fewer per 1000 (from 83 fewer to 197 fewer)
Redo of procedure	0 (0)		Not estimable		
HF incidence or exacerbation – Change in LVEF (higher better)	177 (1) 2 years	VERY LOW[a,b] due to risk of bias, imprecision			The mean change in LVEF in the intervention groups was +1.9% higher

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Laser [PERSISTENT]	Risk difference with RF point by point (95% CI)
					(0.55 higher to 3.25 higher) [MID deemed to be 3.1 points (based on 0.5 x median sd in comparator group)]
Serious AEs	349 (2) 1-2 years	VERY LOW[a,b,e] due to risk of bias, inconsistency, imprecision	RR 0.58 (0.04 to 9.63)	Moderate	
				45 per 1000	19 fewer per 1000 (from 43 fewer to 388 more)
Hospital length of stay	0 (0)		Not estimable		

[a] Risk of bias was graded as very serious if the majority of studies did not report allocation concealment and blinding of patients, carers and assessors was not possible / not carried out. Risk of bias was graded as serious if allocation concealment was reported as having been adequately done, but blinding of patients, carers and assessors was not possible / not carried out.

[b] Imprecision was graded as very serious if the confidence intervals crossed both default 'minimum important differences' (MIDs), and as serious imprecision if the confidence intervals crossed one of the MIDs. If risk differences were used because of zero events in both arms, then imprecision was decided on the basis of the optimum information size (power<0.8=very serious, power 0.8-0.89=serious). For the continuous outcome of Health related quality of life (Minnesota living with HF questionnaire), imprecision was serious because the 95% CIs crossed the single MID of -8.5 points. For the continuous outcome of HF incidence or exacerbation (change in LVEF), imprecision was serious because the 95% CIs crossed the single MID of +3.1%.

[c] Indirectness was graded as serious because the majority of studies did not evaluate recurrence of symptomatic AF as specified in the protocol – instead most studies evaluated any AF (symptomatic or asymptomatic).

[d] Indirectness was graded as serious because hospitalisation was not specifically for AF in the more highly weighted study

[e] Inconsistency was graded as serious if I2 was between 50 and 74% and very serious if 75% or more.

1 **PERSISTENT AF >1 YEAR STRATUM**

2 **Table 23: Clinical evidence summary: RF point by point versus medical care (persistent >1 year)**

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Medical care [pers >1 yr]	Risk difference with RF point by point (95% CI)
Health-related quality of life SF36 Physical	104 (2) 6 months	LOW[a,b] due to risk of bias, imprecision			The mean change in SF36 Physical in the intervention groups was 3.36 higher (1 lower to 6.82 higher) [MID deemed to be 3.9 points (based on 0.5 x median sd in comparator group)]
Health-related quality of life SF 36 Mental	104 (2) 6 months	LOW[a,b] due to risk of bias, imprecision			The mean change in SF36 Physical in the intervention groups was 1.86 lower (8.81 lower to 5.10 higher) [MID deemed to be 4.35 points (based on 0.5 x median sd in comparator group)]
Stroke or thromboembolic complications	114 (2) 6 months	VERY LOW[a,b] due to risk of bias, imprecision	RD 0.02 (-0.04 to 0.07)	Moderate	
				0 per 1000	20 more per 1000 (from 40 fewer to 70 more)
Mortality	166 (3) 6 months – 1 year	VERY LOW[a,b,d] due to risk of bias, imprecision, inconsistency	RD 0.00 (-0.05 to 0.05)	Moderate	
				12 per 1000	0 more per 1000 (from 50 fewer to 50 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Medical care [pers >1 yr]	Risk difference with RF point by point (95% CI)
Recurrent symptomatic AF (post blanking period)	38 (1) 6 months	VERY LOW[a,b,d,e] due to risk of bias, imprecision, indirectness	RR 0.61 (0.43 to 0.88)	Moderate	
				1000 per 1000	390 fewer per 1000 (from 120 fewer to 570 more)
hospitalisation with a primary diagnosis of AF	66 (1) 6 months	VERY LOW[a,b,c] due to risk of bias, imprecision, indirectness[c]	Peto OR 0.12 (0.02 to 0.91)	Moderate	
				121 per 1000	105 fewer per 1000 (from 10 fewer to 118 fewer)
Redo of procedure	0 (0)				
HF incidence or exacerbation	38 (1) 6 months	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 7.45 (0.72 to 76.61)	Moderate	
				0 per 1000	150 more per 1000 (from 20 fewer to 320 more)
Change in LVEF	38 (1) 6 months	VERY LOW[a,b] due to risk of bias, imprecision			The mean change in lvef in the intervention groups was 1.7 higher (4.07 lower to 7.47 higher) [MID deemed to be 3.35 points (based on 0.5 x median sd in comparator group)]
Change in NYHA grade	66 (1) 6 months	MODERATE[a] due to risk of bias			The mean change in LVEF in the intervention group was 0.82 lower (1.13 lower to 0.51 lower) [MID deemed to be 0.25 points (based on 0.5 x median sd in comparator group)]
Serious AEs	156 (3)	VERY LOW[a,b,c] due to risk of bias,	RR 2.18 (0.28 to	Moderate	
				0 per 1000	61 more per 1000

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Medical care [pers >1 yr]	Risk difference with RF point by point (95% CI)
	6 months – 1 year	inconsistency, imprecision	17.21)		(from 37 fewer to 842 more)
Hospital length of stay	0 (0)		Not estimable		

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[a] Risk of bias was graded as very serious if the majority of studies did not report allocation concealment and blinding of patients, carers and assessors was not possible / not carried out. Risk of bias was graded as serious if allocation concealment was reported as having been adequately done, but blinding of patients, carers and assessors was not possible / not carried out.

[b] Imprecision was graded as very serious if the confidence intervals crossed both default 'minimum important differences' (MIDs), and as serious imprecision if the confidence intervals crossed one of the MIDs. If risk differences were used because of zero events in both arms, then imprecision was decided on the basis of the optimum information size (power<0.8=very serious, power 0.8-0.89=serious). For the continuous outcomes of Health related quality of life SF36 physical and Health related quality of life SF36 mental, imprecision was serious because the 95% CIs crossed the single MIDs of +3.9 and +4.35 points respectively. For the continuous outcome of change in LVEF imprecision was very serious because the 95% Cis crossed both MIDs of +3.35 and -3.35.

[c] Indirectness was graded as serious because hospitalisation was not specifically for AF in the more highly weighted study

[d] Inconsistency was graded as serious if I2 was between 50% and 74% and very serious if I2 was 75% or higher

[e] Indirectness was graded as serious because the majority of studies did not evaluate recurrence of symptomatic AF as specified in the protocol – instead most studies evaluated any AF (symptomatic or asymptomatic).

1 See Appendix F: for full GRADE tables.

1.6 Economic evidence

1.6.1 Included studies

Seven health economic studies with relevant comparisons were included in this review. Two of these were included in the previous guideline update CG180.[72, 154, 215]

One study included compared radiofrequency catheter ablation to alternative strategies as first line therapy for AF.[16]

Four studies were included that compared ablation to alternative strategies as second line therapy for AF.[18, 27, 72, 154, 210, 215]

Two studies compared cryoballoon ablation to radiofrequency ablation as second line therapy.[53, 167] These are summarised in the economic evidence profiles below and the economic evidence tables in Appendix H.

Two studies were included in CG180 (Lamotte 2007 and Van Breugel 2011) but are excluded in this update at first sift as they did not meet the protocol. They were comparisons of concurrent cardiac surgery with ablation versus no concurrent ablation as part of cardiac surgery.

No health economic studies were included comparing all interventions together.

1.6.2 Excluded studies

Three studies were selectively excluded due to having less applicability than the included studies (for example, not considering quality of life information), or had more methodological limitations than the included studies (for example, deriving treatment effect and resource utilisation from observational and longitudinal studies).[108, 110, 114]

Two studies were excluded due to very serious methodological limitations.[116, 178] These are summarised in Appendix I, with reasons for their exclusion given.

See also the health economic study selection flow chart in Appendix G:.

1.6.3 Summary of studies included in the economic evidence review

Table 24: Health economic evidence profile: Radiofrequency ablation vs. antiarrhythmic drug therapy as first line treatment

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Aronsson 2015[16] (Sweden)	Partially applicable [(a)]	Potentially serious limitations[(b)]	• Probabilistic model based on single RCT (MANTRA-PAF [56, 253]) and other data sources • Cost-utility analysis (QALYs) • Population: Patients with symptomatic paroxysmal AF • Comparators: 1. Antiarrhythmic drug therapy: either flecainide 200mg OD or propafenone 600mg OD. Class III agents also allowed. 2. Radiofrequency ablation Time horizon: Lifetime	£2,722 [(c)]	0.06 QALYs	£45,385 per QALY gained	Probability ablation cost effective (£20/£30K threshold): NR, when visualising 1,000 samples from PSA on the CE plane, samples are spread across all four quadrants indicating uncertainty. Results of lifetime model also presented stratified by age: • ≤50 years ICER 2 vs 1: £3,082 per QALY. Probability Intervention 2 cost effective (£45K threshold): 90% • >50 years ICER 2 vs. 1: £97,768 per QALY One-way sensitivity analyses conducted for each age strata. Both groups sensitive to the readiness of offering crossovers and changes in the cost of ablation. Older strata sensitive to recurrence of AF and discount rates.

Abbreviations: 95% CI= 95% confidence interval; AF= atrial fibrillation; CE= cost effectiveness; ICER= incremental cost-effectiveness ratio; NR= not reported; OD= once daily; PSA= probabilistic sensitivity analysis; RCT = randomised controlled trial; QALYs= quality-adjusted life years

(a) Swedish health care payer perspective may not reflect current NHS context, does not include all comparators.

(b) Baseline and relative treatment effects not based on systematic review of the literature. Unclear methodological reporting. Effectiveness based on a single RCT and may not reflect full body of evidence. Potential financial conflict of interest funded by manufacturer of ablation instruments

(c) 2012 Euros converted to UK pounds.[182]. Cost components incorporated: Ablation procedure, hospitalisation, stroke care first year (by stroke type) and subsequent years, cardioversion, electrocardiography, transthoracic echocardiogram, transoesophageal echocardiogram, X-Ray, Holter monitoring, computed tomography warfarin, antiarrhythmic drugs.

Table 25: Health economic evidence profile: Radiofrequency catheter ablation vs. antiarrhythmic drug therapy as second line treatment

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Eckard 2009[72] (Sweden)	Partially Applicable (a)	Potentially Serious Limitations (b)	• Probabilistic model based on various sources. • Decision tree and markov model. Main health states include: NSR, AF, stroke, post stroke, and dead • Population was patients with paroxysmal or persistent drug refractory AF. • Comparators: 1: AAD 2: RFCA • Lifetime horizon	Saves £3,120 (c)	0.78 QALYs	RFCA dominated AAD, being less costly and more beneficial.	Probabilistic sensitivity analysis was performed and inspection of cost-effectiveness plane suggests the majority of simulations showed RFCA to be a dominant strategy (no probability reported). Deterministic analysis of annual reversion post 12 months at 5%, 10% and 15% gave cost per QALY estimates of £5888, £16580 and £30271 respectively.
McKenna 2009[154] (UK) Rogers 2009 [215] (UK)	Partially Applicable (d)	Potentially serious limitations (e)	• Probabilistic model based on three RCTs and other sources. • Decision tree and markov model. Main health states include: NSR, AF, stroke, post stroke, and dead	Lifetime treatment effect CHADS2 0 = £10,823 CHADS2 1 = £10,660 CHADS2 2 =	QALYs Lifetime treatment effect CHADS2 0 = 1.39 CHADS2 1 = 1.37	Lifetime treatment effect CHADS2 0 = £7,763 per QALY gained CHADS2 1 = £7,780 per	The probability that the intervention for each CHADS2 score using £20K/£30K threshold presented for each of the two analyses: Lifetime treatment effect CHADS2 0 = 98.3%/99.6% CHADS2 1 = 98.1%/99.6%

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
			• Population: Population was predominantly people with paroxysmal AF • Comparators: 1. AADs 2.Radiofrequency catheter ablation (with no concurrent AAD) • Time horizon: Lifetime • Two alternative basecase analyses: one where treatment effect duration was a lifetime and the second where it was 5 years (f)	£10,470 CHADS2 3 = £10,236 5 year treatment effect CHADS2 0 = £10,822 CHADS2 1 = £10,664 CHADS2 2 = £10,473 CHADS2 3 = £10,233 (g)	CHADS2 2 = 1.35 CHADS2 3 = 1.30 5 year treatment effect CHADS2 0 = 0.39 CHADS2 1 = 0.42 CHADS2 2 = 0.45 CHADS2 3 = 0.49	QALY gained CHADS2 2 = £7,765 per QALY gained CHADS2 3 = £7,910 per QALY gained 5 year treatment effect CHADS2 0 = £27,745 per QALY gained CHADS2 1 = £25,510 per QALY gained CHADS2 2 = £23,202 per QALY gained CHADS2 3 = £20,831 per QALY gained	CHADS2 2 = 98.6%/99.9% CHADS2 3 = 99.2%/100% 5 year treatment effect CHADS2 0 = 9.1%/57.7% CHADS2 1 = 16.5%/68.8% CHADS2 2 = 26.5%/78.6% CHADS2 3 = 41.8%/88.1% Scenario analysis suggests that duration of benefit is likely to be a key determinant of cost effectiveness, with treatment effects of less than 5 years likely to lead to a cost per QALY gained to be over £20,000. No scenario changed the conclusion of cost effectiveness using a lifetime treatment effect assumption and a 20K threshold, including an annual probability of 15% reversion back to AF after RFCA.
Blackhouse 2013[27] / Assasi 2012[18] (Canada)	Partially applicable (h)	Potentially serious limitations (i)	• Probabilistic model based on meta-analysis and other data sources. • Decision tree and markov model. Health states include: NSR, AF, ischaemic stroke, post ischaemic stroke, major bleed, ICH,	£4,835 (j)	0.144 QALYs	£33,576 per QALY gained	Probability Intervention 2 cost effective (£14K/28K/57K threshold): 3%/30%/89% One way sensitivity analyses undertaken: • There was little change when the annual probability of AF recurrence was adjusted.

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
			post-ICH, other major bleeds (GI) and dead • Cost-utility analysis (QALYs) • Population: Men with paroxysmal AF previously unsuccessful with antiarrhythmic drugs. CHADS2 = 2. • Comparators: 1.Amiodarone 200mg OD 2. Catheter ablation (type not specified, assumed to be radiofrequency) • Time horizon: 5 years				• Results varied according to age, gender and CHADS2 score. • Changing the time horizon had a large impact on results: ○ 3 years: £74.014 per QALY ○ 10 years: £8,082 per QALY ○ 20 years: ablation dominant (less costly and more effective) • When it was assumed restoration of NSR had no impact on stroke risk, ICER increased to £48,770 per QALY • Increasing the disutility of having AF compared to NSR reduced (from 0.043 to 0.08) the ICER to £21,738 per QALY • Decreasing the disutility of having AF: (0.02) increased the ICER to £57,237 per QALY

Abbreviations: AAD = antiarrhythmic drugs ; AF= atrial fibrillation; CE= cost effectiveness; da= deterministic analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); GI=gastrointestinal; ICER= incremental cost-effectiveness ratio; NSR = normal sinus rhythm; NR= not reported; OD= once daily; PSA= probabilistic sensitivity analysis; RCT = randomised controlled trial; RFCA =radiofrequency catheter ablation; SD= standard deviation; QALYs= quality-adjusted life years

(a) Swedish health care payer perspective may not reflect current NHS context, does not include all comparators. Discounting incorrect.

(b) Baseline and relative treatment effects not based on systematic review of the literature. It assumed no rate of reversion for CA after the first year. Neither intervention was well specified, and assumed to be similar to the interventions specified in Stabile et al (2006).It is unclear how the literature informed quality of life decrements or how the treatment effect and resource use estimates were derived. It is unclear whether the best source of unit cost was used. Although the model was constructed

probabilistically, the results were only reported graphically. Results were reported for only one deterministic sensitivity analysis in an incremental manner. It is unclear how a different stroke risk in the AF state would have impacted results in this analysis.

(c) 2006 US dollars converted to UK pounds.[182] Cost components incorporated: Single RFA procedure;Complications inc. tamponade, bleeding, pulmonary vein stenosis, stroke, oesophageal fistula;Annual ADD treatment,Annual anticoagulation,Annual cost of stroke

(d) Rogers 2009 in an HTA and McKenna 2009 in a subsequent paper present a UK Economic evaluation comparing radiofrequency catheter ablation (CA) to long term antiarrhythmic drug (AAD) therapy using Amiodarone (200mg daily, per annum). The population was adults with AF (predominantly paroxysmal) refractory to at least one drug, and sub grouped according to CHADS2 score. Evaluation conducted by construction of a decision tree feeding into Markov model which used findings from a systematic review and meta-analysis, with NHS reference costs supplemented with expert opinion and observational study costings where data standard sources not available. Includes 2 of the 7 interventions of interest. Some QoL estimates based on assumption (no references provided) and others mapped from SF36 to EQ5D (detail of estimation not specified)

(e) Treatment effect was extrapolated post 5 years of follow up. May be reasonable to assume that quality of life improvement would be sustained if the patient did not revert to AF. Assume being in NSR reduces stroke risk.

(f) Assumed that the utility improvements with RFCA compared to AADs are either maintained for a lifetime or maintained for a maximum of 5 years only.

(g) 2006 UK pounds. Cost components incorporated: intervention; complications from cardiac tamponade and PV stenosis; Outpatient initiation of amiodarone; AF and NSR health states; Stroke; Warfarin; Aspirin; Toxic event; Reversible toxicity; Irreversible toxicity; Major bleeding event; Minor bleeding event.

(h) Canadian Health care perspective. Includes 2 of the 7 interventions of interest. QALY's derived from EQ-5D as well as other mapped from other measures of quality of life and not all from UK representative population. Discounting incorrect.

(i) Baseline effects not based on systematic reviews of the literature. Relative treatment effects based on 5 RCTs, and may not reflect full body of evidence available. Unit costs from Canadian published sources and may not reflect UK NHS unit costs.

(j) 2010 Canadian dollars converted to UK pounds.[182]. Cost components incorporated: Ablation procedure including inpatient stay, physician fees and follow up in the first year (3 cardiologist consultations and CT scan), Procedural complications (cardiac tamponade, PV stenosis, stroke and TIA), Drug costs: amiodarone (200mg OD) (given to all those in that arm in all cycles), warfarin for those with AF only, stroke and major bleeding.

Table 26: Health economic evidence profile: Cryoballoon catheter ablation vs. antiarrhythmic drug therapy as second line treatment

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Reynolds 2014[210] (UK)	Partially applicable (a)	Potentially serious limitations(b)	• Probabilistic model based single RCT (STOP-AF, Packer 2013[183]) and other data sources. • Markov model. Health states include sinus rhythm post ablation, sinus rhythm on antiarrhythmic drugs, AF post recurrence (rate control only), disabling and non-	£3,535 (c)	0.161QALYs	£21,957 per QALY gained	Probability Intervention 2 cost effective (£20K/30K threshold): ~40%/86% In addition to the probabilistic sensitivity analysis, a number of one-way sensitivity analyses were conducted. Results were sensitive to the following: • Time horizon (2,10 years) (ICER: ~£90,000 per QALY and ~£3,000 per QALY respectively)

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
			disabling stroke and dead. Procedural complications for ablation patients included in model. • Cost-utility analysis (QALYs) • Population: paroxysmal AF patients unsuccessfully treated with ≥1 antiarrhythmic drug • Comparators: 1. Antiarrhythmic drugs. Sequence of drugs modelled : • first line propafenone • second line sotalol • third line amiodarone • finally rate control therapy alone (metoprolol) 2. Cryoballoon ablation Time horizon: 5 years				• Cost of follow up care in patients with recurrent AF (more expensive the care, lower the ICER) • Total initial procedure cost (more expensive the procedure the higher the ICER)

Abbreviations: 95% CI= 95% confidence interval; AF= atrial fibrillation; CE= cost effectiveness; CUA= cost–utility analysis; da= deterministic analysis; ICER= incremental cost-effectiveness ratio; NSR = normal sinus rhythm; NR= not reported; OD= once daily; PSA= probabilistic sensitivity analysis; RCT = randomised controlled trial; SD= standard deviation; QALYs= quality-adjusted life years

(a) Study does not include all treatment options. QALYs derived from utility scores mapped from other measures of quality of life, not clear if tariff is from a UK representative population.

(b) Baseline and relative treatment effects not based on a systematic reviews of the evidence. Analysis is based on a single RCT and so may not reflect full body of available evidence for this comparison; Potential financial conflict of interest funded by industry: Medtronic.

(c) 2011 UK pounds. Cost components incorporated: Ablation procedure, cryoballoon, freezer catheter, drugs (antiarrhythmic drugs, rate control, warfarin, aspirin), ischaemic stroke (non-disabling and disabling), bleeding (disabling haemorrhagic stroke, non-disabling haemorrhagic stroke, major gastrointestinal bleed, minor bleed, warfarin monitoring), procedural AEs, drug related serious AEs, initiation of amiodarone and monitoring.

Table 27: Health economic evidence profile: Point by point radiofrequency catheter ablation vs. "single shot" cryoballoon ablation as second line treatment

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Chun 2017[53] (UK)	Partially applicable [(a)]	Potentially serious limitations[(b)]	• Within trial analysis (FIRE AND ICE RCT, associated clinical paper Kuck 2016[122, 123]). Analysis of individual level data for health outcomes and resource use. Unit costs applied. • Cost consequence analysis (multiple health outcomes) • Population: Patients with drug refractory symptomatic paroxysmal atrial fibrillation • Comparators: 1. Point-to-point radiofrequency ablation 2. "Single shot" cryoballon ablation Follow-up: 1.54 years (trial period)	saves £363.50 [(c)]	**All cause rehospitalisation**: Incremental (2−1): 21% fewer **Cardiovascular rehospitalisation:** Incremental (2−1): 34% fewer **Repeat ablation:** Incremental (2−1): 33% fewer No difference observed between arms in quality of life metrics (SF-12 and EQ-5D-3L).	"Single shot" cryoballoon ablation dominates point-to-point radiofrequency ablation (lower costs better health outcomes)	Bootstrapping analysis was undertaken. 97% and 98% probability of cost saving in the all cause rehospitalisation and cardiovascular rehospitalisation analyses. One way sensitivity analyses demonstrated that the size of the cost saving was most sensitive to payment level for a repeat ablation (higher payment associated with higher saving) and least sensitive to changes in the individual payment levels for other types of health care utilisation.

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Murray 2018[167] (UK)	Parthially applicable[(d)]	Potentially serious limitations[(e)]	• Deterministic model based on meta-analysis and other data sources. • Decision tree model. Clinical outcomes incorporated were success rates after one year, complications and recurrence pf AF. • Cost-utility analysis (QALYs) • Population: Adults with paroxysmal AF • Comparators: 1. Point by point radiofrequency ablation 2. Single shot cryoballoon ablation • Time horizon: 1 year	£1,747[(f)]	0.01143 QALYs	£152,836 per QALY	One way sensitivity analyses were conducted. The results were most sensitive to the changes in the cost of cryoballoon (if the cost is reduced to £15,000, the incremental cost per QALY ablation compared to RF ablation would be £-158,005). Furthermore, if the probability of AF recurrence is assumed to be 0.15 or 0.35, the cost per QALY becomes £57,881 and £429,832, respectively. The cost of cryoballoon complications had a relatively small impact on results.

Abbreviations: 95% CI= 95% confidence interval; AF= atrial fibrillation; CE= cost effectiveness; CUA= cost–utility analysis; da= deterministic analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER= incremental cost-effectiveness ratio; NSR = normal sinus rhythm; NR= not reported; OD= once daily; PSA= probabilistic sensitivity analysis; RCT = randomised controlled trial; SD= standard deviation; QALYs= quality-adjusted life years

(a) QALYs were not used as the health outcome measure. Study does not include all treatment options.

(b) Analysis is based on a single RCT and so may not reflect full body of available evidence for this comparison; Kuck 2016 is 1 of 11 studies included in the clinical review for catheter ablation versus radiofrequency ablation. Potential financial conflict of interest funded by industry: Medtronic.

(c) 2014-15 UK pounds. Cost components incorporated: Cardiovascular rehospitalisation: repeat ablation, AF related cardiovascular rehospitalisation, non-AF related cardiovascular rehospitalisation, cardioversion; non-cardiovascular rehospitalisation. Note: cost of interventions and adverse events related to interventions not included as authors reported no difference between comparators.

(d) It is unclear whether the utilities are representative of UK population as the RCTs included in the meta-analysis are from different perspectives. Study does not include all treatment options. Short time horizon therefore long-term effects are not captured.

(e) The possibility of mortality was not included. Cost year is unclear. Complication rates including stroke unclearly reported. Reports that stroke will impact quality adjusted life expectancy but this is not clearly reported in model. Model does not include cost adjustment for other comorbidities and PbR tariffs may not reveal the true complexity and cost of a patient episode.

(f) *2015/2016 UK pounds (assumed but not clearly reported). Cost components: Variable hospital costs for the ablation visits (procedure costs, supplies and medication) and complication events.*

1.6.4 Health economic modelling

Although a number of health economic studies have been identified in the literature none of the studies compare all types of ablation to each other as well as to usual care or placebo. A limitation noted in the current HE literature is the lack of long term follow up, which limits the usefulness of these health economic analyses as ablation is not considered to be permanent and therefore it is not known when AF will return. Due to the potentially significant resource impact of ablation and the lack of health economic evidence comparing all interventions and on the long term cost effectiveness of these interventions, the committee agreed this was priority for de novo model.

Model methods

A technical report for this analysis including full details of all methods and model inputs is available in a separate PDF: 'J3 Health Economic Analysis Ablation'.

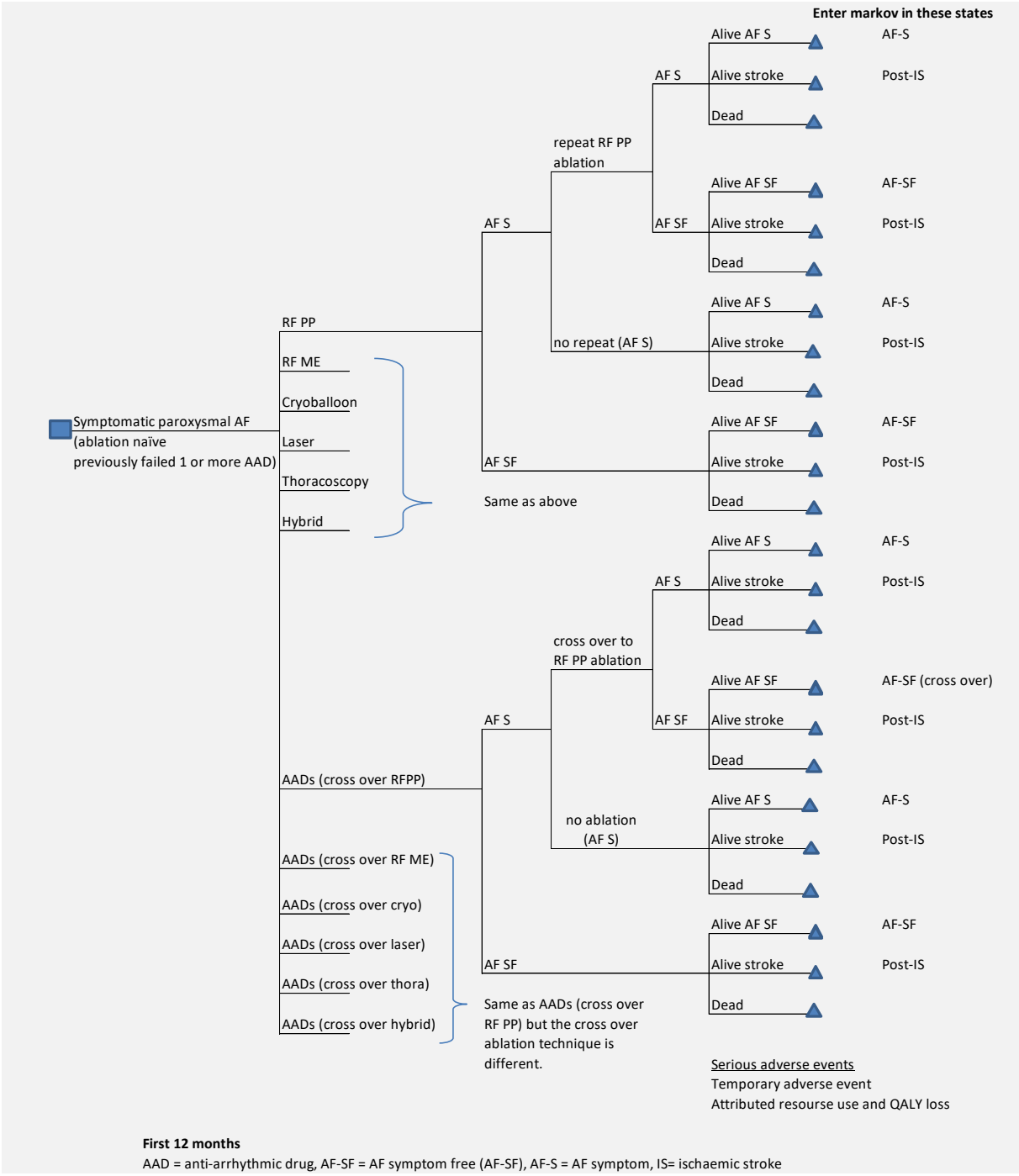
A cost utility analysis was undertaken to compare RF point by point (RF PP), RF multielectrode (ME), cryoballoon, laser, thoracoscopy and hybrid ablation (combination of thoracoscopy and RF PP) to each other as well as to the standard of care, AADs (split into six comparators to allow for cross over to each ablation technique if AF symptoms recur within the first year) in people with paroxysmal AF who are ablation naïve and have failed one or more AAD with an indication for rhythm control. The model was limited to people with paroxysmal AF due to the lack of clinical evidence for persistent AF. This analysis took a current UK NHS and personal social services perspective. A two-part model was constructed which included a decision tree to model events in the first year followed by a Markov model for long term extrapolation in order to calculate lifetime costs and QALYs, using 1 year cycles. Both costs and QALYs were discounted at a rate of 3.5% per annum in line with NICE methodological guidance. An incremental analysis was undertaken.

The clinical outcomes incorporated in the model were: serious adverse events (SAEs) of interventions, freedom of symptoms due to AF, recurrence of symptoms due to AF, stroke, major bleed (intracranial haemorrhage and other major bleeds) and death both due to events and background mortality.

Differential treatment effects that is: SAEs of interventions, freedom of symptoms due to AF, stroke and death were assumed to apply in the first year only. AF symptom recurrence, between those only receiving AADs and those receiving any type of ablation, upfront or as crossover from AADs; and SAEs related to AADs were the only treatment effect to apply beyond the first year. To fully capture the impact of the differences in clinical events in the first year and to capture the differences in rates of AF symptom recurrence between ablation techniques and AADs beyond a year, it was necessary to model the rest of the lifetime of the population.

The decision tree, depicted in **Figure 1**, included four possible events: all stroke, AF symptoms, freedom of AF symptoms and dead. Following an ablation and AF symptom recurrence within the first year year, a proportion would receive a repeat ablation in the first year. All repeat ablations were assumed to be RF PP. In the AAD arms, if AF symptoms recurred within the first year, patients could cross over to ablation. This was modelled for each ablation technique, and therefore 6 AAD comparators were included in the model. A proportion of those initially receiving ablation will receive AADs during a three month blanking period and following an event (AF symptom recurrence or stroke). SAEs vary in nature by comparator. For ablation these were assumed to only occur in year one, whereas for AADs, these could occur over the period these are being taken (both in the decision tree and Markov model). All SAEs were considered to be transient, having an acute cost and short-term impact on quality of life. They do not determine which health state the people enter the Markov model. These were captured in the decision tree and Markov model (for AADs SAE only) by assigning a cost and QALY loss.

Figure 1: Decision tree



At the end of the decision tree, those people alive and free of AF symptoms enter the 'freedom of AF symptoms' state, those alive and with AF symptom recurrence enter the 'AF symptom' state, and finally those who have survived a stroke whether or not they have AF symptoms, enter the 'post-ischaemic stroke' state. For those who were in the AAD comparators but crossed over to ablation in the decision tree, they enter the 'freedom of AF symptom (cross-over)' state.

At each cycle people had a probability of moving between states as depicted in **Figure 2**.

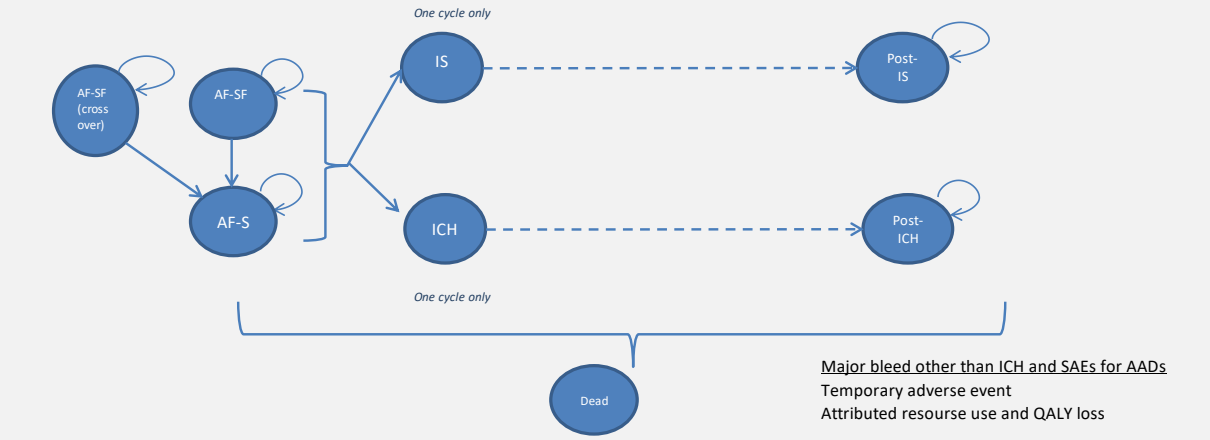
From the freedom of AF symptom states people had a chance of reverting back to symptomatic AF, having an ischaemic stroke, having an intracranial haemorrhage (ICH) or

dying. Those in the AF symptom state have a chance at each cycle of having an ischaemic stroke, an ICH or dying. Ischaemic stroke and ICH were modelled as tunnel health states meaning that people only remained in those states for one cycle (one year), at which point they must transition to dead or post-event health states. People in the post event states remain in these states until death.

At each cycle all those alive in the model, will be at risk of having a major bleed. Of note major bleed in the model excludes ICH which is modelled separately. This was not modelled as an explicit health state as these types of bleed (assumed to be primarily GI bleeds) would not have a permanent impact on the patients in terms of ongoing costs or ongoing health effects. Instead an acute cost and QALY loss was applied for each non-ICH major bleeding event.

SAEs of the ablation interventions were not modelled beyond one year. For AADs, these could occur over the period of time these are being taken in the model.

Figure 2: Markov model



Beyond 1 year
Patients enter model in either AF symptom free (AF-SF), AF symptom (AF-S) or post-ischaemic stroke (Post-IS) health states
For those who had AAD and crossed over to ablation in the first year, they enter the AF-SF (crossover) state.
AF-SF = AF symptom free (AF-SF), AF-S = AF symptom, ICH=Intracranial haemorrhage, IS=Ischaemic stroke
First IS andfirst ICH acute (28 day) fatality modelled as well as all cause mortality

Model inputs are described in full in the separate technical report. The model inputs were taken from the clinical review, including network meta analyses (NMA) of RCTs undertaken for this guideline update, other published evidence identified within the development of this guideline and also based on expert advice from the committee. There was limited longitudinal evidence on the rate of AF recurrence beyond 1 year in the RCTs that met our protocol, and so assumptions were required and other published sources were used to estimate rates of AF recurrence beyond the first year (CABANA trial[185] and observational data from Gaita 2018[81]).

Health-related quality of life weights were based on the published literature. EQ-5D-3L utilities were prioritised where possible (further details on choice of utilities used and their sources available in J3). As with other models, the benefit of the interventions was captured by estimating the proportion of patients who are free of AF symptoms, and thus have an improved quality of life. There was no direct evidence that could estimate the benefit of being free from AF symptoms following ablation or AADs, therefore indirect estimates were sought. A utility decrement associated with having AF symptoms of 0.04 was used in the model, based on evidence from the EuroHeart survey. This was data from a European cohort using EQ-5D and was deemed the most applicable available evidence. UK published costs were used for interventions and health states.

1 An extract of some of the model inputs is reported in Table 28.

2 **Table 28: Extract of model inputs**

Input	Data	Source
Baseline and treatment effects first year (decision tree) – AADs as baseline		
AF recurrence		
AADs	73%	NMA
RF PP ablation	31%	NMA
RF ME ablation	32%	
Cryoballoon ablation	32%	
Laser ablation	36%	
Thoracoscopy	15%	
Hybrid ablation	22%	
Markov model probabilities and HR		
AF recurrence ablation	12-6%	Changes over time and based on data from CABANA RCT for yrs1-4,[185] Gaita 2018[81] yrs 5-10 and then a constant hazard assumed.
AF recurrence AADs	14-7%	Changes over time and based on data from CABANA for yrs1-4[185] then a constant hazard assumed.
Quality of life (utilities)		
Health states		
AF- SF	0.834 in year one (Age and sex dependant)	Age-adjustment (general population utility by age). Calculated using formula from Ara and Brazier 2010.[14] Applied multiplicatively with health state weights.
AF-S utility decrement	0.04	Berg 2010[23] Decrement applied by using AF-SF utility and subtracting this utility decrement when in AF-S state.
IS	0.628	Tengs 2003,[239] weighted according to Youman 2003[273]
post-IS	0.628	
ICH	0.628	
post-ICH	0.628	
Dead	0	By definition
Costs		
Intervention costs		
AADs (annual)	£256	BNF[30] & NHS reference costs,[62, 176] drug and monitoring costs included. Costs applied to all those in AAD arm, 50% ablation for first 3 months (blanking) and a proportion of people in whom AF recurs and who enter stroke/ICH health states (two thirds).
RF PP	£9,286	NHS reference costs2018/2019[62, 176] for procedure, NHS supply chain catalogue for pass through (equipment) costs. Some laser pass through costs based on expert
RF ME ablation	£9,991	
Cryoballoon ablation	£10,951	
Laser ablation	£8,510	

Input	Data	Source
Thoracoscopy	£13,831	advice.
Hybrid ablation	£23,196	Assumes 50% catheter ablation have transoesophageal echocardiogram.

The model was built probabilistically to account for the uncertainty around input parameter point estimates. A probability distribution was defined for each model input parameter. When the model was run, a value for each input was randomly selected simultaneously from its respective probability distribution; mean costs and mean QALYs were calculated using these values. The model was run repeatedly – 10,000 times for the base-case analysis and 5,000 times for each sensitivity analysis – and results were summarised in terms of mean costs and QALYs, and the percentage of time each comparator was the most cost-effective strategy at a threshold of £20,000/£30,000 per QALY gained.

In addition, various one way and scenario sensitivity analyses were undertaken to test the robustness of model assumptions. In these, one or more inputs were changed and the analysis rerun to evaluate the impact on results and whether conclusions on which intervention should be recommended would change.

Results

Base case analysis results are presented in **Table 29**. In the base case analysis, laser ablation was most cost-effective option both at a threshold of £20,000 per QALY and £30,000 per QALY as they had the highest net monetary benefit, with a probability of being the most cost-effective option of 66% and 67% respectively.

A full incremental analysis was also conducted and is depicted graphically in **Figure 3**. Interventions that were ruled out by dominance were AAD (RFPP), AAD (RFME), AAD (cryoballoon), AAD (thoracoscopy), AAD (hybrid), RF ME, thoracoscopy, cryoballoon and hybrid, they were all dominated by RF PP. The ICER was estimated between the remaining non-dominated interventions as represented by the lines. The ICER for laser versus AADs (laser) was £11,754 and for RF PP versus laser was £90,684.

In addition to probabilistic sensitivity analysis a range of one-way and scenario sensitivity analysis were undertaken including varying cohort settings, time horizon, discounting rate, baseline AF recurrence, baseline and relative treatment effects on mortality at 1 year, stroke treatment effects at 1 year, proportion and efficacy of repeat ablations at 1 year, proportion of cross over to ablation at 1 year, AF recurrence after 1 year, impact of AF symptom status on stroke risk, utility decrement for AF symptoms, costs of thoracoscopy and laser ablation, cost of ICH event and proportion of people having a transoesophageal echocardiogram. Threshold analyses around the utility and proportion crossing over to ablation in first year were undertaken. A data validation of the utility data in the model was undertaken.

The conclusions did not change in the majority of sensitivity analyses. The model was sensitive to reductions in the mortality rate in the first year for RFPP. This sensitivity analysis resulted in RFPP being the most cost effective option, followed by laser, with the probability being most cost effective at £20,000 per QALY being 50% and 47% respectively. A sensitivity analysis where the probability of AAD cross over to ablation in the first year following AF symptom recurrence was reduced from 77% in base case to 25% resulted in AAD with cross over to laser ablation being the most cost-effective option (49% probability cost effective at £20,000 per QALY). A threshold analysis found that the proportion cross over would need to be 30% for laser ablation to no longer be the most cost effective option.

The model was sensitive to the costs of laser ablation equipment being increased by 30% to account for potential locally negotiated cost reductions, resulting in RFPP being the most cost effective option, followed by laser ablation (68% and 29% probability most cost effective respectively).

An exploratory analysis where the cost of all catheter ablation was made equal to that of RFPP changed the cost effectiveness ranking to RFPP, followed by cryoballoon and then laser ablation. These results were highly uncertain with the probability of each being the most cost effective being: 27%, 29% and 41% respectively.

When a 5-year time horizon rather than a lifetime horizon was taken, AAD with cross over to laser became the most cost-effective option.

Finally a data validation exercise to see whether the mean treatment difference in terms of utility values by year were similar in our model to those seen in CABANA showed that our resultant utility treatment difference year by year was aligned with the lower confidence interval of the CABANA. A threshold analysis was undertaken to identify what the utility decrement for AF symptoms would need to be to better reflect CABANA. This analysis indicated that a utility decrement of 0.08, rather than 0.04 in the base case would result in similar resultant utility values to CABANA. When the model was run using this utility decrement of 0.08, the model results were similar to the basecase and the conclusions did not change. Overall therefore, these results indicate that we may have slightly underestimated the benefit of ablation, but our results are within the confidence intervals reported by CABANA and when the utility decrement for AF symptoms is increased, the model conclusions are unchanged.

All results and a full discussion of limitations and interpretation of the analysis are included in the full technical report for this analysis available in a separate document ‘J3 Health Economic Analysis Ablation’. The committee’s discussion and interpretation is summarised in section 1.7 of this report.

Table 29: Base case probabilistic results and NMB

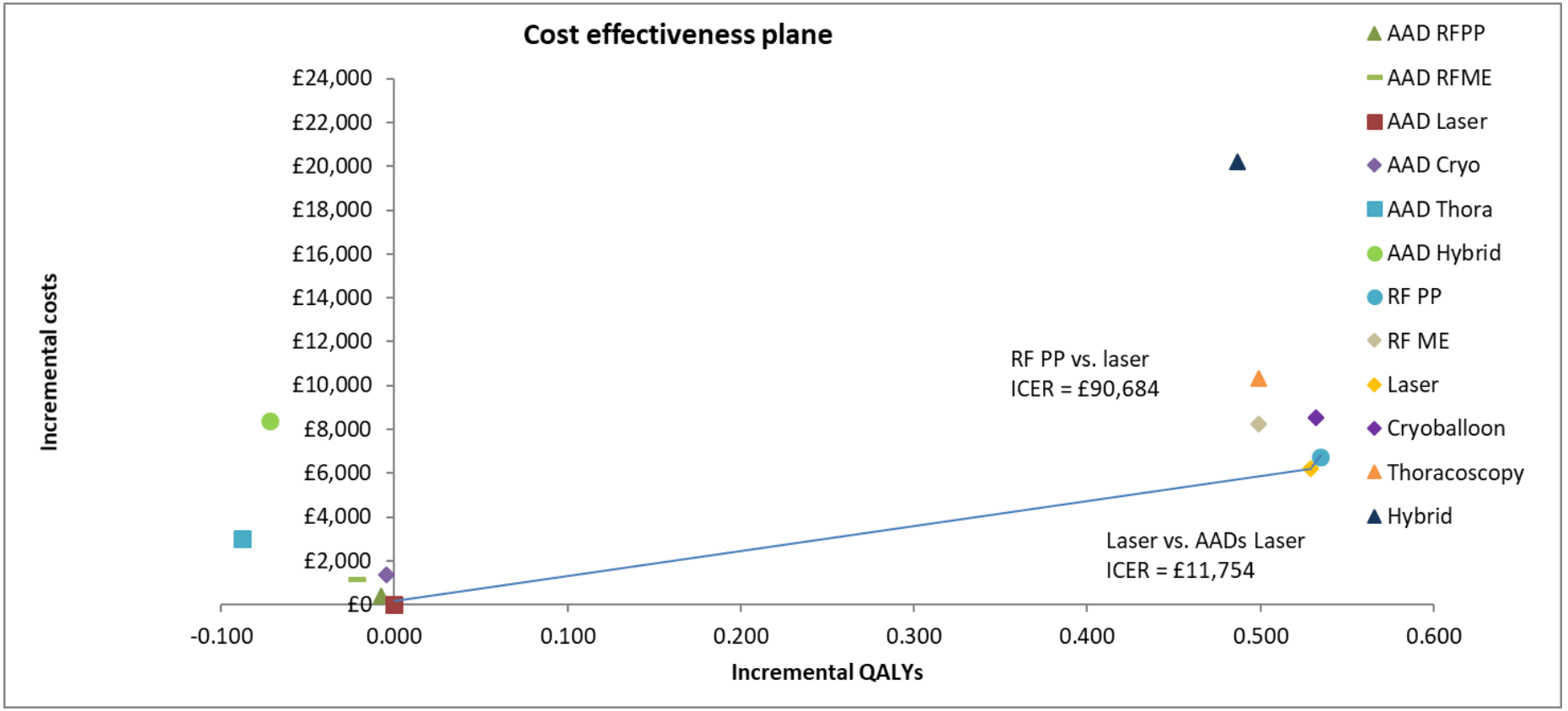
Intervention	Total costs undiscounted	Total costs discounted	Total LY undiscounted	Total LY discounted	Total QALYs undiscounted	Total QALYs discounted	NMB @£20K	Rank @£20K	Rank @£20K LCI	Rank @£20K UCI	% Rank 1 (CE @£20K)
AAD RFPP	£43,560	£29,349	21.847	14.774	15.661	10.844	£187,536	7	3	7	0%
AAD RFME	£44,506	£30,160	21.847	14.775	15.641	10.830	£186,437	9	5	9	0%
AAD Cryo	£44,540	£30,313	21.863	14.782	15.669	10.847	£186,635	8	5	9	0%
AAD Laser	£43,216	£28,967	21.885	14.793	15.679	10.852	£188,066	5	2	7	2%
AAD Thora	£45,919	£31,962	21.563	14.621	15.505	10.764	£183,319	10	9	10	0%
AAD Hybrid	£51,390	£37,355	21.642	14.660	15.543	10.780	£178,240	11	11	12	0%
RF PP	£50,631	£35,709	23.251	15.475	16.687	11.386	£192,016	2	1	3	31%
RF ME	£52,324	£37,187	23.219	15.460	16.631	11.351	£189,823	4	2	8	0%
Cryoballoon	£52,410	£37,483	23.251	15.475	16.683	11.384	£190,187	3	2	8	0%
Laser	£50,114	£35,182	23.251	15.475	16.679	11.380	£192,427	1	1	7	66%
Thoracoscopy	£54,066	£39,291	23.113	15.384	16.630	11.350	£187,716	6	3	10	0%
Hybrid	£63,965	£49,169	23.113	15.384	16.614	11.338	£177,596	12	11	12	0%

Abbreviations: CE = cost effective; disc. = discounted; Incr. = incremental; LCI = lower confidence interval; LY = life years; NMB = net monetary benefit; QALY = quality-adjusted life years; undisc = undiscounted; UCI = upper confidence interval.

** at a threshold of £20,000 per QALY gained*

***at a threshold of £30,000 per QALY gained*

Figure 3: Cost effectiveness plane base case



1.6.5 Health economic evidence statements

Ablation as first line therapy

- One cost-utility analysis found that radiofrequency ablation was not cost effective compared to antiarrhythmic drug therapy as first line rhythm control for people with symptomatic paroxysmal atrial fibrillation (ICER: £45,345 per QALY gained) using a lifetime horizon. This analysis was assessed as partially applicable with potentially serious limitations.

Ablation as second line therapy

- One cost–utility analysis found that radiofrequency catheter ablation was dominant (less costly and more effective) compared to antiarrhythmic drug therapy as second line rhythm control for people with paroxysmal or persistent atrial fibrillation using a lifetime horizon. This analysis was assessed as partially applicable with potentially serious limitations.
- One cost–utility analysis found that radiofrequency catheter ablation was cost effective compared to antiarrhythmic drug therapy as second line rhythm control for people with predominantly paroxysmal atrial fibrillation (ICER: £7,763 to £7,910 per QALY gained, dependent on stroke risk) assuming a lifetime treatment effect duration and that radiofrequency catheter ablation was not cost effective compared to antiarrhythmic drug therapy as second line rhythm control for people with predominantly paroxysmal atrial fibrillation (ICER: £20,831 to £27,745 per QALY gained, dependent on stroke risk) assuming a 5 year treatment effect duration. This analysis was assessed as partially applicable with potentially serious limitations.
- One cost-utility analysis found that catheter ablation was not cost effective compared to antiarrhythmic drug therapy as second line rhythm control for people with paroxysmal atrial fibrillation (ICER: £33,576 per QALY gained) when a 5 year time horizon was taken but was dominant (less costly and more effective) when a 20 year time horizon was taken. This analysis was assessed as partially applicable with potentially serious limitations.
- One cost–utility analysis found that cryoballoon catheter ablation was not cost effective compared to antiarrhythmic drug therapy as second line rhythm control for people with paroxysmal atrial fibrillation (ICER: £21,957 per QALY gained) when a 5 year time horizon was taken but was cost effective (approximately £3,000 per QALY gained) when a 10 year time horizon was taken. This analysis was assessed as partially applicable with potentially serious limitations.
- One cost-consequence analysis found that cryoballoon catheter ablation was dominant (less costly and more effective) compared to radiofrequency point by point catheter ablation as second line rhythm control for people with paroxysmal atrial fibrillation using 1.5 year time horizon. This analysis was assessed as partially applicable with potentially serious limitations.
- One cost–utility analysis found that cryoballoon catheter ablation was not cost effective compared to radiofrequency point by point catheter ablation as second line rhythm control for people with paroxysmal atrial fibrillation (ICER: £152,836 per QALY gained) using a 1 year time horizon. This analysis was assessed as partially applicable with potentially serious limitations.

Ablation for people with paroxysmal AF

- One original cost utility analysis using a lifetime horizon found that laser ablation was cost effective compared to antiarrythmic drugs (with cross over to ablation techniques), radiofrequency point by point, radiofrequency multielectrode, laser and cryoballoon catheter ablation techniques, as well as thoracoscopy and hybrid ablation techniques for people with paroxysmal atrial fibrillation who are ablation naïve and have previously failed one or more antiarrhythmic drug. Antiarrhythmic drugs (with cross over to laser) was dominant (less costly and more effective) compared to antiarrythmic drugs crossing over

to radiofrequency point by pint, radiofrequency multielectrode, cryoballoon and thoracoscopy. Radiofrequency point by point was dominant (less costly and more effective) compared to radiofrequency multielectrode, thoracoscopy, cryoballoon, hybrid ablation and antiarrhythmic drugs with cross over to hybrid ablation. Laser ablation was cost effective compared to antiarrhythmic drugs with cross over to laser (ICER: £11,754 per QALY gained) and RF PP was not cost effective compared to laser (ICER: £90,684 per QALY gained).

1.7 The committee's discussion of the evidence

1.7.1 Interpreting the evidence

1.7.1.1 The outcomes that matter most

Outcomes were quality of life, stroke/systemic embolism, mortality, recurrent symptomatic AF, redo of procedure, hospitalisation with a primary diagnosis of AF, HF/exacerbation of HF, hospital length of stay and serious adverse events. All but hospital length of stay were regarded as critical by the committee, but quality of life, stroke/systemic embolism, mortality, serious adverse events and recurrence were deemed the most relevant for decision-making. These were prioritised over other critical outcomes because 'quality of life' was felt to provide the most comprehensive measure of benefit to the patient, 'stroke and systemic thromboembolism' was regarded as the major serious complication of AF, 'mortality' and 'serious adverse events' were felt to best characterise the harms of treatment, and 'recurrence' was thought to best characterise the benefits of treatment.

1.7.1.2 The quality of the evidence

For the pairwise analyses, the quality of evidence varied. For comparisons between the different ablation techniques, risk of bias tended to be very serious, largely because of a failure to clearly report allocation concealment, and an inability to effectively blind treatments in these studies. Risk of bias tended to be slightly less serious in the studies comparing ablation to usual care. A small number of outcomes exhibited serious heterogeneity, and these were (per protocol) sub-grouped according to the predefined strategies but resolution of heterogeneity was only achieved in one outcome. For some outcomes, downgrading for indirectness was made, due to the study outcomes being slightly different to the protocol outcomes. The other main contributor to overall grading was imprecision. Overall, most outcomes were graded 'low' or 'very low'.

1.7.1.3 Benefits and harms

The relative benefits and harms of interventions in the 4 strata were presented to the committee.

Paroxysmal stratum

Based on the initial pairwise analyses (which were carried out and presented to the committee before a decision to carry out a network meta-analysis was made) the committee agreed that thoracoscopy and the hybrid procedure might have the most benefit compared to other ablation techniques in terms of reducing recurrence of paroxysmal AF and the need for redo of the procedure, but this was based on a small number of studies that had not compared thoracoscopy or the hybrid procedure to many of the possible ablation comparators. In contrast, thoracoscopy and the hybrid procedure appeared to lead to more adverse events than its comparators, making its net balance of risks and benefits roughly similar to the other ablation treatments. The committee also noted that thoracoscopy was only performed in a few centres and so might not be feasible to implement on a nationwide basis. The committee agreed that medical treatment had the highest rate of recurrence but

the lowest rate of stroke, and that the catheter ablation treatments appeared to have similar efficacy and harms to each other. The committee discussed the higher risk of stroke evident from the data for radiofrequency multielectrode (RF ME) treatment, whilst noting that some of the devices responsible for the higher risk had since been discontinued. Based on this pairwise evidence, the committee concluded that the different ablation techniques appeared to have comparable balances of benefits and harms for paroxysmal AF patients. Whilst ablation appeared to be clearly superior to medical care, both for first line patients and those who had failed at least one anti-arrhythmic drug, the committee recognised that comparisons between ablation techniques were made somewhat complex and unclear by the many pairwise comparisons made. Performing a network meta-analysis (NMA) was therefore regarded by the committee as a useful way of clarifying overall results.

The committee discussed the importance of clinical homogeneity in an NMA, and whether this would be threatened by the presence of 1) some trials where, in contrast to most of the trials, the patients were undergoing first line treatment (i.e., they had not been treated with either drugs or ablation before), and 2) trials where the patients had all failed ablation before. The committee voted to keep first line treatments in the proposed NMA on the pragmatic basis that pairwise results showed this made little difference to effect. This was bolstered by the committee's understanding that it was biologically plausible that effect sizes would not be altered. For example, in the between-ablation trials the committee saw no reason why the strength of results would be affected by prior failure of an AAD or not. Similarly, in the ablation versus medical care trials the medical care group were given an alternative drug to that which they had failed so again the committee did not think this would lead to different strength of results in comparison to first line treatment. However the committee voted to remove the trials where patients had previously failed ablation, on the basis that this constituted a very different population of patients; patients failing ablation once would be at a higher probability of failing again, which would create a source of potential heterogeneity.

An NMA based on the above premise was planned and carried out with the assistance of the NICE Guidelines Technical Support Unit (TSU) at the Centre for Advanced Research Synthesis and Decision Science in the Department of Population Health Sciences, Bristol Medical School, University of Bristol. The clinical efficacy results of the NMA showed that whilst thoracoscopy and hybrid were better at preventing AF recurrence than medical treatment (and possibly superior to the catheter ablation treatments as well, though this was uncertain), they led to a greater frequency of serious adverse events. Furthermore, because the studies containing the data for these two treatments were small, the estimates of effect were in general very imprecise. Medical treatment led to less strokes/TIAs than the other treatments, but was inferior in terms of preventing recurrence. The catheter ablation treatments performed similarly to each other, and appeared to have the best compromise of benefits and harms. Of the catheter ablation treatments, RF ME led to the lowest frequency of serious adverse events but also the highest probability of stroke/TIA, whilst RF point to point led to the lowest probability of death. Therefore in terms of clinical efficacy the committee deemed that catheter ablation treatments were probably the most useful approach to use.

The de novo heath economic evaluation showed that the laser ablation was the most cost-effective intervention when compared to other ablation techniques and antiarrhythmic drugs. RF PP was ranked the second most cost effective option an in some sensitivity analyses was the most cost effective option (please see health economics section below). Based on this cost-effectiveness evidence and the uncertainty around whether laser or RF PP was the most cost effective option, the committee agreed to make a consider recommendation for laser or RF PP ablation in symptomatic paroxysmal AF patients if drug treatment is unsuccessful, unsuitable or not tolerated. The committee considered the importance of making a consider rather than an offer recommendation, due to the uncertainty in the results mentioned above but also due to smaller evidence base for laser, which may not fully capture rarer longer term complications

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Persistent < 1 year stratum

Relatively few studies contributed to evidence from this stratum. The committee were confident from the data that RF point to point was better than both laser and medical care in terms of the overall balance of benefits and harms. There were insufficient data available for an NMA.

Persistent >1 year stratum

Only one comparison was available – RF point to point versus medical care. The committee noted that the evidence was less clear about the overall benefits and harms of the two approaches compared to the evidence in the other strata. Whilst RF point to point led to better quality of life in the physical domain, and reduced recurrence and hospitalisation, there was some evidence of greater adverse events and stroke when using RF point to point. There were insufficient data available for an NMA.

For both persistent strata, the data were deemed very limited by the committee. The committee felt that the evidence was sufficient to make a recommendation similar to that for paroxysmal: that ablation should be considered for those who are symptomatic if drug treatment is unsuccessful, unsuitable or not tolerated. Despite being wary of directly extrapolating the findings in paroxysmal patients to persistent patients, given the differences in these patient groups, the committee felt that ablation in those with persistent symptoms could be justified. Given the likely greater propensity of ablation to reduce AF burden, and the possibility of greater AF burden in patients with persistent symptoms, the committee felt it was reasonable to assume that people with persistent symptoms might have as much, if not more, to gain from ablation as people with paroxysmal symptoms. Again, the specific forms of ablation recommended were laser and radiofrequency point by point ablation. This was because these came up as the most cost-effective methods in the paroxysmal AF analysis.

Mixed stratum

The committee discussed the utility of the mixed stratum and whether its evidence would contribute to useful information relevant to any of the three forms of AF. The mixed stratum was formed of studies where no specific type of AF made up >75% of the sample, and most contained samples where the dominant AF type made up considerably less than 75% of the sample. It was suggested by some members of the committee that because the stratum contained patients with persistent AF, the evidence might be used to further inform recommendations concerning the persistent <1 year and >1 year strata. However it was concluded that it was impossible to make recommendations for a specific stratum on the basis of mixed evidence, particularly since the strata had been formed on the basis that the committee expected different strata to yield very different results. Hence the mixed stratum data was not utilised by the committee for decision-making.

1.7.2 Cost effectiveness and resource use

Seven published economic evaluation analyses with relevant comparisons were included in the review. Two of which were included in the previous version of this guideline, CG180.

One Swedish cost utility analysis compared radiofrequency catheter ablation to antiarrhythmic drugs (AADs) as first line therapy for AF and found that ablation was not cost-effective compared to AADs (ICER £45,385). A sensitivity analysis stratifying by age, suggested that ablation was cost effective for people younger than 50. This was a lifetime model based on a single RCT (MANTRA-PAF). The study had unclear methodological reporting, did not include all comparators of interest and effectiveness data was based on a single RCT. Of note, the recurrence data from this RCT could not be used in the clinical review because it was unclear if cumulative data provided in the table included events

occurring in the blanking period. Overall, this study was considered to be partially applicable with potential serious limitations.

Four cost utility analyses studies were included that compared catheter ablation to AADs as second line therapy for AF. Each found that subject to certain assumptions, catheter ablation was cost effective compared to AADs (either dominates AADs or ICER between £7,000 and £21,000). All of these studies were considered to be partially applicable with potentially serious limitations. In particular, none of these studies included all comparators and none included the full body of clinical evidence identified in our clinical review. The assumptions made in these models regarding the rate of AF symptom recurrence was considered to be very favourable towards ablation and not reflective of current evidence. Most of these models assumed that being free of AF symptoms resulted in a reduction in stroke risk, which the committee considered to not be supported by current clinical evidence. Overall therefore the committee were not confident in the conclusion of these studies.

Finally, two studies compared cryoballoon ablation to RF ablation as second line therapy. Both were UK studies with very short time horizons (1-1.5years). One was a within trial cost consequence analysis which suggested that cryoballon dominated (less costly and more effective) RF PP and the other was a cost utility analysis which found that cryoballon was not cost-effective when compared to RF ablation (ICER >£150,000 per QALY). Both studies were judged to be partially applicable with potentially serious limitations. The committee did not think either study provided valuable information to inform decision making.

As a result of the inadequate published health economic evidence, it was agreed to prioritise this area for original economic modelling. A de novo model was conducted to compared all ablation types: RF point by point (RF PP), RF multielectrode (ME), cryoballoon, laser, thoracoscopy and hybrid ablation (combination of thoracoscopy and RF PP) to each other as well as to the standard of care, AADs (split into six comparators to allow for cross over to each ablation technique if AF symptoms recur within the first year). The model was limited to people with paroxysmal AF due to the lack of clinical evidence for persistent AF and was a population who were ablation naïve and who had previously failed one or more AAD. The model included a decision tree to capture short term clinical outcomes and costs associated with the different comparators (up to 1 year). Data for AF recurrence from the NMA conducted as part of the review was used to populate the decision tree. A Markov model structure was used to extrapolate the clinical outcomes and costs over a lifetime. Clinical outcomes and health states included in this model were AF symptom recurrence, ischaemic stroke, intracranial haemorrhage, major bleed, serious adverse events associated with the comparators and death. The model inputs were taken from the clinical review, including NMA, other published evidence identified within the development of this guideline and also based on expert advice from the committee. As noted below in the 'other considerations' section, there was limited longitudinal evidence on the rate of AF recurrence beyond 1 year in the RCTs that met our protocol, and so assumptions were required and other published sources were used to estimate rates of AF recurrence beyond the first year (CABANA trial and observational data from Gaita 2018).

As with other models, the benefit of the interventions was captured by estimating the proportion of patients who are free of AF symptoms, and thus have an improved quality of life. There was no direct evidence that could estimate the benefit of being free from AF symptoms following ablation or AADs, therefore indirect estimates were sought. A utility decrement associated with having AF symptoms of 0.04 was used in the model, based on evidence from the EuroHeart survey. A large number of sensitivity analyses were conducted to explore uncertainty around model parameters and model assumptions.

The base case and most sensitivity analyses found laser ablation was the most cost effective option at a threshold of £20,000 per QALY (probability of being most cost effective 66% in base case). RF PP was ranked second most cost effective at £20,000 per QALY (probability of being most cost effective 31%). In the full incremental analysis, the ICER for

laser ablation versus AAD (cross over laser) was £11,754 per QALY and the ICER for RFPP versus laser was £90,684 per QALY. All other options were dominated (more costly and less effective).

The model was sensitive to reductions in the mortality rate in the first year for RFPP. This sensitivity analysis resulted in RFPP being the most cost effective option, followed by laser, with the probability being most cost effective at £20,000 per QALY being 50% and 47% respectively. A sensitivity analysis where the probability of AAD cross over to ablation in the first year following AF symptom recurrence was reduced from 77% in base case to 25% resulted in AAD with cross over to laser ablation being the most cost-effective option (49% probability cost effective at £20,000 per QALY). A threshold analysis found that the proportion cross over would need to be 30% for laser ablation to no longer be the most cost effective option. The committee noted that in people who have failed 1 or more AAD and remained symptomatic, more than 30% would be considered for ablation in current practice.

The model was sensitive to the costs of laser ablation equipment being increased by 30% to account for potential locally negotiated cost reductions, resulting in RFPP being the most cost effective option, followed by laser ablation (68% and 29% probability most cost effective respectively). An exploratory analysis where the cost of all catheter ablation was made equal to that of RFPP changed the cost effectiveness ranking to RFPP, followed by cryoballoon and then laser ablation. These results were highly uncertain with the probability of each being the most cost effective being: 27%, 29% and 41% respectively. As this exploratory analysis was not based on evidence of equivalent overall cost, the committee could not make recommendations based on this exploratory analysis. However, the committee noted that because of the way the NHS reference cost group procedures together under single HRGs, all catheter ablation procedures had the same procedural cost. As a result potential savings that could be incurred from procedures that have a shorter duration or that do not require general anaesthetic, such as cryoballoon ablation, are not captured in the analysis.

When a 5-year time horizon rather than a lifetime horizon was taken, AAD with cross over to laser became the most cost-effective option. The same was observed with the other published health economic analyses, and highlights the importance of fully capturing the long term benefits of ablation in order to offset the upfront cost of the procedure.

Finally, a data validation exercise to see whether the mean treatment difference in terms of utility values by year were similar in our model to those seen in CABANA showed that our resultant utility treatment difference year by year was aligned with the lower confidence interval of CABANA. A threshold analysis was undertaken to identify what the utility decrement for AF symptoms would need to be to better reflect CABANA. This analysis indicated that a utility decrement of 0.08, rather than 0.04 in the base case would result in similar resultant utility values to CABANA. When the model was run using this utility decrement of 0.08, the model results were similar to the base case and the conclusions did not change. Overall therefore, these results indicate that we may have slightly underestimated the benefit of ablation, but the model results are within the confidence intervals reported by CABANA and when the utility decrement for AF symptoms is increased, the model conclusions are unchanged.

These results were presented to the committee and it was agreed, based on this cost-effectiveness evidence and the uncertainty around whether laser or RF PP was the most cost effective option, to make a consider recommendation for laser or RF PP ablation in symptomatic paroxysmal AF patients if drug treatment is unsuccessful, unsuitable or not tolerated. RF PP was included as an option, as there was uncertainty in the conclusions demonstrated both in the probability of which intervention would be the most cost effective option and also in the outcome of some of the sensitivity analyses such as increasing the cost of laser ablation to account for local discounting. The committee considered the importance of making a consider rather than an offer recommendation, due to the uncertainty

in the results mentioned above but also due to smaller evidence base for laser, which may not fully capture rarer complications. The committee noted that RFPP is widely used in practice, therefore recommending this technique would not represent a change in practice. Regarding laser ablation however, the committee noted that there is limited use of this technique currently in the NHS and therefore the recommendation would represent a change in practice. It was also noted that laser ablation requires specific equipment that is not used for any other procedures and would therefore need to be purchased before it could be used in many cases, due to its limited use in current practice. A similar issue was said to apply to cryoballoon ablation, though it was agreed that this was more widely used in current practice than laser. The same issue was not thought to apply to RFPP as it is more widely used currently and also because it uses equipment that is also used for other, non-AF ablation procedures and would therefore already be available in most cases. In addition, due to its limited use currently, the committee noted that training in laser ablation would be required for many before it could be performed. The committee noted that there was some uncertainty regarding the costs of procedures that are currently only performed in a small number of centres, such as laser ablation and thoracoscopy. The uncertainty in these costs was explored in sensitivity analyses in the model.

Although the recommendation specifies RFPP and laser over other ablation techniques as these were the most cost effective, this does not mean that other techiques such as cryoballoon are prohibited. Furthermore, if patient preferences include factors such as avoiding general anaesthetic, then cryoballoon may be the ablation technique of choice for that individual.

This recommendation was extended to the persistent AF population if drug treatment is unsuccessful, unsuitable or not tolerated. This was done on the assumption that people with persistent symptoms might have as much, if not more, to gain from ablation as people with paroxysmal symptoms and therefore the interventions would be very likely to be cost effective in this population.

1.7.3 Other factors the committee took into account

Other trials not included in the review

During presentation of the ablation review, the existence of a new and related paper (CABANA) came to light. This did not fit into the existing review question but some committee members initially felt it should be included.

Initially, the current question '*What is the clinical and cost effectiveness of different ablative therapies in people with atrial fibrillation?'* was discussed. The committee agreed that this complied with the surveillance review remit to compare between different ablative techniques AND compare ablation to medical care. The committee also agreed that CABANA did not fit into the existing question, as CABANA has a mixed array of catheter-based treatments lumped together versus medical care. However, it was agreed that it was a highly-powered large-scale study with some useful clinical outcomes, and so potential options for including it in some way were explored.

The first option that was discussed involved adding an *extra* question, where undifferentiated catheter ablation is compared to medical care are, using the same papers as in the existing question. This would allow the new question to stand alongside the existing question**.** This would involve many of the single-technique studies in the existing review being used again in this new question, but this time being subsumed into the broader category of 'catheter ablation'. Thus, in this 'lumped' form such studies could be looked at alongside studies like CABANA, which would also qualify for the general category of 'catheter ablation'. However, the committee agreed that it would not be methodologically sound to use the same data in two questions, because this would constitute double counting and represent over-analysis.

The second option that was discussed was to remove the current question and replace it with the new undifferentiated catheter ablation versus medical care question. The committee agreed that this option was also unacceptable because excluding a question that had where the results had been presented particularly if it were agreed by the committee to be a relevant and important question, would contravene the robustness of the reviewing process. Furthermore, the committee agreed that the question comparing the different types of ablation was the priority.

The third option discussed was to have an additional question that only looks at new papers where the ablation techniques have been lumped together versus medical care. An example question could be: *What is the clinical and cost effectiveness of catheter ablation versus medical care?* This would stand alongside the existing question without any overlap; avoiding double counting of data and avoiding exclusion of work already done, thus preventing the problems of the first two options. The committee discussed the advantages and disadvantages of this third approach.

The committee accepted certain benefits of such an approach. For example, given that the NMA showed that the catheter ablation techniques have similar levels of benefits and harms for people with paroxysmal AF, it was felt not unreasonable, at a second step, to consider evidence that used combined 'lumped' ablation evidence to confirm if catheter ablation is better than medical care. This would allow extra data to be considered such as from CABANA.

However, the committee also agreed that there were considerable disadvantages with the third option. Firstly, it was felt that this additional question was not needed because it had already been answered with high fidelity. The NMA, which is part of the existing question, shows (for paroxysmal AF) that medical care is inferior in terms of preventing recurrence to *each different form of* catheter ablation. This is in relation to some very relevant clinical outcomes including recurrence, mortality, stroke and serious adverse events.

It was also noted that whilst the existing question has limited safety data on some modalities, and does lack some power for discerning precise effects relating to stroke and death for some catheter ablation comparisons, CABANA cannot be used to add to the limited safety data because, whatever its other merits, CABANA was flawed by not separating out the type of AF.

In our discussion the generalisability of the results of the NMA due to the tight inclusion criteria of the included studies was also raised. CABANA had more relaxed inclusion criteria and therefore including this data would address this issue. However, as mentioned above, CABANA did not stratify by type of AF.

Furthermore, the committee realised it is methodologically wrong to change a question because we are surprised by the studies excluded/included, as this could be seen as bias.

It was also felt that the addition of this new question would risk adding confusion rather than clarity when it comes to making recommendations. It was agreed that there can only be one set of recommendations for this topic area, but if there are two questions that are devised to provide evidence to inform those recommendations there could well be conflicting findings. It would be difficult in a practical sense, and probably impossible if trying to preserve some methodological integrity, to make a choice between the possible courses of action that might arise. Health economic arguments against the use of the third option were also discussed and are outlined below in the HE section.

Overall, the committee felt that the case for not having the additional question was stronger than the case for including it, and so option 3 was excluded. This left the committee with the remaining option: not adding any new questions, but instead including papers like CABANA in the committee discussion, which could be used to support recommendations. This fourth option was believed to allow clearer recommendations because it would avoid having two

similar but different questions. Hence, the committee agreed that the fourth approach was the strategy that should be used.

HE modelling additional considerations and the use of CABANA

Of note, there was no original health economic modelling around CABANA published. We had planned an original HE model for patients with paroxysmal AF comparing each type of ablation and including medical treatment as a comparator based on the availability of clinical evidence from our existing review. Conducting an additional model comparing catheter ablation (type unspecified) versus medical treatment would be difficult to reconcile with our detailed model which includes costs and effects of each ablation type.

In addition, when it comes to our health economic model, we looked to other sources of evidence to extrapolate the findings of the clinical review (1 year data) to a lifetime horizon. This is a standard approach in modelling. The decision-tree part of the model uses the clinical review data (NMA) to populate the treatment differences at 1 year. This determines the proportion of patients that enter the Markov model (AF symptoms, AF symptom-free and post-stroke). The Markov model then extrapolates this over a lifetime. Movement between health states will depend on whether they have AF symptoms or not and used other sources of data (for movement to stroke, bleed, death). There will be over time however movement between the AF symptom-free and the AF-symptoms health states as it is expected that over time AF symptoms will recur following ablation in some patients. We have not identified this longer term RCT evidence in our clinical review (despite not limiting our time-point for data). In order to identify the most appropriate evidence for use in the model we looked at published longitudinal/observational data and also studies such as CABANA that have a longer follow up. As we did not identify data on AF recurrence beyond a year for each ablation type, an assumption that recurrence rates are the same irrespective of type of ablation was made. It was agreed with the committee, having compared the available longitudinal data, to use the AF recurrence data from CABANA in the Markov model as well as data from an observational study (Gaita 2018), assuming the rate of recurrence is the same for all ablation types (using the catheter arm of CABANA) and use the rate of recurrence of the medical arm of CABANA for the medical comparator in our model.

We were unable to use the CABANA data for stroke, bleeding or mortality data in the model as the model structure is such that after one year the probability of having any of these events is determined by their previous health state and not due to the intervention (that is if at the end of 1 year they are symptom free, then their chance of having a stroke will be the same as all those who are symptom free irrespective of the intervention they originally received). The same applies to quality of life; in the model, quality of life is based on the health state the person is in rather than quality of life over time based on the intervention they received. We have however used the quality of life data from CABANA to validate our model. Further details are provided in the health economic section.

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1 Appendices

2 Appendix A: Review protocols

3 **Table 30: Review protocol: Ablation**

ID	Field	Content
0.	PROSPERO registration number	[Complete this section with the PROSPERO registration number once allocated]
1.	Review title	Clinical and cost effectiveness of different ablative therapies in people with atrial fibrillation
2.	Review question	What is the clinical and cost effectiveness of different ablative therapies in people with atrial fibrillation?
3.	Objective	To identify the clinical effects of the different ablative therapies in this population, including comparison to medical (drug) treatment
4.	Searches	The following databases will be searched: Cochrane Central Register of Controlled Trials (CENTRAL) Cochrane Database of Systematic Reviews (CDSR) Embase MEDLINE Epistemonikos Searches will be restricted by: English language Human studies Letters and comments are excluded. Other searches: Inclusion lists of relevant systematic reviews will be checked by the reviewer. The searches may be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion if relevant. The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Atrial Fibrillation
6.	Population	Inclusion: People aged over 18 with a diagnosis of AF Exclusion: People with AF due to severe valvular disease
7.	Intervention/Exposure/Test	surgical ablation – thorascopic surgical ablation - open (not as a concomitant Rx) Hybrid catheter/surgical radiofrequency catheter ablation - point by point radiofrequency catheter ablation – multi-electrode cryoballoon catheter ablation

ID	Field	Content
		laser catheter ablation
8.	Comparator/Reference standard/Confounding factors	To each other (between any of the 7 classes above – no comparison within any of the 7 classes) Placebo Usual Care (this includes medical care, such as antiarrhythmic drugs) No treatment.
9.	Types of study to be included	Systematic reviews RCTs (including those with a cross-over design). Non-randomised studies will be excluded.
10.	Other exclusion criteria	Non-English language studies. Abstracts will be excluded as it is expected there will be sufficient full text published studies available.
11.	Context	N/A
12.	Primary outcomes (critical outcomes)	health-related quality of life mortality stroke or thromboembolic complications Recurrent symptomatic AF (post-blanking period) hospitalisation with a primary diagnosis of atrial fibrillation Redo of procedure (catheter/surgical) HF/exacerbation of heart failure. Longest follow up point always used
13.	Secondary outcomes (important outcomes)	• Hospital length of stay • Serious AEs Longest follow up point always used
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. Titles and/or abstracts of studies retrieved using the search strategy and those from additional sources will be screened for inclusion. The full text of potentially eligible studies will be retrieved and will be assessed for eligibility in line with the criteria outlined above. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. An in-house developed database; EviBase, will be used for data extraction. A standardised form is followed to extract data from studies (see Developing NICE guidelines: the manual section 6.4) and for undertaking assessment of study quality. Summary evidence tables will be produced including information on: study setting; study population and participant demographics and baseline characteristics; details of the intervention and control interventions; study methodology' recruitment and missing data rates; outcomes and times of measurement; critical appraisal ratings. A second reviewer will quality assure the extracted data. Discrepancies will be identified and resolved through discussion (with

ID	Field	Content
		a third reviewer where necessary).
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. For Intervention reviews the following checklist will be used according to study design being assessed: Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) Randomised Controlled Trial: Cochrane RoB (2.0) Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
16.	Strategy for data synthesis	Where possible, data will be meta-analysed. Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5) to combine the data given in all studies for each of the outcomes stated above. A fixed effect meta-analysis, with weighted mean differences for continuous outcomes and risk ratios for binary outcomes will be used, and 95% confidence intervals will be calculated for each outcome. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. We will consider an I^2 value greater than 50% indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented using random-effects. GRADE pro will be used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. Other bias will only be taken into consideration in the quality assessment if it is apparent. Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. If sufficient data is available to make a network of treatments, WinBUGS will be used for network meta-analysis.
17.	Analysis of sub-groups	Stratification Split analysis 4 ways according to population, defined by AF type: persistent AF (min 75% in study) <1 year versus persistent AF (min 75% in study) >1 year versus paroxysmal AF (min 75% in study) versus mixed AF (if less than 75% of any particular type in a study) In addition, of course, we will stratify by each separate permutation of intervention and comparator. Sub-grouping If serious or very serious heterogeneity (I2>50%) is present within any stratum, sub-grouping will occur according to the following strategies:

ID	Field	Content		
		Existence of HF (yes/No) CHADSVASC score (<2/>2)		
18.	Type and method of review	☒	Intervention	
		☐	Diagnostic	
		☐	Prognostic	
		☐	Qualitative	
		☐	Epidemiologic	
		☐	Service Delivery	
		☐	Other (please specify)	
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date			
22.	Anticipated completion date			
23.	Stage of review at time of this submission	Review stage	Started	Completed
		Preliminary searches	☐	☑
		Piloting of the study selection process	☐	☑
		Formal screening of search results against eligibility criteria	☐	☑
		Data extraction	☐	☑
		Risk of bias (quality) assessment	☐	☑
		Data analysis	☐	☑
24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre		
25.	Review team members	From the National Guideline Centre: Sharon Swain Mark Perry		

ID	Field	Content	
		Nicole Downes Sophia Kemmis Betty Elizabeth Pearton	
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.	
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: [NICE guideline webpage].	
29.	Other registration details		
30.	Reference/URL for published protocol		
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: notifying registered stakeholders of publication publicising the guideline through NICE's newsletter and alerts issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Atrial Fibrillation, ablation, antiarrhythmic drugs	
33.	Details of existing review of same topic by same authors	N/A	
34.	Current review status	☒	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information	N/A	
36.	Details of final publication	www.nice.org.uk	

1

Table 31: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below. For questions being updated from NICE guideline CG180, the search will be run from October 2013, which was the cut-off date for the searches. For questions being updated from the NICE guideline CG36 and for new questions, the search will be run from 2003.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2003, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Studies published after 2003 that were included in the previous guideline(s) will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual.[173] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies.

	Setting: • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2003 or later (including any such studies included in the previous guideline(s)) but that depend on unit costs and resource data entirely or predominantly from before 2003 will be rated as 'Not applicable'. • Studies published before 2003 (including any such studies included in the previous guideline(s)) will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B: Literature search strategies

This literature search strategy was used for the following reviews:

- **What is the clinical and cost effectiveness of different ablative therapies in people with atrial fibrillation?**

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[173]

For more information, please see the Methods Report published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 32: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 31 December 2019	Exclusions Randomised controlled trials Systematic review studies

Database	Dates searched	Search filter used
Embase (OVID)	1974– 31 December 2019	Exclusions Randomised controlled trials Systematic review studies
The Cochrane Library (Wiley)	Cochrane Reviews to 2019 Issue 12 of 12 CENTRAL to 2019 Issue 12 of 12	None
Epistemonikos (Epistemonikos Foundation)	Inception – 31 December 2019	Systematic review studies

1 **Medline (Ovid) search terms**

1.	exp atrial fibrillation/
2.	((atrial or atria or atrium or auricular) adj3 fibrillat*).ti,ab.
3.	AF.ti,ab.
4.	1 or 2 or 3
5.	letter/
6.	editorial/
7.	news/
8.	exp historical article/
9.	Anecdotes as Topic/
10.	comment/
11.	case report/
12.	(letter or comment*).ti.
13.	or/5-12
14.	randomized controlled trial/ or random*.ti,ab.
15.	13 not 14
16.	animals/ not humans/
17.	exp Animals, Laboratory/
18.	exp Animal Experimentation/
19.	exp Models, Animal/
20.	exp Rodentia/
21.	(rat or rats or mouse or mice).ti.
22.	or/15-21
23.	4 not 22
24.	limit 23 to English language
25.	exp Ablation Techniques/
26.	ablat*.ti,ab.
27.	(cryoablat* or cryoballoon* or cryo balloon*).ti,ab.
28.	phased array.ti,ab.
29.	*Pulmonary Veins/
30.	((pulmonary vein adj2 isolation) or PVI or PVAI).ti,ab.
31.	radiofrequency therapy/
32.	((radiofrequenc* or radio frequenc* or RF or hybrid) adj2 (therap* or surg* or procedure*)).ti,ab.
33.	"point by point".ti,ab.
34.	Lasers/

35.	laser*.ti,ab.
36.	(maze adj2 (procedure* or surg*)).ti,ab.
37.	cox-maze.ti,ab.
38.	or/25-37
39.	24 and 38
40.	randomized controlled trial.pt.
41.	controlled clinical trial.pt.
42.	randomi#ed.ab.
43.	placebo.ab.
44.	randomly.ab.
45.	clinical trials as topic.sh.
46.	trial.ti.
47.	or/40-46
48.	Meta-Analysis/
49.	Meta-Analysis as Topic/
50.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
51.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
52.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
53.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
54.	(search* adj4 literature).ab.
55.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
56.	cochrane.jw.
57.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
58.	or/48-57
59.	39 and (47 or 58)

1 **Embase (Ovid) search terms**

1.	exp atrial fibrillation/
2.	((atrial or atria or atrium or auricular) adj3 fibrillat*).ti,ab.
3.	AF.ti,ab.
4.	1 or 2 or 3
5.	letter.pt. or letter/
6.	note.pt.
7.	editorial.pt.
8.	case report/ or case study/
9.	(letter or comment*).ti.
10.	or/5-9
11.	randomized controlled trial/ or random*.ti,ab.
12.	10 not 11
13.	animal/ not human/
14.	nonhuman/
15.	exp Animal Experiment/
16.	exp Experimental Animal/

17.	animal model/
18.	exp Rodent/
19.	(rat or rats or mouse or mice).ti.
20.	or/12-19
21.	4 not 20
22.	limit 21 to English language
23.	exp ablation therapy/
24.	ablat*.ti,ab.
25.	(cryoablat* or cryoballoon* or cryo balloon*).ti,ab.
26.	phased array.ti,ab.
27.	pulmonary vein isolation/ or pulmonary vein/
28.	((pulmonary vein adj2 isolation) or PVI or PVAI).ti,ab.
29.	catheter ablation/
30.	((radiofrequenc* or radio frequenc* or RF or hybrid) adj2 (therap* or surg* or procedure*)).ti,ab.
31.	"point by point".ti,ab.
32.	laser/ or low level laser therapy/ or laser surgery/
33.	laser*.ti,ab.
34.	(maze adj2 (procedure* or surg*)).ti,ab.
35.	cox-maze.ti,ab.
36.	or/23-35
37.	22 and 36
38.	random*.ti,ab.
39.	factorial*.ti,ab.
40.	(crossover* or cross over*).ti,ab.
41.	((doubl* or singl*) adj blind*).ti,ab.
42.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
43.	crossover procedure/
44.	single blind procedure/
45.	randomized controlled trial/
46.	double blind procedure/
47.	or/38-46
48.	systematic review/
49.	Meta-Analysis/
50.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
51.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
52.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
53.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
54.	(search* adj4 literature).ab.
55.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
56.	cochrane.jw.
57.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
58.	or/48-57

59.	37 and (47 or 58)

1 **Cochrane Library (Wiley) search terms**

#1.	MeSH descriptor: [Atrial Fibrillation] explode all trees
#2.	((atrial or atria or atrium or auricular) near/3 fibrillat*):ti,ab
#3.	AF:ti,ab
#4.	#1 or #2 or #3
#5.	MeSH descriptor: [Ablation Techniques] explode all trees
#6.	ablat*:ti,ab
#7.	(cryoablat* or cryoballoon* or cryo balloon*):ti,ab
#8.	phased array:ti,ab
#9.	MeSH descriptor: [Pulmonary Veins] this term only
#10.	"pulmonary vein" near/2 isolation:ti,ab
#11.	(PVI or PVAI):ti,ab
#12.	MeSH descriptor: [Radiofrequency Therapy] this term only
#13.	((radiofrequenc* or radio frequenc* or RF or hybrid) near/2 (therap* or surg* or procedure*)):ti,ab
#14.	"point by point":ti,ab
#15.	MeSH descriptor: [Lasers] this term only
#16.	laser*:ti,ab
#17.	(maze near/2 (procedure* or surg*)):ti,ab
#18.	cox-maze:ti,ab
#19.	(or #5-#18)
#20.	#4 and #19

2 **Epistemonikos search terms**

1.	(title:(atrial fibrillation OR "AF") OR abstract:(atrial fibrillation OR "AF")) OR (title:(atria fibrillat* OR atrium fibrillat* OR auricular fibrillat*) OR abstract:(atria fibrillat* OR atrium fibrillat* OR auricular fibrillat*))

B.2 3 Health Economics literature search strategy

4 Health economic evidence was identified by conducting a broad search relating to the Atrial
5 Fibrillation population in NHS Economic Evaluation Database (NHS EED – this ceased to be
6 updated after March 2015) and the Health Technology Assessment database (HTA). NHS
7 EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD).
8 Additional health economics searches were run on Medline and Embase.

9 **Table 33: Database date parameters and filters used**

Database	Dates searched	Search filter used
Medline	2003– 31 December 2019	Exclusions Health economics studies Quality of life studies
Embase	2003– 31 December 2019	Exclusions Health economics studies Quality of life studies
Centre for Research and Dissemination (CRD)	NHSEED - 2003 to March 2015 HTA - 2003 –31 December 2019	None

1 Medline (Ovid) search terms

1.	exp atrial fibrillation/
2.	((atrial or atria or atrium or auricular) adj3 fibrillat*).ti,ab.
3.	AF.ti,ab.
4.	1 or 2 or 3
5.	letter/
6.	editorial/
7.	news/
8.	exp historical article/
9.	Anecdotes as Topic/
10.	comment/
11.	case report/
12.	(letter or comment*).ti.
13.	or/5-12
14.	randomized controlled trial/ or random*.ti,ab.
15.	13 not 14
16.	animals/ not humans/
17.	exp Animals, Laboratory/
18.	exp Animal Experimentation/
19.	exp Models, Animal/
20.	exp Rodentia/
21.	(rat or rats or mouse or mice).ti.
22.	or/15-21
23.	4 not 22
24.	limit 23 to English language
25.	economics/
26.	value of life/
27.	exp "costs and cost analysis"/
28.	exp Economics, Hospital/
29.	exp Economics, medical/
30.	Economics, nursing/
31.	economics, pharmaceutical/
32.	exp "Fees and Charges"/
33.	exp budgets/
34.	budget*.ti,ab.
35.	cost*.ti.
36.	(economic* or pharmaco?economic*).ti.
37.	(price* or pricing*).ti,ab.
38.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
39.	(financ* or fee or fees).ti,ab.
40.	(value adj2 (money or monetary)).ti,ab.
41.	or/25-40
42.	quality-adjusted life years/

43.	sickness impact profile/
44.	(quality adj2 (wellbeing or well being)).ti,ab.
45.	sickness impact profile.ti,ab.
46.	disability adjusted life.ti,ab.
47.	(qal* or qtime* or qwb* or daly*).ti,ab.
48.	(euroqol* or eq5d* or eq 5*).ti,ab.
49.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
50.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
51.	(hui or hui1 or hui2 or hui3).ti,ab.
52.	(health* year* equivalent* or hye or hyes).ti,ab.
53.	discrete choice*.ti,ab.
54.	rosser.ti,ab.
55.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
56.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
57.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
58.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
59.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
60.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
61.	or/42-60
62.	24 and (41 or 61)

1 **Embase (Ovid) search terms**

1.	exp atrial fibrillation/
2.	((atrial or atria or atrium or auricular) adj3 fibrillat*).ti,ab.
3.	AF.ti,ab.
4.	1 or 2 or 3
5.	letter.pt. or letter/
6.	note.pt.
7.	editorial.pt.
8.	case report/ or case study/
9.	(letter or comment*).ti.
10.	or/5-9
11.	randomized controlled trial/ or random*.ti,ab.
12.	10 not 11
13.	animal/ not human/
14.	nonhuman/
15.	exp Animal Experiment/
16.	exp Experimental Animal/
17.	animal model/
18.	exp Rodent/
19.	(rat or rats or mouse or mice).ti.
20.	or/12-19
21.	4 not 20
22.	limit 21 to English language

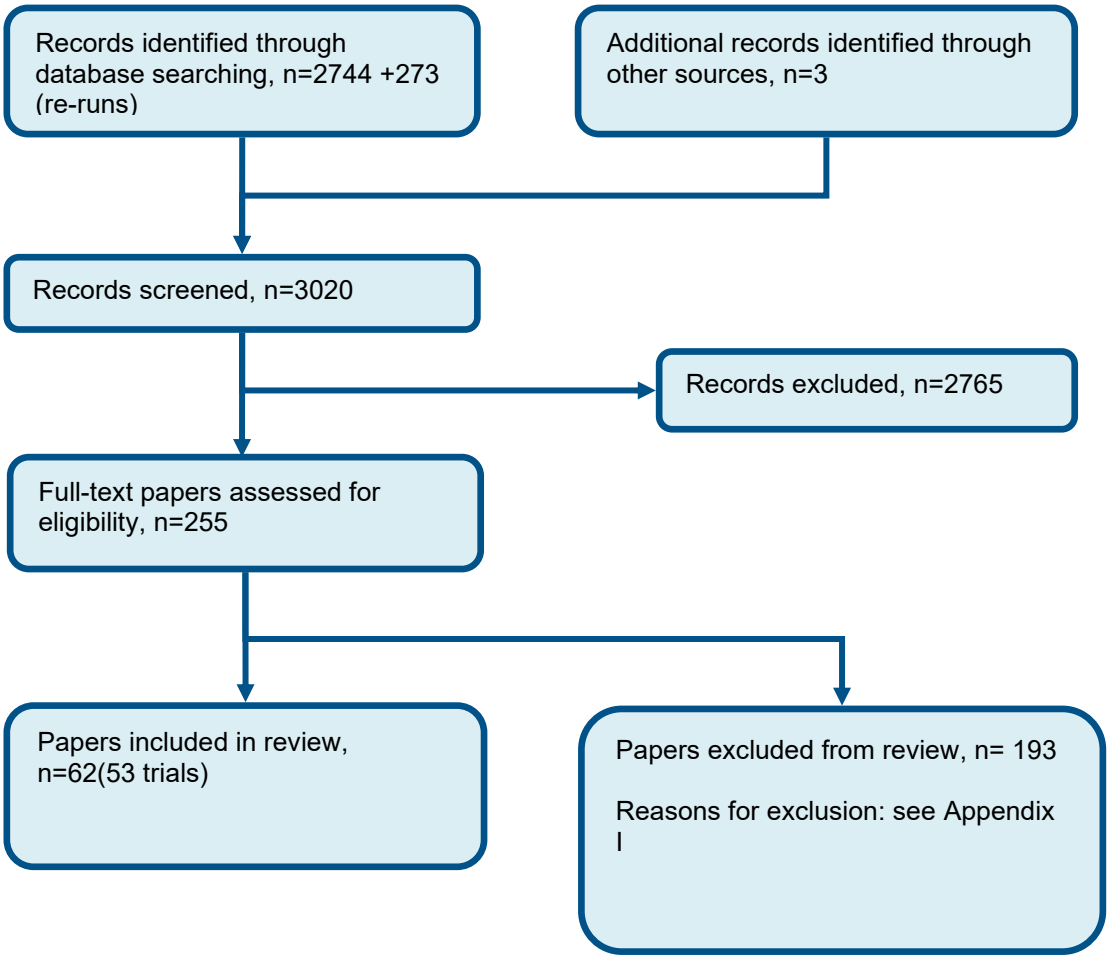
23.	health economics/
24.	exp economic evaluation/
25.	exp health care cost/
26.	exp fee/
27.	budget/
28.	funding/
29.	budget*.ti,ab.
30.	cost*.ti.
31.	(economic* or pharmaco?economic*).ti.
32.	(price* or pricing*).ti,ab.
33.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
34.	(financ* or fee or fees).ti,ab.
35.	(value adj2 (money or monetary)).ti,ab.
36.	or/23-35
37.	quality-adjusted life years/
38.	"quality of life index"/
39.	short form 12/ or short form 20/ or short form 36/ or short form 8/
40.	sickness impact profile/
41.	(quality adj2 (wellbeing or well being)).ti,ab.
42.	sickness impact profile.ti,ab.
43.	disability adjusted life.ti,ab.
44.	(qal* or qtime* or qwb* or daly*).ti,ab.
45.	(euroqol* or eq5d* or eq 5*).ti,ab.
46.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
47.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
48.	(hui or hui1 or hui2 or hui3).ti,ab.
49.	(health* year* equivalent* or hye or hyes).ti,ab.
50.	discrete choice*.ti,ab.
51.	rosser.ti,ab.
52.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
53.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
54.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
55.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
56.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
57.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
58.	or/37-57
59.	22 and (36 or 58)

1 **NHS EED and HTA (CRD) search terms**

#1.	MeSH DESCRIPTOR Atrial Fibrillation EXPLODE ALL TREES
#2.	(((atrial or atria or atrium or auricular) adj3 fibrillat*))
#3.	(AF)
#4.	(#1 or #2 or #3)

Appendix C: Clinical evidence selection

Figure 4: Flow chart of clinical study selection for the review of ablation



Appendix D: Clinical evidence tables

Study	Andrade, 2020[9]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=346)
Countries and setting	Conducted in Canada
Line of therapy	2nd line
Duration of study	Follow up (post intervention): 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	paroxysmal
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged >18 years with symptomatic paroxysmal AF refractory to at least 1 Class I or Class III AAD and referred for a first catheter ablation procedure were enrolled. At least 1 electrocardiographic-documented episode of AF was required within 24 months of randomization.
Exclusion criteria	None reported
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age – Range of means: 58.2 to 59.6 Gender (M:F): 231:115. Ethnicity: unclear
Further population details	1. CHADSVASC: <2 (73.5% <2). 2. Heart failure: No HF (LA diam 41mm).
Extra comments	CHADSVASC >70%<2; hypertension 34.8%/24.6%; previous TIA/stroke 3.5%/5.2%; paroxysmal

	91.3%/96.1%%; Failed ADDs 2/2; LVEF 59.1/59.3
Indirectness of population	No indirectness
Interventions	(n=230) Intervention 1: Radiofrequency catheter ablation - point by point - RF point by point. patients randomized to the CF-RF group underwent PVI guided by a three-dimensional nonfluoroscopic mapping system (CARTO3; Biosense Webster, Diamond Bar, CA) using an irrigated-tip contact force–sensing radiofrequency ablation catheter (Thermocool SmartTouch or SmartTouch Surround Flow; Biosense Webster). Circumferential ablation lesions were delivered around each of the PV ostia until each vein was isolated electrically from the left atrium (ie, bidirectional conduction block). No additional left atrial lesions were permitted.. Duration Single procedure. Concurrent medication/care: After catheter ablation, patients received oral anticoagulation for at least 3 months. AADs (except amiodarone) were allowed during the first 3 months after ablation (blanking period) but were discontinued 5 half-lives before the end of the 3-month blanking period. Indirectness: No indirectness (n=230) Intervention 2: Cryoballoon. Patients randomized to cryoballoon ablation underwent PVI using a 23- or 28-mm cryoballoon (Arctic Front Advance;Medtronic). The balloon was placed at each PV until it was occluded and then the tissue was cooled until bidirectional conduction block was achieved. After PVI, a single additional cryoapplication was delivered after the rewarming phase. Cryoablation was performed with a lesion duration of 4 minutes or 2 minutes depending on treatment allocation. These two cryoballon groups have been combined for this review. No additional left atrial lesions were permitted and no focal ablation catheters were used. Duration Single procedure. Concurrent medication/care: After catheter ablation, patients received oral anticoagulation for at least 3 months. AADs (except amiodarone) were allowed during the first 3 months after ablation (blanking period) but were discontinued 5 half-lives before the end of the 3-month blanking period. Indirectness: No indirectness
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RF POINT BY POINT versus CRYOBALLOON

Protocol outcome 1: Mortality
- Actual outcome for paroxysmal: death at 12months; Group 1: 0/115, Group 2: 1/231
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 1 (reason unclear)

Protocol outcome 2: Stroke and systemic embolism - Actual outcome for paroxysmal: Stroke/TIA at 12months; Group 1: 0/115, Group 2: 2/231 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 1 (reason unclear) Protocol outcome 3: Recurrence of symptomatic AF - Actual outcome for paroxysmal: AF recurrence at 12months; Group 1: 24/115, Group 2: 56/231 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness (symptomatic) ; Group 1 Number missing: 0 ; Group 2 Number missing: 1 (reason unclear) Protocol outcome 4: Redo of procedure - Actual outcome for paroxysmal: AF recurrence at 12months; Group 1: 16/115, Group 2: 36/231 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 1 (reason unclear) Protocol outcome 5 Serious Adverse Events - Actual outcome for paroxysmal: complications at 12months; Group 1: 3/115, Group 2: 13/231; Comments: RF: 3 with one or more of the following: pericardial effusion, pericarditis, hematoma requiring intervention, pseudoaneurysm requiring intervention, esophageal perforation; Cryoballoon: unclear how many people had the following but the following 13 serious AEs were recorded: 1 pericardial effusion, 3 pericarditis, 1 MI, 1 atypical chest pain, 1 HF exacerbation, 1 AV fistula, 3 persistent phrenic nerve palsies, 1 esophageal injury, 1 acute pulmonary infection. Risk of bias: All domain - All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 1 (reason unclear)	
Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; HF or exacerbation of HF ; Length of stay

1
2

Study	Gal, 2014 trial: Gal 2014[82]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=460)
Countries and setting	Conducted in Netherlands
Line of therapy	1st line
Duration of study	Follow up (post intervention): 43 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	paroxysmal
Subgroup analysis within study	Not applicable
Inclusion criteria	Symptomatic AF; accepted for primo PVI
Exclusion criteria	None reported
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Mean (SD): 56.3(10). Gender (M:F): 347:113. Ethnicity: unclear
Further population details	1. CHADSVASC: <2 (73.5% <2). 2. Heart failure: No HF (LA diam 41mm).
Extra comments	CHADSVASC 73.5%<2; hypertension 35%; DM 6.5%; previous TIA/stroke 5.4%; structural heart disease 11.5%; paroxysmal 81.5%; Failed ADDs 1.58; LA diam 41mm
Indirectness of population	No indirectness

Interventions	(n=230) Intervention 1: Radiofrequency catheter ablation - point by point - RF point by point. 3.5 mm tip electrode (thermocool) used to apply 30W-40W. Circular lesions applied to PV antrum. . Duration Single procedure. Concurrent medication/care: Under GA; heparin during procedure; septal punctures under fluoroscopic guidance. Indirectness: No indirectness (n=230) Intervention 2: Radiofrequency catheter ablation - multielectrode - RF multielectrode. PVAC used to deliver energy to PVs required to raise tissue temperatures to 60 degrees. Duration Single procedure. Concurrent medication/care: Under GA; heparin during procedure; septal punctures under fluoroscopic guidance. Indirectness: No indirectness
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RF POINT BY POINT versus RF MULTIELECTRODE

Protocol outcome 1: Mortality
- Actual outcome for paroxysmal: death at 5 years; Group 1: 0/230, Group 2: 0/230
Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0

Protocol outcome 2: Stroke and systemic embolism
- Actual outcome for paroxysmal: Stroke/TIA at 5 years; Group 1: 0/230, Group 2: 0/230
Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Recurrence of symptomatic AF
- Actual outcome for paroxysmal: AF recurrence at 5 years; DATA EXCLUDED AS UNCLEAR IF CUMULATIVE OR POINT DATA
Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Not symptomatic recurrence; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Serious Adverse Events
- Actual outcome for paroxysmal: complications at 5 years; Group 1: 6/230, Group 2: 3/230; Comments: 1 patient with permanent effects from retinal infarction in multielectrode group. Other AEs occurred but all temporary - these were femoral vascular access (5/0), pneumonia (4/1), atrial perforation (2/0), transient global amnesia (0/1)
Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low,

Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing:0 ; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; Redo of procedure ; HF or exacerbation of HF ; Length of stay

Study	A4 study, 2008 trial: Jais 2008[95]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=112)
Countries and setting	Conducted in Multiple countries
Line of therapy	1st line
Duration of study	Follow up (post intervention): 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	paroxysmal
Subgroup analysis within study	Not applicable
Inclusion criteria	symptomatic, documented paroxysmal AF over a span of □6 months with at least 2 episodes during the preceding month
Exclusion criteria	contraindications to >2 AADs in different classes or to oral anticoagulants, prior AF ablation, an intracardiac thrombus, AF from a potentially reversible cause, pregnancy, or a contraindication to the discontinuation of oral anticoagulation
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Mean (SD): 51.1(11.1). Gender (M:F): 94:18. Ethnicity: unclear
Further population details	1. CHADSVASC: Not stated / Unclear 2. Heart failure: No HF (LA diam 41.2mm).
Extra comments	AF episodes per month 12; duration episodes 5.5 hrs; DM 2.7%; embolic events 7.1%; ischaemic structural heart disease (SHD) 8%; valvular SHD 8%; idiopathic SHD 3.6%; hypertrophic SHD 1.8%; hypertension 26.4%; LA transverse diam 41.2mm

Indirectness of population	Serious indirectness: 8% with valvular disease
Interventions	(n=53) Intervention 1: Radiofrequency catheter ablation - point by point - RF point by point. Isolation of all 4 pulmonary veins was performed using circumferential applications of radiofrequency energy and verified with a circular mapping catheter (Lasso Catheter, Biosense Webster, Inc, Diamond Bar, Calif). The ablation catheter was either a 3.5- or 5-mm irrigated tip (Thermocool, Biosense Webster; n=95) or a 4-mm nonirrigated tip (n=13). For safety reasons, a power limit of <35 W with a tip temperature of <50°C was used according to standard practice. Pulmonary vein angiography was performed after the procedure to assess vein calibre. The use of navigation systems and delivery of additional lesions outside the pulmonary vein regions were left to the discretion of the operator.. Duration Single procedure. Concurrent medication/care: Therapeutic anticoagulation with warfarin (international normalized ratio maintained between 2 and 3) was required for at least 1 month before and 1 month after each procedure. Transoesophageal echocardiography was performed in all patients before an ablation procedure to exclude the presence of left atrial thrombus.. Indirectness: No indirectness (n=59) Intervention 2: usual care - Other usual care. Once included in the study, patients received “new” AADs (ie, monotherapy or combinations of drugs never administered before enrollment). The following AADs, either alone or in combination, were considered acceptable: amiodarone, quinidine, disopyramide, flecainide, propafenone, cibenzoline, dofetilide, and sotalol. No specific regimen was mandated, although physicians were encouraged to comply with published guidelines for AAD use and dosing. When amiodarone was prescribed, a loading dose of 600 mg/d for 21 days followed by 200 mg/d was recommended, with an increase to 300 mg daily if required. Sotalol, dofetilide, or amiodarone was recommended in patients with a left ventricular ejection fraction <50%. Alternative drug(s) were introduced in the event of recurrent AF 1 month after the initiation of treatment, with up to 3 attempts at modifying pharmacological therapy during the treatment stabilization period.. Duration unclear. Concurrent medication/care: Cross-over to ablation if failure at 3 month allowed (n=37 crossed over at 192 days). Indirectness: No indirectness
Funding	Other author(s) funded by industry

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RF POINT BY POINT versus OTHER USUAL CARE

Protocol outcome 1: Quality of life
- Actual outcome for paroxysmal: SF-36 quality of life questionnaire - physical at 12 months; Group 1: mean 52 (SD 7.6); n=53, Group 2: mean 48.9 (SD 7.2); n=59
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low,

Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1 (withdrew consent); Group 2 Number missing: 3 (poor compliance) - Actual outcome for paroxysmal: SF-36 quality of life questionnaire - mental at 12 months; Group 1: mean 56.6 (SD 7.8); n=53, Group 2: mean 51.9 (SD 9.7); n=59 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1 (withdrew consent); Group 2 Number missing: 3 (poor compliance) Protocol outcome 2: Mortality - Actual outcome for paroxysmal: All cause mortality at 12 months; Group 1: 0/53, Group 2: 2/59 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: No reported as symptomatic; Group 1 Number missing: 1 (withdrew consent); Group 2 Number missing: 3 (poor compliance) Protocol outcome 3: Recurrence of symptomatic AF - Actual outcome for paroxysmal: recurrence of AF requiring AADs at 12 months; Group 1: 7/53, Group 2: 42/55 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: No reported as symptomatic; Group 1 Number missing: 1 (withdrew consent); Group 2 Number missing: 3 (poor compliance) Protocol outcome 4: Serious Adverse Events - Actual outcome for paroxysmal: serious AEs at 12 months; DATA NOT USED AS UNCLEAR. AUTHORS CONTACTED BUT NO RESPONSE Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: No reported as symptomatic; Group 1 Number missing: 1 (withdrew consent); Group 2 Number missing: 3 (poor compliance)	
Protocol outcomes not reported by the study	Hospitalisation ; Stroke and systemic embolism ; Redo of procedure ; HF or exacerbation of HF ; Length of stay

Study	AATAC, 2016 trial: Di biase 2016[64]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=203)
Countries and setting	Conducted in Multiple countries
Line of therapy	1st line
Duration of study	Follow up (post intervention): 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	persistent <1 year
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients ≥18 years of age with persistent AF, dual-chamber implantable cardioverter defibrillator or cardiac resynchronization therapy defibrillator, New York Heart Association functional class II to III, and LV ejection fraction (LVEF) ≤40% within the past 6 months
Exclusion criteria	Patients were excluded if AF was caused by a reversible etiology, and if they had valvular or coronary heart disease requiring surgical intervention, early postoperative AF (within 3 months of surgery), or a life expectancy ≤2 years. Other exclusions included prolonged QT interval, hypothyroidism, history of severe pulmonary disease, and liver failure. Patients receiving a regular dose of AMIO (≥200 mg/d) were also excluded.
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Range of means: 60-62. Gender (M:F): 151:52. Ethnicity: unclear
Further population details	1. CHADSVASC: Not stated / Unclear 2. Heart failure: HF (Patients with CHF).

Extra comments	RF pt to pt/amiodarone: hypertension 45%/48%; DM 22%/24%; CAD 62%/65%; LA diam 47mm/48mm; LVEF 29%/30%
Indirectness of population	No indirectness
Interventions	(n=102) Intervention 1: Radiofrequency catheter ablation - point by point - RF point by point. Open irrigation tip catheter used with circular mapping catheter.. Duration Single procedure. Concurrent medication/care: Dofeltilide discontinued 4-5 days pre-ablation but patients on low dose amiodarone allowed to discontinue drug after blanking period. Double transeptal puncture performed. IV heparin given. Indirectness: No indirectness (n=101) Intervention 2: usual care - medical therapy. Amiodarone. Started with loading dose of around 10g in first 2 weeks - 400mg orally twice daily for 2 weeks. This was followed by 400mg daily for the next 2 weeks. Then the maintenance dose of 200mg daily was started. Duration 3 months. Concurrent medication/care: Digoxin discontinued if possible or dose reduced by 50%. Indirectness: No indirectness
Funding	Other author(s) funded by industry

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RF POINT BY POINT versus MEDICAL THERAPY

Protocol outcome 1: Quality of Life
- Actual outcome for persistent <1 year: Change in Minnesota living with HF Questionnaire at 2 years (range 0-105, lower better); Group 1: -11(19) [n=94], Group 2: -6 (17)[n=83].
Risk of bias: All domain – Very High, Selection - Low, Blinding – High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 8; Group 2 Number missing: 18

Protocol outcome 2: Heart failure
- Actual outcome for persistent <1 year: Change in LVEF (higher better); Group 1: 8.1(4) [n=94], Group 2: 6 (6.2)[n=5].
Risk of bias: All domain – Very High, Selection - Low, Blinding – High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 8; Group 2 Number missing: 18

Protocol outcome 3: Hospitalisation
- Actual outcome for persistent <1 year: unplanned hospitalisation at 2 years; Group 1: 32/102, Group 2: 58/101
Risk of bias: All domain - High, Selection - Low, Blinding – High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Mortality - Actual outcome for persistent <1 year: mortality at 2 years; Group 1: 8/102, Group 2: 18/101 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 5: Recurrence of symptomatic AF - Actual outcome for persistent <1 year: recurrence of AF at 2 years; Group 1: 31/102, Group 2: 67/101 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Not symptomatic AF; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 6: Serious Adverse Events - Actual outcome for persistent <1 year: serious adverse events at 2 years; Group 1: 1/102, Group 2: 7/101; Comments: Pericardial effusion in RF group; 7 in amiodarone group were thyroid toxicity (4), pulmonary toxicity (2) and liver dysfunction. In RF group, 1 had pericardial effusion, deemed by reviewer to be a serious AE. 2 with groin hematoma, not deemed serious. Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Stroke and systemic embolism ; Redo of procedure ; Length of stay

Study	ADIYAMAN, 2018 trial: Adiyaman 2018[2]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=52)
Countries and setting	Conducted in Netherlands
Line of therapy	1st line
Duration of study	Follow up (post intervention): >=2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Mixed (<75% in any category)/unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	symptomatic paroxysmal or early persistent (<3 months) with failure of at least 1 classI or III AADs; >=18 years; at least 1 symptomatic episode of AF required in prior 6 months
Exclusion criteria	Structural heart disease; permanent or persistent AF >3 months; LVEF <30%; LA diam >50mm; amiodarone use in prior 6 months; history of CVD; pregnancy; life expectancy <1 year; previous LA ablation
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Range of means: 55-59. Gender (M:F): 39:11. Ethnicity: unclear
Further population details	1. CHADSVASC: <2 (Majority <2 (68%/80%)). 2. Heart failure: No HF (Excluded LA diam >50mm).
Extra comments	RF/thoracoscopy: LVEF 55/55; LA diam 40/39mm; CHADSVASC >=2: 32%/20%; DM 7.4%/8.7%; hypertension 40.7%/47.8%
Indirectness of population	No indirectness

Interventions	(n=26) Intervention 1: Radiofrequency catheter ablation - point by point - RF point by point. 3.3 mm irrigated tip catheter with CARTO navigation used for PVI of all PVs; power limit of 40W on anterior LA and 30W on posterior LA. . Duration Single procedure. Concurrent medication/care: Under GA; VKAs discontinued for 3-5 days pre-ablation. TEE performed; Heparin bolus given. Indirectness: No indirectness (n=26) Intervention 2: Thorascopic surgical ablation. Irrigated bipolar clamp device used for PVI (using RF energy). Duration Single procedure. Concurrent medication/care: Under GA; VKAs discontinued for 3-5 days pre-ablation. TEE performed; Heparin bolus given. Indirectness: No indirectness
Funding	Study funded by industry (Medtronic)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RF POINT BY POINT versus THORASCOPIC SURGICAL ABLATION

Protocol outcome 1: Length of stay
- Actual outcome for Mixed (<75% in any category)/unclear: Hospital duration at 2 years;
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1 (non cardiac death); Group 2 Number missing: 1 (exclusion due to contraindications)

Protocol outcome 2: Mortality
- Actual outcome for Mixed (<75% in any category)/unclear: Death (any cause) at 2 years; Group 1: 0/25, Group 2: 1/26
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; 1 (exclusion due to contraindications)

Protocol outcome 3: Recurrence of symptomatic AF
- Actual outcome for Mixed (<75% in any category)/unclear: Recurrence of AF at 2 years; Group 1: 15/27, Group 27/23
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; 1 (non cardiac death); Group 2 Number missing: 1 (exclusion due to contraindications)

Protocol outcome 4: Serious Adverse Events
- Actual outcome for Mixed (<75% in any category)/unclear: Major adverse events at 2 years; Group 1: 1/26, Group 2: 8/23; RF 1 pericarditis (URTI and UTI not counted as serious); thoracoscopy 2 pericarditis, 1 pleurocarditis, 1 pericardial effusion, 1 conversion to sternotomy, 1 phrenic nerve paralysis, 1 lung herniation requiring surgery, 1 laryngeal nerve palsy (infection not counted as serious)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low,

Crossover - Low; Indirectness of outcome: 1 (non cardiac death); Group 2 Number missing: 1 (exclusion due to contraindications)	
Protocol outcomes not reported by the study	Quality of life ; Stroke and systemic embolism ; Redo of procedure ; HF or exacerbation of HF ; Hospitalisation

Study	AF-COR trial: Malmborg 2013[145]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=110)
Countries and setting	Conducted in Sweden; Setting: Unclear
Line of therapy	1st line
Duration of study	Follow up (post intervention): 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Mixed (<75% in any category)/unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	Symptomatic 12 lead ECG-verified AF; failed at least 1 AAD; Vaughan William Class I or III; scheduled for AF ablation.
Exclusion criteria	long standing persistent or permanent AF; previous ablation; CHF with NYHA class IV; LVEF <30%; LA diam >6cm.
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Range of means: 59 to 62. Gender (M:F): 83:27. Ethnicity: Unclear
Further population details	1. CHADSVASC: <2 (likely as CHADS <1). 2. Heart failure: No HF (all those with LVEF <30% excluded).
Extra comments	cryo/RF: atrial size 40/42mm; hypertension 40.7%/62.5%; IHD 7.4%/10.7%; CHD 18.5%/0%; CHADS 0.6/0.9; Paroxysmal 72.2%/66.1%; number of AADss tried 2/2; ongoing amiodarone 27.7%/16.1%
Indirectness of population	No indirectness

Interventions	(n=56) Intervention 1: Radiofrequency catheter ablation - multielectrode - RF multielectrode. Performed with the PVAC, a 9F decapolar, circular catheter with phased RF energy that can be delivered simultaneously through up to 5 electrode pairs, independently selectable. The PVAC was positioned in the antrum of the veins under flouroscopic guidance and 60s RF applications delivered to electrodes with good tissue contact. 7F decapolar 4mm tip RF ablation catheter used for touch-ups.. Duration Single procedure. Concurrent medication/care: Warfarin INR 2-3 for 3 weeks prior to procedure. Bridged by LMWH. Patient awake, with diazepam and Ketobemidone as analgesia. . Indirectness: No indirectness (n=54) Intervention 2: Cryoballon catheter ablation - Cryoballoon. Performed with a 10.5F cryoballoon catheter with the use of N2O. The 28mm cryoballoon was used. Two 5 minute deliveries were given per vein. If needed a conventional 9F quadripolar cryoablation catheter was used. Duration Single procedure. Concurrent medication/care: Warfarin INR 2-3 for 3 weeks prior to procedure. Bridged by LMWH. Patient awake, with diazepam and Ketobemidone as analgesia. Indirectness: No indirectness
Funding	Academic or government funding (Swedish Heart and Lung Foundation)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RF MULTIELECTRODE versus CRYOBALLOON

Protocol outcome 1: Quality of life
- Actual outcome for Mixed (<75% in any category)/unclear: Swedish SF-36 at 12 months; Raw data not available in paper

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 4 (problems with cryocatheter)

Protocol outcome 2: Recurrence of symptomatic AF
- Actual outcome for Mixed (<75% in any category)/unclear: Not free from symptoms at 12 months; Group 1: 37/56, Group 2: 27/50
Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 4 (problems with cryocatheter)

Protocol outcome 3: Redo of procedure
- Actual outcome for Mixed (<75% in any category)/unclear: Redo of procedure at 12 months; Group 1: 10/56, Group 2: 7/50
Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 4 (problems with cryocatheter)

Protocol outcome 4: Serious Adverse Events

- Actual outcome for Mixed (<75% in any category)/unclear: major complications at 12 months; Group 1: 1/56, Group 2: 2/50; Comments: Did not count 2 phrenic nerve injuries in cryo gp that resolved in 24 hours (considered minor) Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 4 (problems with cryocatheter)	
Protocol outcomes not reported by the study	Hospitalisation ; Mortality ; Stroke and systemic embolism ; HF or exacerbation of HF ; Length of stay

Study (subsidiary papers)	APAF study, 2011 trial: Pappone 2011[189] (Pappone 2006[187])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=198)
Countries and setting	Conducted in Italy
Line of therapy	1st line
Duration of study	Follow up (post intervention): 4 years
Method of assessment of guideline condition	--
Stratum	paroxysmal
Subgroup analysis within study	Not applicable
Inclusion criteria	Age >18 or <70 years, AF history >6 months, and AF burden >2 episodes per month in the last 6 months as assessed by daily transtelephonic monitoring.
Exclusion criteria	Persistent AF, LA diameter >65 mm, LVEF <35%, heart failure symptoms, and New York Heart Association functional class II
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Range of means: 55-57. Gender (M:F): Not reported. Ethnicity: unclear
Further population details	1. CHADSVASC: Not stated / Unclear 2. Heart failure: No HF (LVEF 60-61%).
Extra comments	RF point by point/usual care: LA diam 40/38; DM 5.1%/4%; hypercholesterolaemia 17%/21%; hypertension 56%/57%; LVEF 60%/61%; CAD 2%/2%; valvular heart disease 3%/1%; congenital heart disease 2%/1%; number of previously ineffective drugs 2/2

Indirectness of population	No indirectness
Interventions	(n=99) Intervention 1: Radiofrequency catheter ablation - point by point - RF point by point. Using 3D-electoanatomic mapping systems, left- and right-sided PVs were isolated by creating large circumferential lesions up to 2 cm from the PV ostia, excluding 20–30% of the left atrium. To prevent postablation LA tachycardias, an ablation line was applied to the mitral isthmus (between the mitral annulus and left inferior PV) and between contralateral superior veins. The end point was PV isolation by voltage abatement around and within ablated areas. The completeness of the lines was assessed with voltage and activation maps within the circles. Cavotricuspid isthmus block to prevent isthmus-dependent atrial flutter was also performed. If AF did not terminate during RFA, transthoracic cardioversion was performed at the end of the procedure.. Duration Single procedure. Concurrent medication/care: Heparin was administered intravenously for 24 hours. Heparin was started 3 hours after the sheath removal at 1000 U/h without a bolus. Low-molecular-weight heparin, 0.5 mg/kg SQ bid, was administered for 4 days after the discharge. Warfarin was started immediately after the procedure. All patients were maintained on the assigned antiarrhythmic agent for 6 weeks after the ablation procedure, and recurrences within this period were not considered as a failure (blanking period). Indirectness: No indirectness (n=99) Intervention 2: usual care - medical therapy. Oral AADs therapy - monotherapy or combinations of 3 drugs (flecainide, sotalol, and amiodarone) never administered before enrollment. Oral flecainide was given at an initial dosage of 100 mg every 12 hours, sotalol at an initial dose of 80 mg every 8 hours, and amiodarone at an initial loading of 600 mg/d for the first week, 400 mg/d for the next week, after which a daily maintenance dose of 200 mg a day was given. The maximum tolerable dosage (300 mg/d for flecainide, 320 mg/d for sotalol) was based on the clinical response and/or the occurrence of side effects. Doses were reduced if intolerable adverse reactions occurred, and treatment was stopped if they persisted. . Duration Unclear. Concurrent medication/care: None. Indirectness: No indirectness
Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RF POINT BY POINT versus MEDICAL THERAPY

Protocol outcome 1: Quality of life
- Actual outcome for paroxysmal: SF36 physical at 4 years; Group 1: mean 52.3 (SD 9); n=99, Group 2: mean 52.6 (SD 8); n=99
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for paroxysmal: SF36 mental at 4 years; Group 1: mean 52.9 (SD 9); n=99, Group 2: mean 51.9 (SD 9); n=99

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Recurrence of symptomatic AF - Actual outcome for paroxysmal: recurrence of AF at 4 years; DATA UNCLEARLY REPORTED: NOT USED. Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Not symptomatic AF; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: HF or exacerbation of HF - Actual outcome for paroxysmal: new onset heart failure at 4 years; Group 1: 0/99, Group 2: 0/99 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 4: Serious Adverse Events - Actual outcome for paroxysmal: Serious AEs at 4 years; Group 1: 3/99, Group 2: 10/99; Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 5: Stroke and systemic embolism - Actual outcome for paroxysmal: Serious AEs at 4 years; Group 1: 1/99, Group 2: 0/99; Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Hospitalisation ; Mortality ; Redo of procedure ; Length of stay

Study	BITTNER, 2011 trial: Bittner 2011[26]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=80)
Countries and setting	Conducted in Multiple countries
Line of therapy	1st line
Duration of study	Follow up (post intervention): mean 254 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Mixed (<75% in any category)/unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	Symptomatic paroxysmal or persistent AF with failure of at least 1 AAD, referred for first AF ablation procedure and in whom PV isolation had been planned
Exclusion criteria	Longstanding persistent AF; moderate or severe mitral valve stenosis or regurgitation, CHF with NYHA class III or IV; LVEF<40%; severe COPD; prior cardiac surgery other than coronary revascularisation; prior ablation; other supraventricular tachycardia; LA thrombus; contraindications to OACs; pregnancy
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Range of means: 57-59. Gender (M:F): 51:29. Ethnicity: unclear
Further population details	1. CHADSVASC: Not stated / Unclear 2. Heart failure: No HF (HF excluded).
Extra comments	PVAC/pt to pt: paroxysmal 53%/58%; hypertension 65%/53%; DM 13%/3%; structural heart disease 8%'/10%; LV systolic dysfunction 3%/0; LA diam 43/42; mean number AADs 1.5/1.5

Indirectness of population	No indirectness
Interventions	(n=40) Intervention 1: Radiofrequency catheter ablation - point by point - RF point by point. 4mm open tip irrigated catheter used for antral point by point circumferential ablation around ipsilateral PVs, using Ensite NavX Velocity navigation.. Duration Single procedure. Concurrent medication/care: VKAs stopped 1 day before admission and bridged with heparin; conscious sedation used; CT used prior to ablation; TEE used to exclude LA thrombi (n=40) Intervention 2: Radiofrequency catheter ablation - multielectrode - RF multielectrode. PVAC used; rotated around PV ostium looking for the earliest PV potential to completely isolate the vein. Duration Single procedure. Concurrent medication/care: VKAs stopped 1 day before admission and bridged with heparin; conscious sedation used; CT used prior to ablation; TEE used to exclude LA thrombi. Indirectness: No indirectness
Funding	Other author(s) funded by industry (Astra Zeneca, Biosense Webster, Biotronik, Boehringer Ingelheim, Guidant, medtronic, Sanofi aventis)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RF POINT BY POINT versus RF MULTIELECTRODE

Protocol outcome 1: Mortality
- Actual outcome for Mixed (<75% in any category)/unclear: death at 254 days; Group 1: 0/40, Group 2: 0/40
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Stroke and systemic embolism
- Actual outcome for Mixed (<75% in any category)/unclear: SSE at 254 days; Group 1: 0/40, Group 2: 0/40
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Recurrence of symptomatic AF
- Actual outcome for Mixed (<75% in any category)/unclear: symptomatic or documented asymptomatic episodes of recurrent AF at 254 days; Group 1: 13/40, Group 2: 11/40
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Included asymptomatic recurrences; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Redo of procedure - Actual outcome for Mixed (<75% in any category)/unclear: Reablation at 254 days; Group 1: 4/40, Group 2: 5/40 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 5: Serious Adverse Events - Actual outcome for Mixed (<75% in any category)/unclear: Serious complications at 254 days; Group 1: 2/40, Group 2: 0/40; Comments: In pt to pt group there was a femoral hematoma requiring hospitalisation and a femoral DVT Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; HF or exacerbation of HF ; Length of stay

Study	BULAVA, 2010 trial: Bulava 2010[39]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=102)
Countries and setting	Conducted in Czech Republic
Line of therapy	1st line
Duration of study	Follow up (post intervention): 200 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	paroxysmal
Subgroup analysis within study	Not applicable
Inclusion criteria	At least 3 documented AF occurrences on previous 6 months despite AADs
Exclusion criteria	AF as a sole documented rhythm for 6 months or more prior to inclusion; previous ablation; CAD; CHF with NYHA class III and IV; unstable angina or acute MI within past 3 months; LVEF <0.4; LA diameter >50mm; severe mitral regurgitation or stenosis; contraindications to VKAs; known bleeding disorders; presence of LA thrombi; previous cardiac or pulmonary surgery; severe COPD, chronic liver or kidney disease; psychiatric disease; drug or alcohol abuse; pregnancy
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Mean (SD): 57.6(11). Gender (M:F): 66:36. Ethnicity: unclear
Further population details	1. CHADSVASC: Not stated / Unclear 2. Heart failure: No HF (LVEF <40% excluded).
Extra comments	Hypertension 32%; DM 10%; CAD 5%; LA diam 40.3mm; LVAF 68.6%; AF occurrences in past month

	2.7(1.5); Amiodarone tried 28%
Indirectness of population	No indirectness
Interventions	(n=51) Intervention 1: Radiofrequency catheter ablation - point by point - RF point by point. 3.5mm irrigated tip NAVISTAR THERMOCOOL catheter used with CARTO navigation. Duration Single procedure. Concurrent medication/care: CT 1 day prior to ablation. Indirectness: No indirectness (n=51) Intervention 2: Radiofrequency catheter ablation - multielectrode - RF multielectrode. PVAC used 60 second 60 degree applications of bipolar/unipolar RF energy simultaneously at all electrode pairs. Duration Single procedure. Concurrent medication/care: As for pt to point. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RF POINT BY POINT versus RF MULTIELECTRODE Protocol outcome 1: Recurrence of symptomatic AF - Actual outcome for paroxysmal: recurrence of AF at 200 days; Group 1: 15/51, Group 2: 12/51 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Very serious indirectness, Comments: Not symptomatic; blanking period only 1 month (not 3 months as for other studies); Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Serious Adverse Events - Actual outcome for paroxysmal: serious adverse events at 200 days; Group 1: 0/51, Group 2: 0/51 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; Mortality ; Stroke and systemic embolism ; Redo of procedure ; HF or exacerbation of HF ; Length of stay

Study	CAMERA-MRI study, 2017 trial: Prabhu 2017[206]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=68)
Countries and setting	Conducted in Australia
Line of therapy	1st line
Duration of study	Follow up (post intervention): 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	persistent >1 year
Subgroup analysis within study	Not applicable
Inclusion criteria	1) 18 to 85 years of age; 2) had New York Heart Association (NYHA) functional class >II; 3) had persistent AF; 4) had an LVEF <45% on baseline cardiac magnetic resonance (CMR); 5) had significant coronary artery disease excluded via conventional or computed tomography–guided angiography or functional imaging; and 6) had no other identifiable cause explaining the left ventricular dysfunction
Exclusion criteria	1) if they were unable or unwilling to consent or commit to follow-up requirements; 2) if they had any contraindication to AF ablation; 3) if they had any contraindication to cardiac magnetic resonance imaging (MRI); or 4) if they had paroxysmal AF.
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Range of means: 59-62. Gender (M:F): 60:6. Ethnicity: unclear
Further population details	1. CHADSVASC: >=2 (Mean CHADSVASC 2.4). 2. Heart failure: HF (Population with idiopathic cardiomyopathy).

Extra comments	RF pt to pt / medical: CHADSVASC 2.42/2.36; hypertension 39%/36%; DM 12%/15%; Stroke or TIA 6.1%/0; ACE inh or ARB 94%/94%; NYHA class 2.55/2.45
Indirectness of population	No indirectness
Interventions	(n=34) Intervention 1: Radiofrequency catheter ablation - point by point - RF point by point. Mapping of the left atrium and pulmonary veins was performed with a 20 pole circular mapping catheter and ablation with a 3.5-mm irrigated-tipped catheter (SmartTouch Thermocool, Biosense Webster) following direct current cardioversion (DCCV) to restore sinus rhythm (power range: 25 W [posteriorly] to 30 W; contact force range: 10 to 40 g anteriorly and 10 to 25 g posteriorly). Pulmonary vein isolation was achieved with wide antral circumferential ablation with additional roof and inferior lines performed to achieve posterior wall isolation . Duration Single procedure. Concurrent medication/care: Oral anticoagulation was discontinued 24 h before the procedure with the exception of vitamin K antagonists or dabigatran, which were continued. Antiarrhythmic medication was discontinued 5 half-lives pre-procedure with the exception of amiodarone. All procedures were performed under general anesthesia with the assistance of a 3-dimensional mapping system (Carto, Biosense Webster, Irvine, California). After exclusion of intracardiac thrombus, trans-oesophageal echocardiographic-guided double trans-septal punctures were performed. Unfractionated heparin was administered to achieve an activated clotting time >350 s.. Indirectness: No indirectness (n=33) Intervention 2: usual care - medical therapy. Patients randomized to ongoing MRC underwent 24-h Holter monitoring at 3 and 6 months after randomization, with medical therapy titrated to achieve a resting rate <80 beats/min, an average 24-h ventricular rate <100 beats/min, and a post-exercise (6MWT) rate <110 beats/min in accordance with current guidelines. Although cross-over to CA before the 6-month CMR assessment was discouraged, it was permitted at the discretion of the treating physician.. Duration Unclear. Concurrent medication/care: None. Indirectness: No indirectness
Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RF POINT BY POINT versus MEDICAL THERAPY

Protocol outcome 1: Quality of life
- Actual outcome for persistent >1 year: SF36 Physical at 6 months; MD; 1.3 (95%CI -3.9 to 6.5);
Risk of bias: All domain – Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low;

Indirectness of outcome: No indirectness; Group 1 Number missing: 1, Reason: withdrew; Group 2 Number missing: 1, Reason: protocol violation (paroxysmal)
- Actual outcome for persistent >1 year: SF36 mental at 6 months; MD; 1.6 (95%CI -3.1 to 6.3);
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: withdrew; Group 2 Number missing: 1, Reason: protocol violation (paroxysmal)

Protocol outcome 2: Hospitalisation
- Actual outcome for persistent >1 year: Unplanned admissions at 6 months; Group 1: 0/33, Group 2: 4/33
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: withdrew; Group 2 Number missing: 1, Reason: protocol violation (paroxysmal)

Protocol outcome 3: Mortality
- Actual outcome for persistent >1 year: death at 6 months; Group 1: 0/33, Group 2: 0/33
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: withdrew; Group 2 Number missing: 1, Reason: protocol violation (paroxysmal)

Protocol outcome 4: Stroke and systemic embolism
- Actual outcome for persistent >1 year: stroke/TIA at 6 months; Group 1: 0/33, Group 2: 0/33
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: withdrew; Group 2 Number missing: 1, Reason: protocol violation (paroxysmal)

Protocol outcome 5: Recurrence of symptomatic AF
- Actual outcome for persistent >1 year: Recurrence of AF at 6 months; Data not used as not cumulative data; point data only provided; Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Not symptomatic AF; Group 1 Number missing: 1, Reason: withdrew; Group 2 Number missing: 1, Reason: protocol violation (paroxysmal)

Protocol outcome 6: HF or exacerbation of HF
- Actual outcome for persistent >1 year: Change in NYHA class at 6 months; MD; -0.82 (95%CI -1.13 to -0.51);
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: withdrew; Group 2 Number missing: 1, Reason: protocol violation (paroxysmal)

Protocol outcome 7: Serious Adverse Events
- Actual outcome for persistent >1 year: Serious AEs at 6 months; Group 1: 2/33, Group 2: 4/33; Comments: Bleeding requiring transfusion and also pneumonia in RF group; 2 decompensated HF and 2 requiring implantable cardiac device .
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: withdrew; Group 2 Number missing: 1, Reason: protocol violation (paroxysmal)

Redo of procedure ; Length of stay

Protocol outcomes not reported by the study

Study	CAMTAF trial, 2014 trial: Hunter 2014[93]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=55)
Countries and setting	Conducted in United Kingdom
Line of therapy	1st line
Duration of study	Follow up (post intervention): 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	persistent >1 year
Subgroup analysis within study	Not applicable
Inclusion criteria	Persistent AF, symptomatic HF (New York Heart Association [NYHA] class II–IV), and LV systolic dysfunction (ejection fraction [EF] <50%). Patients had to have adequate ventricular rate control as defined in the stricter guidelines in place at the time of the study design (since inadequate rate control would arguably have mandated some sort of intervention), with a heart rate <80 bpm at rest and <110 bpm on moderate exertion as assessed on ambulatory monitoring and exercise testing. Male and female patients aged ≥18 years were considered. There was no requirement for AF to be symptomatic, or for patients to have failed antiarrhythmic drug therapy or DC cardioversion
Exclusion criteria	HF that had a suspected reversible cause, previous left atrial ablation, any contraindication to catheter ablation, AF that was paroxysmal, symptoms that were clearly attributable to AF rather than HF (ie, palpitations or dizziness) that might arguably mandate a rhythm control strategy, any event during the past 6 months that might continue to effect on LV function (including implantation of a pacemaker or cardiac resynchronization therapy device, cardiac surgery, myocardial infarction, or coronary revascularization), or a realistic expectation of these occurring within the next year.
Recruitment/selection of patients	consecutive

Age, gender and ethnicity	Age - Range of means: 55-60. Gender (M:F): 48:2. Ethnicity: unclear
Further population details	1. CHADSVASC: Not stated / Unclear 2. Heart failure: HF (HF population).
Extra comments	RF/medical: long lasting persistent 96%/87.5%; AADs failed 1/1; prev attempt at rhythm control 53.8%/41.7%; hypertension 30.7%/33.3%; IHD 23.1%/29.2%; dilated cardiomyopathy 30.7%/29.2%; NYHA III 57.7%/50%; LA diam 52/50mm; LVEF 31.8%/33.7%
Indirectness of population	No indirectness
Interventions	(n=26) Intervention 1: Radiofrequency catheter ablation - point by point - RF point by point. Catheter ablation was performed using radiofrequency energy with an irrigated-tip catheter, with power and temperature generally limited to 30 W and 50°C. The pulmonary veins were isolated by wide area circumferential ablation, with lesions placed 1 to 2 cm outside the pulmonary vein ostia to isolate them as ipsilateral pairs. Electrical isolation was confirmed using the pulmonary vein mapping catheter. Complex or fractionated electrograms were then targeted throughout the left and right atria until all were abolished or sinus rhythm restored. If patients remained in AF, linear lesions were then added at the mitral isthmus and the roof. A cavotricuspid isthmus line was added only in patients with a history of typical right atrial flutter. If at any point AF organized into atrial tachycardia, this was mapped and ablated. If sinus rhythm was not restored following these lesions, the patient was cardioverted. Single procedure. Concurrent medication/care: Patients underwent transoesophageal echocardiography preprocedure, and heparin was administered to maintain an activated clotting time of 300 to 400 seconds. Antiarrhythmic drugs were not stopped preprocedure. Under local anaesthetic (lidocaine) and moderate sedation (midazolam and diamorphine), a decapolar catheter was inserted into the coronary sinus and, after double trans-septal puncture, a pulmonary vein mapping catheter and ablation catheter were introduced to the left atrium. All procedures were guided by 3-dimensional mapping systems either Carto (Biosense Webster Inc, Diamond Bar, CA) or Ensite NavX (St Jude Medical, Minneapolis, MN), with computerized tomography or MRI image integration.. Indirectness: No indirectness (n=24) Intervention 2: usual care - medical therapy. Once recruited, patients had HF treatment optimized during a 3-month period before baseline investigations and randomization. This also ensured all patients had been adequately rate controlled for ≥3 months before baseline investigations. All patients were taking β-blockers, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers, and in selected patients spironolactone (if NYHA class ≥III and LV EF <35%). All patients were anticoagulated with warfarin with a target international normalized ratio of 2 to 3. These therapies were continued throughout the study period regardless of subsequent treatment allocation, although changes to medications were allowed.. Duration 6 months. Concurrent medication/care: None. Indirectness: No indirectness

Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RF POINT BY POINT versus MEDICAL THERAPY

Protocol outcome 1: Quality of life
- Actual outcome for persistent >1 year: SF36 at 6 months; ;
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1 (death); Group 2 Number missing: 1 (stroke)

Protocol outcome 2: Mortality
- Actual outcome for persistent >1 year: death at 6 months; Group 1: 0/24, Group 2: 1/24
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 1 (stroke)

Protocol outcome 3: Stroke and systemic embolism
- Actual outcome for persistent >1 year: stroke at 6 months; Group 1: 1/25, Group 2: 0/23
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1 (death); Group 2 Number missing: 0

Protocol outcome 4: Recurrence of symptomatic AF
- Actual outcome for persistent >1 year: Recurrence of AF at 6 months; Group 1: 5/25, Group 2: 23/23
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Not symptomatic; Group 1 Number missing: 1 (death); Group 2 Number missing: 1 (stroke)

Protocol outcome 5: HF or exacerbation of HF
- Actual outcome for persistent >1 year: NYHA score at 6 months; Group 1: mean 1.6 (SD 0.62); n=24, Group 2: mean 2.4 (SD 0.61); n=23
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 1 (death); Group 2 Number missing: 1 (stroke)

Protocol outcome 6: Serious Adverse Events
- Actual outcome for persistent >1 year: serious AEs at 6 months; Group 1: 2/24, Group 2: 0/23
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1 (death); Group 2 Number missing: 1 (stroke)

Hospitalisation ; Redo of procedure ; Length of stay

Protocol outcomes not reported by the study

Study	CATCAAF, 2006 trial: Stabile 2006[231]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=137)
Countries and setting	Conducted in Italy
Line of therapy	1st line
Duration of study	Follow up (post intervention): 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Mixed (<75% in any category)/unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	patients with paroxysmal or persistent AF who were intolerant of antiarrhythmic drugs or in whom two or more antiarrhythmic drug regimens had failed.
Exclusion criteria	(1) age ,18 or .80 years; (2) permanent AF (AF was the sole rhythm for the last 12 months); (3) AF secondary to a transient or correctable abnormality, including electrolyte imbalance, trauma, recent surgery, infection, toxic ingestion, and endocrinopathy; (4) persistence of AF episodes triggered by another uniform arrhythmia (i.e. atrial flutter or atrial tachycardia) despite previous supraventricular tachycardia ablation; (5) intra-atrial thrombus, tumour, or other abnormality precluding catheter insertion; (6) Wolff–Parkinson–White syndrome; (7) heart failure with NYHA class III or IV or EF □35%; (7) unstable angina or acute myocardial infarction within 3 months; (8) cardiac revascularization or other cardiac surgery within 6 months or with prior atrial surgery; (9) renal failure requiring dialysis, or hepatic failure;(10) an implanted device (pacemaker or cardioverter-defibrillator);(11) left atrial diameter >60 mm
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Range of means: 62.2 - 62.3. Gender (M:F): 81:56. Ethnicity: unclear

Further population details	1. CHADSVASC: Not stated / Unclear 2. Heart failure: No HF (HF excluded).
Extra comments	RF pt to pt/control: paroxysmal 62%/72%; LA diam 46mm/45.4mm; LVEF 59.1/57.9; heart disease 63.2%/62.3%; hypertension 52.9%/49.3%;
Indirectness of population	No indirectness
Interventions	(n=68) Intervention 1: Radiofrequency catheter ablation - point by point - RF point by point. Radiofrequency pulses were delivered using an 8 mm tip catheter (with a temperature setting of 608C and a radiofrequency energy up to 100 W) in the first 17 patients, and a 3.5mm cooled-tip catheter (with a temperature setting up to 458C and a radiofrequency energy up to 50 W) in the remaining patients. When ablation was performed in the posterior wall, radiofrequency power was reduced to 50 or 25W, using the 8 and 3.5mm tip catheter, respectively, to reduce the risk of injuring the surrounding structure. In both cases, radiofrequency energy was delivered for up to 120 s until local electrogram amplitude was reduced >80%. The ablation lines consisted of contiguous focal lesions deployed at a distance □5 mm from the ostia of the PVs, creating a circumferential line around each PV. Another ablation line was created by connecting the left inferior PV to the mitral annulus (mitral isthmus). Remapping was performed in all patients in sinus rhythm, during coronary sinus pacing, using the pre-ablation anatomic map for acquisition of new points. The end-point of the ablation procedure was low peak-to-peak bipolar potentials (|<0.1 mV) inside the lesion, as determined by local electrogram analysis and voltage maps. A minimum of five points for each circumferential line was sampled. If sites of high voltage (>0.1 mV) were still present, additional ablations were performed, both along the encircling ablation lines and within them. Also received same AADs as control group. The antiarrhythmic drug preferentially administered was amiodarone. In patients with a history of side-effects or intolerance to amiodarone, a class IC antiarrhythmic drug was administered. The final decision was left to the physician in accordance with local practice. . Duration Single procedure. Concurrent medication/care: All patients received effective oral anticoagulation (international normalized ration between 2 and 3) for □1 month before ablation. Heparin anticoagulation replaced oral anticoagulants <72 h before ablation, and was stopped 4 h before the procedure. After transseptal puncture, an intravenous bolus of heparin (5000 IU) was administered, followed by infusion or additional boluses to maintain an activated clotting time >250 s. Oral anticoagulation was usually restarted before hospital discharge. Indirectness: No indirectness (n=69) Intervention 2: usual care - medical therapy. The antiarrhythmic drug preferentially administered was amiodarone. In patients with a history of side-effects or intolerance to amiodarone, a class IC antiarrhythmic drug was administered. The final decision was left to the physician in accordance with local practice. . Duration unclear. Concurrent medication/care: None. Indirectness: No indirectness

Funding	Funding not stated (Statement of no conflicts of interest)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RF POINT BY POINT versus MEDICAL THERAPY Protocol outcome 1: Mortality - Actual outcome for Mixed (<75% in any category)/unclear: Mortality at 1 year; Group 1: 1/68, Group 2: 2/69 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2 (stroke, withdrawal); Group 2 Number missing: 2 (withdrawal, refusal to have tele-monitoring) Protocol outcome 2: Stroke and systemic embolism - Actual outcome for Mixed (<75% in any category)/unclear: Stroke/TIA at 1 year; Group 1: 1/68, Group 2: 1/69 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1 (withdrawal); Group 2 Number missing: 2 (withdrawal, refusal to have tele-monitoring) Protocol outcome 3: Recurrence of symptomatic AF - Actual outcome for Mixed (<75% in any category)/unclear: Recurrence of AF at 1 year; Group 1: 26/68, Group 2: 63/69; Comments: 4 with atrial flutter in RF group not added Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Not symptomatic AF; Group 1 Number missing: 2 (stroke, withdrawal); Group 2 Number missing: 2 (withdrawal, refusal to have tele-monitoring) Protocol outcome 4: Serious Adverse Events - Actual outcome for Mixed (<75% in any category)/unclear: serious AEs at 1 year; Group 1: 1/68, Group 2: 0/69; Comments: 1 with pericardial effusion in RF group; 2 patients in usual care group intolerant to amiodarone and felcainide. Not deemed serious AES Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 2 (stroke, withdrawal); Group 2 Number missing: 2 (withdrawal, refusal to have tele-monitoring)	
Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; Redo of procedure ; HF or exacerbation of HF ; Length of stay

Study	COR trial: Perez-castellano 2014[195]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=50)
Countries and setting	Conducted in Spain; Setting: Institution in Spain
Line of therapy	1st line
Duration of study	Follow up (post intervention): 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	paroxysmal
Subgroup analysis within study	Not applicable
Inclusion criteria	symptomatic recurrent paroxysmal AF (>2 episodes in last 2 months) refractory to one or more antiarrhythmic drugs and an anatomic pattern comprising 4 single PVs
Exclusion criteria	aged <18 or >75 years; prior AF ablation; prior cardiac surgery; moderate to severe valvular heart disease; AP diameter of left atrium >50mm; hyperthyroidism; intracardiac thrombus; contraindications for anticoagulant therapy; concomitant acute illness; pregnancy.
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Mean (SD): 57. Gender (M:F): 39:11. Ethnicity: unclear
Further population details	1. CHADSVASC: Not stated / Unclear 2. Heart failure: Not stated / Unclear
Extra comments	Cryo/RF: hypertension 24%/32%; DM 16%/8%; structural heart disease 16%/16%; prior antiarrhythmic drugs 2/2

Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Radiofrequency catheter ablation - point by point - RF point by point. 3.5mm open-irrigated tip ablation catheter and a 15mm Lasso catheter advanced into LA via a single transeptal puncture. Ablation strategy was ostial electrical isolation of all PVs aided with the CARTO electroanatomical mapping system.. Duration Single procedure. Concurrent medication/care: General anesthesia; systemic anticoagulation with IV heparin. All had ICM implanted as well. . Indirectness: No indirectness (n=25) Intervention 2: Cryoballon catheter ablation - Cryoballoon. Single Arctic Front cryoballoon catheter (23 or 28mm0 was selected depending on size of PV ostia and physician preference. balloon introduced to LA through the 12 FG deflectable transeptal sheath. Baloon position and PV occlusion evaluated by intracardiac echocardiography and contrast venography. 2 consecutive 300-second cryoenergy applications were delivered.. Duration single procedure. Concurrent medication/care: General anaesthesia; systemic IV heparin; all had ICM implanted. Indirectness: No indirectness
Funding	Academic or government funding (National Institute of Health Carlos II and The Spanish society of Cardiology)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RF POINT BY POINT versus CRYOBALLOON

Protocol outcome 1: Recurrence of symptomatic AF
- Actual outcome for paroxysmal: AF recurrence at 12 months; Group 1: 8/25, Group 2: 13/25
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Did not state symptomatic AF; Baseline details: Cryo/RF: male 68%/88%; DM: 16%/8%; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Redo of procedure
- Actual outcome for paroxysmal: repeat ablation at 12 months; Group 1: 0/25, Group 2: 6/25
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Cryo/RF: male 68%/88%; DM: 16%/8%; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Serious Adverse Events
- Actual outcome for paroxysmal: serious complications at 12 months; Group 1: 1/25, Group 2: 1/25;
Risk of bias: All domain - : Indirectness of outcome: No indirectness

	Quality of life ; Hospitalisation ; Mortality ; Stroke and systemic embolism ; HF or exacerbation of HF ; Length of stay
	Protocol outcomes not reported by the study

Study	DAVTYAN 2018 trial: Davtyan 2018[58]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=89)
Countries and setting	Conducted in Russia
Line of therapy	1st line
Duration of study	Follow up (post intervention): 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	paroxysmal
Subgroup analysis within study	Not applicable
Inclusion criteria	At least 1 documented ECG occurence of NV symptomatic paroxysmal AF lasting >30 seconds within 90 days of enrollment that was refractory (or intolerance) to at least 1 AAD (including beta blockers); age 18 to 79 inc.; LA diam <50mm; LVEF at least 50% during sinus rhythm
Exclusion criteria	History of MI or cardiac surgery within 90 days of enrollment; history of stroke/TIA within 1 year of enrollment; uncontrolled thyroid function; unable to tolerate OACs
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Range of means: 55.6 to 57.6. Gender (M:F): 41:48. Ethnicity: Unclear
Further population details	1. CHADSVASC: <2 (mean of 1.3). 2. Heart failure: No HF (Needed to have at least 50% LVEF).
Extra comments	Multielectrode RF/Cryo: LA diam 4/4.1cm; CHADSVASC 1.3/1.3; history of TIA 9.1%/11.1%; IHD 4.5%/8.9%; hypertension 77.3%/77.8%; DM 13.6%/4.4%; AADs 100%/100%; anticoagulation 100%/100%

Indirectness of population	No indirectness
Interventions	(n=44) Intervention 1: Radiofrequency catheter ablation - point by point - RF point by point. Circular mapping catheter (LASSO) positioned at level of each pulmonary vein before each ablation. 3.5mm irrigated tip catheter used with 35 W power delivered. . Duration Single procedure. Concurrent medication/care: A multielectrode circular diagnostic catheter placement was also used. Sedation using general anaesthesia; visualization using US; Fractionated heparin administered. Indirectness: No indirectness (n=45) Intervention 2: Cryoballon catheter ablation - Cryoballoon. Cryo Balloon delivered to left atrium over guidewire using a dedicated cryo balloon catheter sheath. Only 28mm cryo balloon used. . Duration Single procedure. Concurrent medication/care: Sedation via GA; visualization by flouroscopy; fractionated heparin administered. Indirectness: No indirectness
Funding	Funding not stated (Statement of no conflicts of interest made)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RF POINT BY POINT versus CRYOBALLOON

Protocol outcome 1: Mortality
- Actual outcome for paroxysmal: mortality at 12 months; Group 1: 0/44, Group 2: 0/45
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: No symptomatic AF; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Stroke and systemic embolism
- Actual outcome for paroxysmal: thromboembolic events at 12 months; Group 1: 0/44, Group 2: 0/45
Risk of bias: All domain - --, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Recurrence of symptomatic AF
- Actual outcome for paroxysmal: AF recurrence as detected by implantable loop recorder at 12 months; DATA NOT USED; UNCLEAR IF EVENTS COUNTED IN BLANKING PERIOD, OR IF DATA CUMULATIVE.

Protocol outcome 4: Redo of procedure
- Actual outcome for paroxysmal: Re-do of procedure at 12 months; Group 1: 6/44, Group 2: 13/45
Risk of bias: All domain - --, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 5: Serious Adverse Events

- Actual outcome for paroxysmal: Serious adverse events at 12 months; Group 1: 2/44, Group 2: 0/45; Comments: 2 with arteriovenous fistulae in RF group. Assumed to be serious. Risk of bias: All domain - ; Indirectness of outcome: Serious indirectness, Comments: No symptomatic AF	
Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; HF or exacerbation of HF ; Length of stay

Study (subsidiary papers)	**FAST trial: Boersma 2012[31] (Castella 2019[42])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	2 (n=129)
Countries and setting	Conducted in Netherlands, Spain
Line of therapy	1st line
Duration of study	Follow up (post intervention): 6-10 years (unclear)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Mixed (<75% in any category)/unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	Documented, symptomatic paroxysmal and/or persistent AF for at least 12 months that was refractory to or intolerant of at least 1 AAD, age between 30 and 70 years, and mentally able and willing to give informed consent.
Exclusion criteria	Patients excluded if they had longstanding AF □1 year, cardiac CA or a surgical cardiac procedure in the last 3 months, previous stroke or transient ischemic attack, LA thrombus, LA size >65 mm, left ventricular ejection fraction <45%, mitral or aortic valve regurgitation above grade 2, moderate to severe mitral or aortic stenosis, active infection or sepsis, pregnancy, unstable angina, myocardial infarction within the previous 3 months, AF secondary to electrolyte imbalance, thyroid disease, other reversible or non-cardiovascular causes for AF, history of blood-clotting abnormalities, known sensitivity to heparin or warfarin, life expectancy of <12 months, involvement in another clinical study involving an investigational drug or device, pleural adhesions, prior thoracotomy, prior cardiac surgery, and elevated hemidiaphragm
Recruitment/selection of patients	Consecutive

Age, gender and ethnicity	Age - Mean (SD): 56. Gender (M:F): 100:24. Ethnicity: Unclear
Further population details	1. CHADSVASC: Not stated / Unclear 2. Heart failure: No HF (mean LVEF around 56).
Extra comments	Point by point/thoracoscopy: prior MI 3.2%/0%; LVEF 55.5%/57.7%; LA diam 43.2/42.5; prior failed catheter ablation 60.3%/73.8%; paroxysmal AF 58.8%/73.8%; persistent AF 41.2%/26.2%; prior AAD use 100%/100%; amiodarone 41.3%/29.2%; CHADS 2 2 or above 13.4%/6.7%
Indirectness of population	No indirectness
Interventions	(n=66) Intervention 1: Radiofrequency catheter ablation - point by point - RF point by point. Slightly different techniques at the two sites. At one site used a standard 4mm single tip RF catheter with maximum power of 35W. At other site a 3.5mm irrigated tip RF catheter was used with 3D CARTO navigation.. Duration Single procedure. Concurrent medication/care: VKAs discontinued prior to ablation; IV heparin given during procedure; Local anaesthesia given with lidocaine and during ablation patients given conscious sedation with diazepam combined with fentanyl.. Indirectness: No indirectness (n=63) Intervention 2: Thorascopic surgical ablation. Thoracoscopy using Wolf/Edgerton method. PVI carried out from the epicardial side with a bipolar RF ablation clamp provided by study sponsors.. Duration single procedure. Concurrent medication/care: Video assisted thoracoscopy under GA. . Indirectness: No indirectness
Funding	Equipment / drugs provided by industry (AtriCure)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RF POINT BY POINT versus THORASCOPIC SURGICAL ABLATION

Protocol outcome 1: Length of stay
- Actual outcome for Mixed (<75% in any category)/unclear: median duration of hospitalisation at 7 years; ;
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 3 (withdrawal of consent); Group 2 Number missing: 2 (change in surgery)

Protocol outcome 2: Mortality
- Actual outcome for Mixed (<75% in any category)/unclear: all cause mortality at 7 years: Group 1: 5/63, Group 2: 4/61

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3 (withdrawal of consent); Group 2 Number missing: 2 (change in surgery) Protocol outcome 3: Stroke and systemic embolism - Actual outcome for Mixed (<75% in any category)/unclear: cerebrovascular event at 7 years; Group 1: 6/63, Group 2: 5/61 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3 (withdrawal of consent); Group 2 Number missing: 2 (change in surgery) Protocol outcome 4: Recurrence of symptomatic AF - Actual outcome for Mixed (<75% in any category)/unclear: Recurrence of atrial fibrillation at 7 years; Group 1: 55/63, Group 2: 32/61 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Not symptomatic AF; Group 1 Number missing: 3 (withdrawal of consent); Group 2 Number missing: 2 (change in surgery) Protocol outcome 5: Redo of procedure - Actual outcome for Mixed (<75% in any category)/unclear: Redo of procedure at 7 years; Group 1: 31/63, Group 2: 8/61 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 3 (withdrawal of consent); Group 2 Number missing: 2 (change in surgery) Protocol outcome 6: Serious Adverse Events - Actual outcome for Mixed (<75% in any category)/unclear: serious AEs at 12 months; Group 1: 7/63, Group 2: 19/61; RF: 1 pericardial effusion/tamponase, 2 pneumonia, 2 HF, 1 SAB, 1 ileus (not including stroke/TIA); thoracoscopy: 1 pericardial effusion, 6 pneumothorax, 1 hemothorax, 1 rib fracture, 1 sternotomy, 3 pneumonia, 2 PM implant, 2 hydrothorax, 1 pericarditis, 1 ileus (TIA/stroke and fever not counted) Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 3 (withdrawal of consent); Group 2 Number missing: 2 (change in surgery)	
Protocol outcomes not reported by the study	Quality of life ; HF or exacerbation of HF ; Hospitalisation

Study (subsidiary papers)	FIRE AND ICE trial: Kuck 2016[122] (Kuck 2016[123])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=762)
Countries and setting	Conducted in Multiple countries; Setting: 16 centres in 8 European countries
Line of therapy	1st line
Duration of study	Follow up (post intervention): 1.5 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	paroxysmal
Subgroup analysis within study	Not applicable
Inclusion criteria	Symptomatic PAF with at least two episodes and at least one episode documented (30 seconds episode length, documented by ECG within last 12 months); documented treatment failure for effectiveness of at least one anti-arrhythmic drug (AAD Type I or III, including β-blocker and AAD intolerance); ≥18 and ≤75 years of age; patients who are mentally and linguistically able to understand the aim of the trial and to show sufficient compliance in following the trial protocol; patient is able to verbally acknowledge and understand the associated risks, benefits, and treatment alternatives to therapeutic options of this trial: cryoballoon ablation system or standard RF ablation technique. The patients, by providing informed consent, agree to these risks and benefits as stated in the patient informed consent document. All the details have been presented to him and he has signed the informed consent form for the trial.
Exclusion criteria	Any disease that limits life expectancy to less than one year; participation in another clinical trial (of a drug, device or biologic), either within the past two months or ongoing; pregnant women or women of childbearing potential not on adequate birth control: only women with a highly effective method of contraception [oral contraception or intra-uterine device (IUD)] or sterile women can be randomized; breastfeeding women; Substance misuse; Active systemic infection; Cryoglobulinaemia; patients with prosthetic valves; any previous

	LA ablation or surgery; any cardiac surgery or percutaneous coronary intervention (PCI) within three months prior to enrolment; unstable angina pectoris; myocardial infarction within three months prior to enrolment; symptomatic carotid stenosis; chronic obstructive pulmonary disease with detected pulmonary hypertension; any condition contraindicating chronic anticoagulation; stroke or transient ischemic attack within six months prior to enrolment; any significant congenital heart defect corrected or not (including atrial septal defects or PV abnormalities) but not including patent foramen ovale; New York Heart Association (NYHA) class III or IV congestive heart failure; EF < 35 % (determined by echocardiography within 60 days of enrolment as documented in patient medical history); Anteroposterior LA diameter > 55 mm (by trans-thoracic echocardiography (TTE orTEE) within three months to prior enrolment); LA thrombus (TEE diagnostic performed on admission); Intracardiac thrombus; PV diameter > 26 mm in right sided PVs; Mitral prosthesis; Hyperthrophic cardiomyopathy; 2° (Type II) or 3° atrioventricular block; Brugada syndrome or long QT syndrome; Arrhythmogenic right ventricular dysplasia; Sarcoidosis; PV stent; Myxoma; Thrombocytosis (platelet count > 600,000 / µl), thrombocytopenia (platelet count <100,000 / µl).; Any untreated or uncontrolled hyperthyroidism or hypothyroidism; Severe renal dysfunction (stage V, requiring or almost requiring dialysis, glomerular filtration rate (GFR) < 15 ml / min).
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Mean (SD): 60. Gender (M:F): 457:293. Ethnicity: Unknown
Further population details	1. CHADSVASC: <2 (Mean <2 in both groups). 2. Heart failure: No HF (73.9%/70.3% no heart failure).
Extra comments	RF/Cryo: CHADSVASC 1.8/1.9; NYHA II 15.5%/17.1%; previous stroke 1.1%/1.3%; previous MI 2.4%/2.4%; previous CABG 1.1%/0.5%; CAD 8.5%/8.3%; hypertension 58.8%/57.5%; DMII 5.9%/9.9%; anticoagulants 72.9%/75.4%
Indirectness of population	No indirectness
Interventions	(n=384) Intervention 1: Radiofrequency catheter ablation - point by point - RF point by point. In the radio-frequency group, operators attempted pulmonary vein isolation by creating a contiguous circular lesion around each pulmonary-vein antrum with point-by-point applications of radiofrequency energy, using electroanatomical navigation. Duration Single procedure. Concurrent medication/care: None. Indirectness: No indirectness (n=378) Intervention 2: Cryoballon catheter ablation - Cryoballoon. In the cryoballoon group, operators attempted pulmonary vein isolation by placing the device (with fluoroscopic guidance) at each pulmonary-vein antrum, advancing it toward the pulmonary vein to achieve occlusion, and then cooling the tissue by filling the

	balloon with a liquid refrigerant.. Duration single procedure. Concurrent medication/care: None. Indirectness: No indirectness
Funding	Study funded by industry (Medtronic)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RF POINT BY POINT versus CRYOBALLOON

Protocol outcome 1: Quality of life
- Actual outcome for paroxysmal: SF12 mental at 12 months; Group 1: mean 50.7 (SD 9.2); n=230, Group 2: mean 51.2 (SD 9.4); n=236
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 4 (lost to follow up); Group 2 Number missing: 5 (lost to follow up)
- Actual outcome for paroxysmal: SF12 physical at 12 months; Group 1: mean 47.8 (SD 8.4); n=230, Group 2: mean 47 (SD 9.2); n=236
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 4 (lost to follow up); Group 2 Number missing: 5 (lost to follow up)
- Actual outcome for paroxysmal: EQ-5D-3L at 12 months; Group 1: mean 0.88 (SD 0.13); n=254, Group 2: mean 0.88 (SD 0.13); n=257
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 4 (lost to follow up); Group 2 Number missing: 5 (lost to follow up)

Protocol outcome 2: Hospitalisation
- Actual outcome for paroxysmal: cardiovascular rehospitalisations at 1.5 years; Group 1: 135/376, Group 2: 89/374
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4 (lost to follow up); Group 2 Number missing: 5 (lost to follow up)

Protocol outcome 3: Mortality
- Actual outcome for paroxysmal: death from any cause at 1.5 years; Group 1: 0/376, Group 2: 2/374
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4 (lost to follow up); Group 2 Number missing: 5 (lost to follow up)

Protocol outcome 4: Stroke and systemic embolism
- Actual outcome for paroxysmal: stroke or TIA from any cause at 1.5 years; Group 1: 2/376, Group 2: 2/374
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4 (lost to follow up); Group 2 Number missing: 5 (lost to follow up)

Protocol outcome 5: Recurrence of symptomatic AF
- Actual outcome for paroxysmal: recurrent atrial arrhythmia at 1.5 years; Group 1: 143/376, Group 2: 138/374
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low,

Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Not stated that symptomatic; Group 1 Number missing: 4 (lost to follow up); Group 2 Number missing: 5 (lost to follow up) Protocol outcome 6: Redo of procedure - Actual outcome for paroxysmal: repeat ablation at 30 months; Group 1: 66/376, Group 2: 44/374 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4 (lost to follow up); Group 2 Number missing: 5 (lost to follow up) Protocol outcome 7: Serious Adverse Events - Actual outcome for paroxysmal: non-arrhythmia related serious adverse events at 1.5 years; Group 1: 29/376, Group 2: 25/374 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Not stated that symptomatic; Group 1 Number missing: 4 (lost to follow up); Group 2 Number missing: 5 (lost to follow up)	
Protocol outcomes not reported by the study	HF or exacerbation of HF ; Length of stay

Study	FORLEO, 2009 trial: Forleo 2009[79]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=70)
Countries and setting	Conducted in Italy
Line of therapy	1st line
Duration of study	Follow up (post intervention): 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Mixed (<75% in any category)/unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	Type II DM patients with symptomatic paroxysmal AF for >6 months refractory to 1-3 AADs
Exclusion criteria	age <18 or >75 years; LVEF <30%; LA diam >55mm; <12 months life expectancy; prior cardiac surgery or ablation
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Range of means: 63.2 - 64.8. Gender (M:F): 43:27. Ethnicity: unclear
Further population details	1. CHADSVASC: Not stated / Unclear 2. Heart failure: No HF (LA diam had to be <55mm).
Extra comments	RF pt to pt/drug: paroxysmal AF 45.7%/37.1%; previous ineffective AADs 1.5/1.8; hypertension 62.9%/68.6%; structural heart disease 45.7%/54.3%; CAD 20%/20%; valve disease 5.7%/11.4%
Indirectness of population	Serious indirectness: 8.5% with valve disease

Interventions	(n=35) Intervention 1: Radiofrequency catheter ablation - point by point - RF point by point. RF given by 3.5mm cooled tip catheter with maximal power of 35W. Applied to circumferential line around each PV vestibule. Nav X mapping system used. . Duration Single procedure. Concurrent medication/care: IV heparin. AADs continued until clinically not indicated post procedure (but not after 3 months). Indirectness: No indirectness (n=35) Intervention 2: usual care - medical therapy. Variable medications. Recommended medication regimen was oral flecainide 100mg every 12 hours, oral propafenone 150-300mg 3x daily, oral sotalol at initial dose of 80mg 3X daily and oral amiodarone 600mg/day for 2 weeks, 400mg/day for next 2 weeks and 200mg daily thereafter. . Duration unclear. Concurrent medication/care: Warfarin maintained. Indirectness: No indirectness
Funding	Other author(s) funded by industry

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RF POINT BY POINT versus MEDICAL THERAPY

Protocol outcome 1: Hospitalisation
- Actual outcome for Mixed (<75% in any category)/unclear: Hospitalisations at 1 year; Group 1: 3/35, Group 2: 12/35
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Stroke and systemic embolism
- Actual outcome for Mixed (<75% in any category)/unclear: thrombolic events at 1 year; Group 1: 0/35, Group 2: 0/35
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Recurrence of symptomatic AF
- Actual outcome for Mixed (<75% in any category)/unclear: recurrence of AF at 1 year; Group 1: 7/35, Group 2: 20/35
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Not symptomatic AF; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Serious Adverse Events
- Actual outcome for Mixed (<75% in any category)/unclear: serious AEs at 1 year; Group 1: 2/35, Group 2: 3/35; Comments: 2 bleeds in each group, and bradycardia requiring treatment in medical group

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low,

Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Mortality ; Redo of procedure ; HF or exacerbation of HF ; Length of stay

Study (subsidiary papers)	FREEZE AF trial: Luik 2017[137] (Luik 2015[138])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	2 (n=315)
Countries and setting	Conducted in Unknown; Setting: unclear
Line of therapy	1st line
Duration of study	Follow up (post intervention): 30 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	paroxysmal
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with at least 2 episodes of paroxysmal AF (of which at least one was documented) within the 3 months prior to enrolment; aged 18-75; documented inefficacy of at least one AAD.
Exclusion criteria	LA > 55mm; LA thrombus; previous LA Surgery or ablation; ejection fraction <40%; NYHA class III or IV; mitral prosthesis; MI in past 3 months; PCI or cardiac surgery in previous 3 months; stroke/TIA in past 6 months; pregnancy; life expectancy of <1 year
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Median (IQR): 61(54.8 to 67). Gender (M:F): 176:116. Ethnicity: Unclear
Further population details	1. CHADSVASC: Not stated / Unclear (50.2% <2 and 49.8% 2 or more.). 2. Heart failure: No HF (ejection fraction <40% exclusion criterion).
Extra comments	CAD 12.7%; hypertension 64%; vascular disease 5.1%; common ostium 18.8%; DOACs 26%; VKA 73.3%; antiplatelets 11.9%

Indirectness of population	No indirectness
Interventions	(n=159) Intervention 1: Radiofrequency catheter ablation - point by point - RF point by point. Irrigated tip catheter in conjunction with a 3D navigation system. Duration single procedure. Concurrent medication/care: Transesophageal echo used in conjunction. All received anticoagulation in 4 weeks prior to the ablation. . Indirectness: No indirectness (n=156) Intervention 2: Cryoballon catheter ablation - Cryoballoon. CB performed predominantly with using Arctic Front cardiac Cryoablation Catheter System and FlexCath steerable sheath. 23mm balloon used preferentially but 28mm used where needed. . Duration single procedure. Concurrent medication/care: Anticoagulation given in previous 4 weeks; Transesophageal echo used. Indirectness: No indirectness
Funding	Equipment / drugs provided by industry (Holter monitors provided by CryoCath/Medtronic)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RF POINT BY POINT versus CRYOBALLOON

Protocol outcome 1: Stroke and systemic embolism
- Actual outcome for paroxysmal: TIA/stroke at 12 months; Group 1: 0/159, Group 2: 0/156
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: did not specify symptomatic; Baseline details: Vascular disease RF 7.5%, CB 2.8%; common ostium RF 23.8%, CB 13.8%; Group 1 Number missing: 12 (loss to follow u); Group 2 Number missing: 11 (loss to follow up)

Protocol outcome 2: Recurrence of symptomatic AF
- Actual outcome for paroxysmal: recurrence of AF at 30 months; Group 1: 88/147, Group 2: 84/145
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: did not specify symptomatic; Baseline details: Vascular disease RF 7.5%, CB 2.8%; common ostium RF 23.8%, CB 13.8%; Group 1 Number missing: 12 (loss to follow u); Group 2 Number missing: 11 (loss to follow up)

NOT USED as not a pure recurrence outcome – included complications

Protocol outcome 3: Redo of procedure
- Actual outcome for paroxysmal: patients with re-do procedures at 30 months; Group 1: 54/147, Group 2: 51/145
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Vascular disease RF 7.5%, CB 2.8%; common ostium RF 23.8%, CB 13.8%; Group 1 Number missing: 12 (loss to follow u); Group 2 Number missing: 11 (loss to follow up)

Protocol outcome 4: Serious Adverse Events - Actual outcome for paroxysmal: serious AEs at 30 months; Group 1: 3/159, Group 2: 11/156 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Vascular disease RF 7.5%, CB 2.8%; common ostium RF 23.8%, CB 13.8%; Group 1 Number missing: 12 (loss to follow u); Group 2 Number missing: 11 (loss to follow up)	
Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; Mortality ; HF or exacerbation of HF ; Length of stay

Study	Giannopoulos, 2018 trial: Giannopoulos 2018[85]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=30)
Countries and setting	Conducted in Greece
Line of therapy	1st line
Duration of study	Follow up (post intervention): 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	paroxysmal
Subgroup analysis within study	Not applicable
Inclusion criteria	Paroxysmal AF; 2 episodes of AF within past 12 months, either self-terminating or cardioverted in <48 hrs; at least 2 had to be symptomatic; at least 1episode should have occurred during treatment with a class I or III AAD
Exclusion criteria	Previous left atrial ablation procedure; LA diam >50mm; primary electrical heart disease; atrial thrombus; prosthetic valve; moderate/severe mitral stenosis; severe mitral regurgitation; active infectious disease or malignancy; child pugh class B or C; eGFR <20.
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Mean (range): 58 (55-64). Gender (M:F): 19:11. Ethnicity: unclear
Further population details	1. CHADSVASC: >=2 (Median was 2 so likely that vast majority >=2). 2. Heart failure: No HF (LA diam >50mm excluded).
Extra comments	Cryo/RF: DM 0/20%; hypertension 67%/40%; CAD 33%/20%; CHADSVASC 2 (1-3); LVEF 55/51; LA diam

	45/43mm; EHRA class 2/2
Indirectness of population	No indirectness
Interventions	(n=15) Intervention 1: Radiofrequency catheter ablation - point by point - RF point by point. Antral PVI with irrigated RF ablation catheter with realtime contact force sensing with aid of electroanatomic mapping with CARTO3. . Duration Single procedure. Concurrent medication/care: Standard TEE performed prior to ablation. . Indirectness: No indirectness (n=15) Intervention 2: Cryoballon catheter ablation - Cryoballoon. Cryothermal energy applied for 240 seconds via 28mm cryoballoon (Arctic Front Advance). . Duration Single procedure. Concurrent medication/care: TEE performed prior to procedure. Indirectness: No indirectness
Funding	Study funded by industry (CryoLAEF)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RF POINT BY POINT versus CRYOBALLOON Protocol outcome 1: Recurrence of symptomatic AF - Actual outcome for paroxysmal: AF recurrence (either clinically or on 24 hour ambulatory recordings) at 3 months; Group 1: 4/15, Group 2: 3/15 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Not necessarily symptomatic; Group 1 Number missing: 0; Group 2 Number missing: 0 <u>NOT INCLUDED IN ANALYSIS AS EVENTS OCCURRED DURING BLANKING PERIOD</u>	
Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; Mortality ; Stroke and systemic embolism ; Redo of procedure ; HF or exacerbation of HF ; Serious Adverse Events ; Length of stay

Study	**Giannopoulos, 2019 trial: Giannopoulos 2019[86]**

Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=120)
Countries and setting	Conducted in Greece
Line of therapy	1st line
Duration of study	Follow up (post intervention): 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	paroxysmal
Subgroup analysis within study	Not applicable
Inclusion criteria	Paroxysmal AF; 2 symptomatic episodes of AF within past 12 months, either self-terminating in 7 days or cardioverted in <48 hrs; Failure of at least one class I or III AAD; eage 40-80; slated for PVI
Exclusion criteria	Previous left atrial ablation procedure; LA diam >50mm; primary electrical heart disease; atrial thrombus; prosthetic valve; moderate/severe mitral stenosis; severe mitral regurgitation; active infectious disease or malignancy; child pugh class B or C; eGFR <20.
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age – Range of means: 58-61. Gender (M:F): unclear. Ethnicity: unclear
Further population details	1. CHADSVASC: <2 (median was 1 in both groups; 52.5% were 0 or 1). 2. Heart failure: No HF (LA diam >50mm excluded; only 3.3% with diagnosed HF).
Extra comments	Cryo/RF: DM 11.3/15%; hypertension 51.3%/45%; CAD 7.5%/5%; CHADSVASC 1 (1-2); LVEF 60/60; LA diam 40/41.5mm; EHRA class 2/2
Indirectness of population	No indirectness

Interventions	(n=40) Intervention 1: Radiofrequency catheter ablation - point by point - RF point by point. Antral PVI with irrigated RF ablation catheter with realtime contact force sensing with aid of electroanatomic mapping with CARTO3. . Duration Single procedure. Concurrent medication/care: Standard TEE performed prior to ablation. . Indirectness: No indirectness (n=80) Intervention 2: Cryoballon catheter ablation - Cryoballoon. Cryothermal energy applied for 240 seconds via 28mm cryoballoon (Arctic Front Advance). . Duration Single procedure. Concurrent medication/care: TEE performed prior to procedure. Indirectness: No indirectness
Funding	Study funded by industry (Medtronic)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RF POINT BY POINT versus CRYOBALLOON Protocol outcome 1: Recurrence of symptomatic AF - Actual outcome for paroxysmal: arrhythmia recurrence (24 hr ambulatory ECG) at 6 months; Group 1: 10/38 (26.3% risk given in paper; this implies the impossible 10.5 people out of 40, but if we assume only 38 were included this gives almost exactly 10 as the numerator; this is an assumption and risks reducing power, but, importantly, it provides a result which is consistent with the risk given in the paper); Group 2: 19/80 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Not necessarily symptomatic; Group 1 Number missing: 0; Group 2 Number missing: 2 (possibly, based on the results, but not reported) <u>DATA NOT USED: UNCLEAR IF CUMULATIVE OR POINT DATA</u>	
Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; Mortality ; Stroke and systemic embolism ; Redo of procedure ; HF or exacerbation of HF ; Serious Adverse Events ; Length of stay

Study	GUNAWARDINE, 2018 trial: Gunawardene 2018[87]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=60)
Countries and setting	Conducted in Germany
Line of therapy	1st line
Duration of study	Intervention time: mean 309 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	paroxysmal
Subgroup analysis within study	Not applicable
Inclusion criteria	Documented symptomatic paroxysmal AF within past year; history of prior electrical cardioversion allowed if cardioversion performed within the initial 48 hrs after symptom onset; age >18 <85 yrs; structurally normal heart (LVEF >35%, LA diam <5cm;no valvular disease defined as <2nd degree valvular dysfunction.
Exclusion criteria	Patients with previous ablation; intracardiac thrombi; pregnancy; life expectancy <1 year; contraindications to OACs; hyperthyroidism
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Mean (SD): 59.7 (10.2). Gender (M:F): 70:30. Ethnicity: unclear
Further population details	1. CHADSVASC: Not stated / Unclear (median 1 in RF group but median 2 in cryoballoon group). 2. Heart failure: No HF (Structurally normal hearts (ie LA diam <5cm) was inclusion criterion).
Extra comments	hypertension 55%; CHADSVASC 1; HAS-BLED 1; EHRA score 2; LVEF 59.5%; mean number of prior AADs 1; duration of longest AF episode 10 hrs

Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Cryoballon catheter ablation - Cryoballoon. Octapolar diagnostic catheter placed in the coronary sinus via femoral approach. After a single transeptal puncture 29mm Arctic Front Advance cryo catheter introduced to LA via a 12F steerable sheath. Pulmonary vein mapping to record electrograms performed. Duration single procedure. Concurrent medication/care: Performed under deep sedation using propofol and fentanyl. Heparin boluses used for intraprocedural anticoagulation. Transoesophageal echo used to rule out thrombus formation in LA appendage.. Indirectness: No indirectness (n=30) Intervention 2: Radiofrequency catheter ablation - point by point - RF point by point. Irrigated contact force sensing tip radiofrequency current ablation catheter provided max 30Watts for 30-60 seconds. Maximum of 25 Watts when ablating the posterior wall. PVI followed by bipolar pacing of the entire ablation line.. Duration single procedure. Concurrent medication/care: Performed under deep sedation using propofol and fentanyl. Heparin boluses used for intraprocedural anticoagulation. Transoesophageal echo used to rule out thrombus formation in LA appendage.. Indirectness: No indirectness
Funding	Funding not stated (Declaration of no conflicts of interest made)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CRYOBALLOON versus RF POINT BY POINT

Protocol outcome 1: Mortality
- Actual outcome for paroxysmal: death at mean 309 days; Group 1: 0/30, Group 2: 0/30
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Recurrence of symptomatic AF
- Actual outcome for paroxysmal: Recurrence of AF at mean 309 days; Group 1: 6/30, Group 2: 3/30
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Not symptomatic recurrence; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Redo of procedure
- Actual outcome for paroxysmal: Redo procedure at <3 months; Group 1: 2/30, Group 2: 0/30; Comments: Performed during 3 month blanking period
Risk of bias: All domain - ; Indirectness of outcome: Serious indirectness, Comments: Not symptomatic recurrence

Protocol outcome 4: Serious Adverse Events - Actual outcome for paroxysmal: severe complications at mean 309 days; Group 1: 0/30, Group 2: 0/30 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; Stroke and systemic embolism ; HF or exacerbation of HF ; Length of stay

Study	Herrera Siklody, 2012 trial: Herrera siklody 2012[90]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=60)
Countries and setting	Conducted in France, Germany; Setting: Unclear
Line of therapy	1st line
Duration of study	Follow up (post intervention): 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Mixed (<75% in any category)/unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	Symptomatic, drug refractory paroxysmal or persistent AF
Exclusion criteria	Long persistent AF (>12 months); LA diam >55mm; intracardiac thrombi; MI or cardiac surgery in previous 3 months; previous ablation
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Range of means: 56-57. Gender (M:F): Define. Ethnicity: unclear
Further population details	1. CHADSVASC: Not stated / Unclear 2. Heart failure: No HF (LA diam 40-41mm).
Extra comments	Cryo/RF: paroxysmal 70%/56.7%; failed AAD 2.9/2.7; organic heart disease 26.7%/36.7%; hypertension 43.3%/46.7%; LA diam 41.4mm/40mm
Indirectness of population	No indirectness

Interventions	(n=30) Intervention 1: Radiofrequency catheter ablation - point by point - RF point by point. Transeptal PVI with open irrigated tip RF. Navigation with NavX system.. Duration Single procedure. Concurrent medication/care: OACs stopped 2 days prior to ablation to achieve INR of 1.8-2.5, and restarted immediately after. For patients with persistent AF cardioversion performed 6 weeks prior to ablation. AADs suspended day before procedure. GA with remifentanil and profolol. Transesophageal echo used to guide transeptal puncture. Heparin given IV.. Indirectness: No indirectness (n=30) Intervention 2: Cryoballon catheter ablation - Cryoballoon. PVI performed under transesophageal echo using Arctic Front balloon. . Duration Single procedure. Concurrent medication/care: OACs stopped 2 days prior to ablation to achieve INR of 1.8-2.5, and restarted immediately after. For patients with persistent AF cardioversion performed 6 weeks prior to ablation. AADs suspended day before procedure. GA with remifentanil and profolol. Transesophageal echo used to guide transeptal puncture. Heparin given IV.. Indirectness: No indirectness
Funding	Study funded by industry (CryoCath)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RF POINT BY POINT versus CRYOBALLOON

Protocol outcome 1: Recurrence of symptomatic AF
- Actual outcome for Mixed (<75% in any category)/unclear: recurrence of symptomatic AF at 12 months; Group 1: 6/30, Group 2: 11/30
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Redo of procedure
- Actual outcome for Mixed (<75% in any category)/unclear: redo of procedure at 12 months; Group 1: 6/30, Group 2: 10/30
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Serious Adverse Events
- Actual outcome for Mixed (<75% in any category)/unclear: complications at post-procedure; Group 1: 0/30, Group 2: 1/30; Comments: In cryo group there was 1 groin bleed, 1 pseudoaneurysm and 2 transient phrenic nerve injuries. Only psudoaneurysm deemed by the reviewer to represent serious adverse events.
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Quality of life ; Hospitalisation ; Mortality ; Stroke and systemic embolism ; HF or exacerbation of HF ; Length of stay	
Protocol outcomes not reported by the study	

Study	HUMMEL, 2014 trial: Hummel 2014[91]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=210)
Countries and setting	Conducted in USA
Line of therapy	1st line
Duration of study	--:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	persistent <1 year
Subgroup analysis within study	Not applicable
Inclusion criteria	18-70 years; symptomatic persistent AF lasting 7 days to 1 year or 1-4 years (unclear on proportions so categorised as mixed); failed >1 class I or III AAD; continuous AF / flutter on 48 hr holter monitor; failed DCCV
Exclusion criteria	Prior AF ablation; treated ventricular tachyarrythmia; active infection; history of CVA; pregnancy; active LA thrombus; contrast media allergy; reversible cause of AF; blood clotting abnormalities; sensitivity to heparin/warfarin; severe pulmonary disease; LVEF <40%; NYHA III or IV; severe comorbidity preventing FU; significant structural heart disease
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Range of means: 59.6 to 60.7. Gender (M:F): 83:17. Ethnicity: unclear
Further population details	1. CHADSVASC: <2 (CHADS 0.8). 2. Heart failure: No HF (LVEF >40%).
Extra comments	RF ME/Medical: LA diam 45mm/46mm; LVEF% 54.7/54.9; persistent AF 69.6%/79.2%; number of failed AADs 1.4/1.1; DM 15.9%/11.1%; CAD 20.3%/16.7%; congestive HF 5.8%/11.1%; hypertension 60.9%/55.6%;

	cardiomyopathy 6.5%/13.9%; valvular disease 5.1%/11.1%; CHADS score 0.8/0.8; congenital heart disease 0.7%/0; pacemaker of implantable cardioverter-defibrillator 2.9%/4.2%
Indirectness of population	No indirectness
Interventions	(n=138) Intervention 1: Radiofrequency catheter ablation - multielectrode - RF multielectrode. PVAC used. CFAE ablation performed on the left intraatrial septum with the MASC and in the LA body using the MAAC. Duration Single procedure. Concurrent medication/care: TEE performed within 72 hours to rule out pre-existing intracardiac thrombus; Patients discontinued OACs and bridged with LMWH to maintain activated clotting time of >300 seconds. Indirectness: No indirectness (n=72) Intervention 2: usual care - medical therapy. New dosages of previously failed AAD or a new medication. Patients prescribed amiodarone were allowed a loading dosage. Duration unclear but at least 6 months. Concurrent medication/care: DCCVs, changes to AAD and/or dosage were allowed during the follow-up period. Indirectness: No indirectness
Funding	Study funded by industry (Medtronic)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RF MULTIELECTRODE versus MEDICAL THERAPY

Protocol outcome 1: Quality of life
- Actual outcome for Mixed (<75% in any category)/unclear: Symptom severity and QoL surveys physical well being at >30 days; ;
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for Mixed (<75% in any category)/unclear: Symptom severity and QoL surveys mental well being at >30 days; ;
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Mortality
- Actual outcome for Mixed (<75% in any category)/unclear: death at >30 days; Group 1: 5/138, Group 2: 0/72
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Stroke and systemic embolism

- Actual outcome for Mixed (<75% in any category)/unclear: stroke at >30 days; Group 1: 1/138, Group 2: 0/72 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 4: Serious Adverse Events - Actual outcome for Mixed (<75% in any category)/unclear: acute events at 30 days; Not used as data unclear and heavily biased towards ablation events Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for Mixed (<75% in any category)/unclear: chronic events at >30 days; Group 1: 8/138, Group 2: 3/72; RF ME: 5 PV stenosis, 1 persistent ASD, 1 pericarditis, 1 pericardial effusion; Medical: 2 GI bleeds and AF with rapid ventricular response Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Hospitalisation ; Recurrence of symptomatic AF ; Redo of procedure ; HF or exacerbation of HF ; Length of stay

Study	JAN, 2018 trial: Jan 2018[96]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=50)
Countries and setting	Conducted in Slovenia
Line of therapy	1st line
Duration of study	Follow up (post intervention): mean 30.5 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	paroxysmal
Subgroup analysis within study	Not applicable
Inclusion criteria	Paroxysmal AF; no others reported
Exclusion criteria	None reported
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Mean (SD): 59.2 (8.9). Gender (M:F): 37:13. Ethnicity: Unclear
Further population details	1. CHADSVASC: <2 (51% in hybrid and 70% in catheter ablation group <2; mean was 1.2 to 1.5.). 2. Heart failure: No HF (Mean LVEF 63-65).
Extra comments	Hybrid/RF pt pt: arterial hypertension 75%/54%; DM 8%/7%; HF 0/0; stroke/TIA 0/0; vascular disease 8%/11%; LAV 32.4/34.2; LVEF 65.6/63.3; EHRA score 2.8/2.7; CHADSVASC 1.5/1.2; Prior use of AADs 58%/69%
Indirectness of population	No indirectness

Interventions	(n=24) Intervention 1: Hybrid thoracoscopy/ablation. Epicardial access to the posterior LA was achieved by endoscopically creating a pericardial window through the central tendon of the diaphragm and pericardium just above the liver margin and at least 1 cm away from the falciform ligament using laparoscopic instruments inserted through two 5-mm and one 10-mm abdominal trocars. Abdominal insufflation allowed visualization of the central tendon of the diaphragm while creating a pericardial window using a monopolar L-hook electrocoagulation probe. After creating the pericardial window, a Subtle R cannula (Atricure, Inc., Mason, OH, USA), designed to allow simultaneous passage of an ablation device and an endoscope, was inserted abdominally through the pericardial window into the oblique sinus. The 5- or 7-mm, 0 degree endoscope provided direct visualization of the posterior LA while a vacuum lumen within the cannula removed any fluid to maintain optics while manipulating devices within the pericardial space. The 3-cm Numeris R or Epi-Sense R epicardial ablation device (Atricure, Inc.) was inserted through the cannula, beside the endoscope, and positioned along the posterior LA. Radiofrequency (RF) energy at predefined power (30W)and time (90 seconds) settings was used to create epicardial lesions. An esophageal temperature probe was utilized, if temperature increased to ≥38◦C the RF energy was discontinued. Additionally, pericardial sac was filled with cooled (5◦C) saline during each RF delivery to ensure additional cooling and to prevent conductive heating of the oesophagus. Epicardial lesions were inspected with endoscopic visualization to confirm they interconnect everywhere except at the attachments between the pericardium and atrium.. Duration single procedure. Concurrent medication/care: See above. Indirectness: No indirectness (n=26) Intervention 2: Radiofrequency catheter ablation - point by point - RF point by point. CoolFlex R catheters (St. Jude Medical, Little Canada, MN, USA) were used to create endocardial lesions at a power of 25–35W. Electroanatomic navigation system was used to create a3Dshell of the LA. With the use of the3Dshell, circumferential antral PVI was performed ensuring that endocardial lesions connected the previously created epicardial lesions for the CVP group. Ablation on the circumferential antral line was performed at sites where bipolar voltage was detected. If there was no voltage (no bipolar signals), the site was tagged as scar (actual necrosis from prior epicardial ablation) on the 3D shell and not ablated. For the CA group, ablation on the circumferential antral line was performed in standard fashion to complete the PVI. Duration Single procedure. Concurrent medication/care: See above. Indirectness: No indirectness
Funding	Funding not stated (Statement of 'no disclosures' so industry funding assumed to be unlikely)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: HYBRID ABLATION versus RF POINT BY POINT

Protocol outcome 1: Mortality
- Actual outcome for paroxysmal: death at 30.5 months: Group 1: 0/24, Group 2: 0/26

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Stroke and systemic embolism - Actual outcome for paroxysmal: stroke/TIA at 30.5 months; Group 1: 0/24, Group 2: 0/26 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Recurrence of symptomatic AF - Actual outcome for paroxysmal: Recurrence of AF/AT/AFL at 30.5 months; Group 1: 10/24, Group 2: 17/26 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Not symptomatic recurrence; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 4: Redo of procedure - Actual outcome for paroxysmal: Redo of procedure at 30.5 months; Group 1: 4/24, Group 2: 9/26 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 5: Serious Adverse Events - Actual outcome for paroxysmal: periprocedural major complications at 30.5 months; Group 1: 3/24, Group 2: 0/26 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; HF or exacerbation of HF ; Length of stay

Study	Jones, 2013 trial: Jones 2013[99]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=52)
Countries and setting	Conducted in United Kingdom
Line of therapy	1st line
Duration of study	Follow up (post intervention): 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	persistent >1 year
Subgroup analysis within study	Not applicable
Inclusion criteria	The enrollment criteria were 18 to 80 years of age, persistent AF (>7 days), symptomatic HF (New York Heart Association functional class II to IV) on optimal HF therapy, and left ventricular ejection fraction (EF) >35%.
Exclusion criteria	Cardiovascular implantable electronic device insertion or cerebrovascular event within 6 months; coronary revascularization or atrioventricular nodal ablation within 3 months; reversible causes of AF or HF including thyroid dysfunction, alcohol, primary valvular disease, or recent major surgery; prior heart transplant or on urgent transplant waiting list; pregnancy; active malignancy; severe renal impairment; single chamber pacemaker and atrioventricular block; and contraindications to general an- esthesia or oral anticoagulation
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Range of means: 62-64. Gender (M:F): 45:7. Ethnicity: unclear
Further population details	1. CHADSVASC: Not stated / Unclear 2. Heart failure: HF (HF population).

Extra comments	RF/med: coronary artherosclerosis 50%/42%; NYHA 2.5/2.46; LA diam 46/50;
Indirectness of population	No indirectness
Interventions	(n=26) Intervention 1: Radiofrequency catheter ablation - point by point - RF point by point. Radiofrequency ablation was performed with a 3.5-mm irrigated-tip catheter (ThermoCool, Biosense Webster, Diamond Bar, California) and comprised the following stepwise strategy: 1) pulmonary-vein isolation; 2) linear ablation at the left atrial roof and mitral isthmus; and 3) ablation of left atrial complex fractionated electrograms guided by high-density multipolar mapping. If atrial tachycardia occurred, the protocol was terminated, and the tachycardia was mapped and ablated. If AF persisted, sinus rhythm was restored by external cardioversion, followed by cavotricuspid isthmus ablation. Duration single procedure. Concurrent medication/care: The procedure was performed under general anesthesia. Transesophageal echocardiography was performed to exclude left atrial thrombus and to guide transseptal puncture. Patients were heparinized to maintain the activated clotting time over 300 s. Atrial anatomy was reconstructed with the NavX mapping system with an AFocusII catheter. Indirectness: No indirectness (n=26) Intervention 2: usual care - medical therapy. Patients received pharmacological therapy (beta-blockers and/or digoxin) targeted to achieve a mean heart rate (assessed by apical auscultation over 30 s) <80 beats/min at rest before and <110 beats/min after a 6-min walk (7,8). If rate-control criteria were not met at baseline or during follow-up, patients re-attended at 4-week intervals for repeat assessment and adjustment of drug therapy until targets were achieved. In patients with pacemakers, if the base rate (□80 beats/min) was not exceeded, no additional medication was prescribed for rate control. Atrioventricular node ablation and pacing was not adopted as a protocol, because it had just been reported to be inferior to pulmonary vein isolation. Duration unclear. Concurrent medication/care: None. Indirectness: No indirectness
Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RF POINT BY POINT versus MEDICAL THERAPY

Protocol outcome 1: Mortality
- Actual outcome for persistent >1 year: death at 1 year; Group 1: 1/26, Group 2: 0/26
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low,

Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Serious Adverse Events - Actual outcome for persistent >1 year: serious AEs at 1 year; Group 1: 2/26, Group 2: 0/26; tamponade and pulmonary oedema Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; Stroke and systemic embolism ; Recurrence of symptomatic AF ; Redo of procedure ; HF or exacerbation of HF ; Length of stay

Study	KRITTAYAPHONG, 2003 trial: Krittayaphong 2003[121]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=30)
Countries and setting	Conducted in Thailand
Line of therapy	1st line
Duration of study	Follow up (post intervention): 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Mixed (<75% in any category)/unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	male and female aged 15-75 years; symptomatic paroxysmal or persistent AF > 6 months; refractory to at least 1 antiarrythmic medication including class 1A or class IC agents, digitalis, beta-blockers or Ca channel blockers; never had amiodarone
Exclusion criteria	transient AF or treatable cause of AF; bleeding disorders; thyroid disorders; previous stroke; severe underlying illness limiting life expectancy to <1 year; psychiatric disorders; valvular heart disease
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Range of means: 48.6 to 55.3. Gender (M:F): 19:11. Ethnicity: Unclear
Further population details	1. CHADSVASC: Not stated / Unclear 2. Heart failure: No HF (LVEF >60%).
Extra comments	RF Pt/pt/Medical: DM 6.7%/20%; hypertension 26.7%/46.7%; IHD 6.7%/6.7%; dilated cardiomyopathy 0/6.7%; prolapsed mitral valve 6.7%/0; pulmonary hypertension 0/6.7%; paroxysmal 73.3%/60%; LA diam 39.6/39.2mm; LVEF% 63.7/61.8

Indirectness of population	No indirectness
Interventions	(n=15) Intervention 1: Radiofrequency catheter ablation – point by point - RF point by point. Navistar quadripolar catheter used with CARTO mapping system. Ablation lines were drawn as a series of contiguous dots. Lines included a circular line isolating the ostia of the pulmonary veins.. Duration single procedure. Concurrent medication/care: All patients on Warfarin for at least 3 weeks (INR 2-3) prior to procedure. GA used. Indirectness: No indirectness (n=15) Intervention 2: usual care - medical therapy. Amiodarone given at 1200mg qd for 1 week, 600mg qd for 2 weeks and then 200mg qd thereafter. . Duration Unclear though at least 1 year.. Concurrent medication/care: Doppler echo, thyroid function test, liver function test, chest roentgenography and eye exam performed during administration. If serious side effects occurred amiodarone discontinued and class 1A or IC agents given. Indirectness: No indirectness
Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RF POINT BY POINT versus MEDICAL THERAPY

Protocol outcome 1: Quality of life
- Actual outcome for Mixed (<75% in any category)/unclear: Quality of life at 1 year; data not useable as only bar graph given
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Stroke and systemic embolism
- Actual outcome for Mixed (<75% in any category)/unclear: Stroke at 1 year; Group 1: 1/15, Group 2: 0/15
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Recurrence of symptomatic AF
- Actual outcome for Mixed (<75% in any category)/unclear: data not used as unclear if events immediately after ablation were counted (events in blanking period)

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: not symptomatic; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Serious Adverse Events - Actual outcome for Mixed (<75% in any category)/unclear: serious adverse effects at 1 year; Group 1: 1/15, Group 2: 3/15 [RF: 1 with sinus node dysfunction (groin hematoma and GI effects not counted as serious); usual care: 2 with corneal microdeposits, hypothyroidism and abnormal liver function tests, 1 with hyperthyroidism and sinus node dysfunction (GI side effects not counted as serious)] Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Hospitalisation ; Mortality ; Redo of procedure ; HF or exacerbation of HF ; Length of stay

Study	MacDONALD, 2011 trial: Macdonald 2011[142]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=41)
Countries and setting	Conducted in United Kingdom
Line of therapy	1st line
Duration of study	Follow up (post intervention): minimum 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	persistent >1 year
Subgroup analysis within study	Not applicable
Inclusion criteria	Men and women aged 18e80 years, with New York Heart Association functional class II-IV symptoms despite optimal heart failure treatment for at least 3 months, ejection fraction <35% measured by radionuclide ventriculography, persistent AF and no contraindication to cardiovascular MRI were eligible.
Exclusion criteria	Paroxysmal AF; QRS duration >150 ms (or QRS 120e150 with evidence of mechanical cardiac dysynchrony15); any contraindication to oral anti-coagulant drugs; primary valvular disease or acute myocarditis as the cause of heart failure; coronary revascularisation within the preceding 6 months; pregnancy and expected cardiac transplantation within 6 months.
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Range of means: 62.3-64.4. Gender (M:F): 32:9. Ethnicity: unclear
Further population details	1. CHADSVASC: Not stated / Unclear 2. Heart failure: HF (HF population (LVEF <20)).

Extra comments	RF pt/pt / Med: LVEF 19.6/16.1; AF duration 64m/44m; NYHA class II or higher: 89%/91%; CHD 47%/50%;DM 21%/32%; hypertension 58%/64%;
Indirectness of population	No indirectness
Interventions	(n=22) Intervention 1: Radiofrequency catheter ablation - point by point - RF point by point. RFA was performed with an irrigated tip ablation catheter (ThermoCool, Biosense Webster). If AF persisted after pulmonary vein isolation, radiofrequency lesions were delivered in a linear fashion between the right and left superior pulmonary veins, and then at sites of complex fractionated atrial electrograms on the interatrial septum, mitral annular region, left atrial roof, left atrial free wall and around the base of the left atrial appendage. In most cases radiofrequency energy was also delivered inside the coronary sinus at sites of complex electrograms. If the patient remained in AF following ablation, sinus rhythm was restored by internal cardioversion under intravenous sedation. If the patient had a history of atrial flutter (or if atrial flutter was seen during the procedure) cavotricuspid isthmus ablation was also performed, and bidirectional isthmus block was confirmed after ablation.. Duration Single procedure. Concurrent medication/care: RFA was performed a median of 43 days from randomisation using the Bordeaux technique.13 All procedures were performed in a single centre, by an experienced operator. A decapolar mapping catheter was advanced into the coronary sinus. After trans-septal puncture, intravenous unfractionated heparin was given to achieve an activated clotting time of 300 s. Pulmonary vein and left atrial anatomy was delineated with pulmonary venous angiography and three-dimensional reconstruction of the left atrium using Nav-X mapping system (St JudeMedical,Minnesota, USA). . Indirectness: No indirectness (n=19) Intervention 2: usual care - medical therapy. All patients received optimal heart failure treatment for 3 months. If mean heart rate was >80 bpm over a 24 h period then digoxin was added to treatment.. Duration 3 months. Concurrent medication/care: None. Indirectness: No indirectness
Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RF POINT BY POINT versus MEDICAL THERAPY

Protocol outcome 1: Quality of life
- Actual outcome for persistent >1 year: SF36 physical at 6 months; Group 1: mean 4 (SD 9.5); n=20, Group 2: mean -1 (SD 4.4); n=18
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2 (stroke, contraindications); Group 2 Number missing: 1 (withdrew consent)

- Actual outcome for persistent >1 year: SF36 mental at 6 months; Group 1: mean 0.4 (SD 9.5); n=20, Group 2: mean 5.9 (SD 8.5); n=18 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2 (stroke, contraindications); Group 2 Number missing: 1 (withdrew consent) Protocol outcome 2: Recurrence of symptomatic AF - Actual outcome for persistent >1 year: Recurrent AF at 6 months; Group 1: 12/20, Group 2: 18/18 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Not symptomatic Group 1 Number missing: 2 (stroke, contraindications); Group 2 Number missing: 1 (withdrew consent) Protocol outcome 3: HF or exacerbation of HF - Actual outcome for persistent >1 year: Change in LVEF at 6 months; Group 1: mean 4.5 (SD 11.1); n=20, Group 2: mean 2.8 (SD 6.7); n=18 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2 (stroke, contraindications); Group 2 Number missing: 1 (withdrew consent) - Actual outcome for persistent >1 year: worsening HF at 6 months; Group 1: 3/20, Group 2: 0/18 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Not symptomatic AF; Group 1 Group 1 Number missing: 2 (stroke, contraindications); Group 2 Number missing: 1 (withdrew consent) Protocol outcome 4: Serious Adverse Events - Actual outcome for persistent >1 year: serious AEs at 6 months; Group 1: 5/20, Group 2: 0/18; 2 cardiac tamponade and 3 worsening HF Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2 (stroke, contraindications); Group 2 Number missing: 1 (withdrew consent)	
Protocol outcomes not reported by the study	Hospitalisation ; Mortality ; Stroke and systemic embolism ; Redo of procedure ; Length of stay

Study (subsidiary papers)	MACPAF trial: Koch 2012[117] (Schirdewan 2017[219])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=44)
Countries and setting	Conducted in Germany
Line of therapy	1st line
Duration of study	Not clear: <6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	paroxysmal
Subgroup analysis within study	Not applicable
Inclusion criteria	Symptomatic paroxysmal AF; prior ineffective AAd treatment; no previous ablation; no unstable structural heart disease; lifespan at least 2 years; contraindications for MRI.
Exclusion criteria	None (see inclusion criteria)
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Median (IQR): 63 (54-68). Gender (M:F): 25:19. Ethnicity: Unclear
Further population details	1. CHADSVASC: >=2 (median is 2 so majority had score of 2 or above). 2. Heart failure: No HF (HF only 2.3%).
Extra comments	Median CHADSVASC 2 (IQR 1-3); HF 2.3%; hypertension 54.5%; DM 13.6%; previous stroke 11.4%; CAD 22.7%; beta blockers 97.7%; AADs 43.2%; antiplatelets 56.8%; VKAs 59.1%
Indirectness of population	No indirectness

Interventions	(n=21) Intervention 1: Radiofrequency catheter ablation - multielectrode - RF multielectrode. Bard's HD Mesh ablator is a balloon-like catheter providing multielectrode RF. HD mesh ablator positioned at the PV ostium in fully deployed shape. Circumferential pulsed RF energy administered . Target temperature set to 58 degrees with maximum energy output of 80-100W. Duration single procedure. Concurrent medication/care: OACs stopped 7 days pre-ablation. Propofol and fentanyl sedation. Transeptal puncture done with flouroscopic guidance. Heparin bolus used.. Indirectness: No indirectness (n=23) Intervention 2: Cryoballon catheter ablation - Cryoballoon. Arctic Front Cryoablation balloon catheter. 28mm cryoballoon catheter placed at the PV antrum via guidewire. Each PV received at least 2 cryo applications of 300s. . Duration Single procedure. Concurrent medication/care: OACs stopped 7 days pre-ablation. Propofol and fentanyl sedation. Transeptal puncture done with flouroscopic guidance. Heparin bolus used.. Indirectness: No indirectness
Funding	Academic or government funding (Also some authors receive industry funding)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RF MULTIELECTRODE versus CRYOBALLOON

Protocol outcome 1: Length of stay
- Actual outcome for paroxysmal: Hospital length of stay at unclear ; ;
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6 (withdrew consent, technical problems and contraindications) Group 2 Number missing: 6 (withdrew consent, technical problems and contraindications)

Protocol outcome 2: Mortality
- Actual outcome for paroxysmal: death at unclear ; Group 1: 0/15, Group 2: 0/17
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6 (withdrew consent, technical problems and contraindications) Group 2 Number missing: 6 (withdrew consent, technical problems and contraindications)

Protocol outcome 3: Stroke and systemic embolism
- Actual outcome for paroxysmal: Stroke at unclear ; Group 1: 0/15, Group 2: 0/17
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6 (withdrew consent, technical problems and contraindications) Group 2 Number missing: 6 (withdrew consent, technical problems and contraindications)
Protocol outcome 4: Recurrence of symptomatic AF

- Actual outcome for paroxysmal: Recurrence of AF at 12 months; Group 1: 10/15, Group 2: 13/22 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Not symptomatic; Group 1 Number missing: 6 (withdrew consent, technical problems and contraindications) Group 2 Number missing: 6 (withdrew consent, technical problems and contraindications) Protocol outcome 5: Serious Adverse Events - Actual outcome for paroxysmal: Major complications at unclear ; Group 1: 2/15, Group 2: 1/17 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6 (withdrew consent, technical problems and contraindications) Group 2 Number missing: 6 (withdrew consent, technical problems and contraindications)	
Protocol outcomes not reported by the study	Quality of life ; Redo of procedure ; HF or exacerbation of HF ; Hospitalisation

Study (subsidiary papers)	MANTRA-PAF trial: Cosedis nielsen 2012[56] (Nielsen 2017[177], Walfridsson 2015[253])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	2 (n=294)
Countries and setting	Conducted in Denmark
Line of therapy	1st line
Duration of study	Follow up (post intervention): 5 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	paroxysmal
Subgroup analysis within study	Not applicable
Inclusion criteria	At least two episodes of symptomatic paroxysmal atrial fibrillation within the preceding 6 months but no episode of atrial fibrillation that was longer than 7 days (without spontaneous termination or cardioversion).
Exclusion criteria	Age of more than 70 years, previous or ongoing treatment with class IC or class III antiarrhythmic drugs, contraindication to both class IC and class III agents, previous ablation for atrial fibrillation, a left atrial diameter of more than 50 mm, a left ventricular ejection fraction of less than 40%, contraindication to oral anticoagulation therapy, moderate-to-severe mitral valve disease, severe heart failure (New York Heart Association functional class III to IV at the time of enrollment), expected surgery for structural heart disease, and secondary atrial fibrillation (due to cardiac surgery, infection, or hyperthyroidism)
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Range of means: 54-56. Gender (M:F): 206:88. Ethnicity: Unclear
Further population details	1. CHADSVASC: <2 (Most CHADS2 below 1). 2. Heart failure: No HF (Most NYHA I).

Extra comments	RF/medical: CAD 4%/1%; hypertension 29%/36%; valvular disease 5%/10%; previous valvular intervention 1%/1%; pacemaker 3%/4%; LVEF >60%: 79.5%/81.2%; NYHA I 90%/86%; CHADS >1:11.6%/12.8%
Indirectness of population	Serious indirectness: 7.5% with valvular disease
Interventions	(n=146) Intervention 1: Radiofrequency catheter ablation - point by point - RF point by point. Percutaneous transvenous radiofrequency catheter ablation was performed by encircling the left- and right-sided pulmonary veins with either a 3.5-mm catheter with an irrigated tip (NaviStar ThermoCool, Biosense Webster) or an 8-mm solid-tip catheter (for 15 procedures; NaviStar DS, Biosense Webster). The irrigated catheter (saline flow, 17 ml per minute) had a maximum power setting of 40 W, and the solid-tip catheter had a maximum power setting of 80 W; both had a target temperature of 55°C. Reduced power was used in the left atrial posterior wall to avoid excessive heating of the oesophagus and other adjacent structures. The goal of ablation was the elimination of all high-frequency electrical activity with an amplitude exceeding 0.2 mV inside the encircled areas, which was documented by electroanatomical mapping or by the use of circular multipolar catheters (which were used for 138 procedures) at the operator's discretion. Additional ablation sites inside the encircled areas but outside the pulmonary veins were allowed in order to achieve the ablation goal.. Duration Single procedure. Concurrent medication/care: Oral anticoagulation with a stable international normalized ratio of 2.0 or higher was ensured for at least 3 weeks before ablation. Transesophageal echocardiography was performed within 24 hours before the procedure to rule out the presence of left atrial thrombi. After transseptal puncture of the interatrial septum, intravenous heparin was administered according to institutional standards. The ablation procedure was guided by electroanatomical mapping (CARTO, Biosense Webster).. Indirectness: No indirectness (n=148) Intervention 2: usual care - medical therapy. The first-line medication was a class IC agent (either flecainide at a dose of 200 mg per day or propafenone at a dose of 600 mg per day). If class IC agents were contraindicated, a class III agent (either amiodarone at a dose of 200 mg per day or sotalol at a dose of 160 mg per day) was used. During treatment with class IC agents, supplementary use of a beta-blocker, a calcium-channel blocker, or digoxin was recommended. Combinations of class IC and class III agents were not allowed. An aggressive rhythm-control strategy, with the use of direct-current cardioversion and trial of all clinically appropriate antiarrhythmic drugs, was recommended for any patient with recurrent atrial fibrillation. If antiarrhythmic drug therapy failed, supplementary ablation of atrial fibrillation was offered as clinically indicated.. Duration Unclear. Concurrent medication/care: None. Indirectness: No indirectness
Funding	Study funded by industry (Biosense Webster. Also by Danish Heart Foundation)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RF POINT BY POINT versus MEDICAL THERAPY

Protocol outcome 1: Quality of life
- Actual outcome for paroxysmal: SF36 physical at 5 years; Group 1: mean 51 (SD 36.96); n=146, Group 2: mean 52 (SD 27.96); n=148; Comments: sds calculated form 95% CIs
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for paroxysmal: SF36 mental at 5 years; Group 1: mean 54 (SD 30.8); n=146, Group 2: mean 54 (SD 21.64); n=148; Comments: sds calculated from CIs
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for paroxysmal: EQ5D index at 2 years; Group 1: mean 0.9 (SD 0.16); n=146, Group 2: mean 0.86 (SD 0.16); n=148; Comments: Comparable at baseline
Risk of bias: All domain - ; Indirectness of outcome: No indirectness
- Actual outcome for paroxysmal: EQ5D VAS at 2 years; Group 1: mean 79.5 (SD 15.7); n=146, Group 2: mean 79.8 (SD 14.5); n=148; Comments: RFA lower at baseline (67.6 vs 71). Thus final results alone obscure a greater improvement for RFA. The group x time analysis in paper indicated that there was a significant group x time benefit to RFA (p=0.018)
Risk of bias: All domain - ; Indirectness of outcome: No indirectness
- Actual outcome for paroxysmal: ASTA index at 2 years; Group 1: mean 0.47 (SD 0.06); n=146, Group 2: mean 0.57 (SD 0.06); n=148; Comments: Comparable at baseline
Risk of bias: All domain - ; Indirectness of outcome: No indirectness

Protocol outcome 2: Hospitalisation
- Actual outcome for paroxysmal: Hospitalisation at 2 years; Group 1: 0/146, Group 2: 2/148
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Mortality
- Actual outcome for paroxysmal: Death at 5 years; Group 1: 5/146, Group 2: 7/148
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Stroke and systemic embolism
- Actual outcome for paroxysmal: stroke/TIA at 2 years; Group 1: 2/146, Group 2: 1/148
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 5: Recurrence of symptomatic AF - Actual outcome for paroxysmal: recurrence of symptomatic AF at 5 years; DATA NOT USED AS UNCLEAR IF CUMULATIVE DATA INCLUDES BLANKING PERIOD Protocol outcome 6: Redo of procedure - Actual outcome for paroxysmal: redo of ablation (or new ablation for medical) at 5 years; Group 1: 96/146, Group 2: 76/148 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 7: Serious Adverse Events - Actual outcome for paroxysmal: Serious AEs at 2 years; Group 1: 15/146, Group 2: 12/148 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	HF or exacerbation of HF ; Length of stay

Study	MYSTIC-PAF, 2016 trial: Boersma 2016[32]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=120)
Countries and setting	Conducted in Belgium, Netherlands
Line of therapy	1st line
Duration of study	Follow up (post intervention): 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	paroxysmal
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged 18 to 70 years, with a history of symptomatic paroxysmal AF documented in the past 12 months, and refractory to ≥1 antiarrhythmic drug (AAD) could participate in the trial.
Exclusion criteria	Patients were excluded if any of the following were present: significant structural heart disease (including previous cardiac surgery other than coronary artery bypass grafting), heart failure of New York Heart Association class >2, left ventricular ejection fraction <40%, left atrial diameter >50 mm, ongoing myocardial ischemia, myocardial infarction within the previous 3 months, valvular disease >grade II, congenital heart disease (not including atrial septal defect or patent foramen ovale without a right to left shunt), previous atrial septal defect or patent foramen ovale closure, hypertrophic cardiomyopathy >15 mm, pulmonary hypertension (PA pressure >50 mm Hg), previous LA ablation for AF, any ablation within the previous 3 months,cardioversion <7 days before CA, enrollment in any other ongoing arrhythmia study protocol, any ventricular tachycardia with treatment that might interfere with the study, active infection or sepsis, history of cerebral vascular disease (including stroke or transient ischemic attack), pregnancy or lactation, untreatable contrast media allergy, any diagnosis of AF secondary to reversible or noncardiovascular causes, history of blood clotting (bleeding or thrombotic) abnormalities, known sensitivities to heparin or warfarin, severe chronic obstructive pulmonary disease (forced expiratory volume 1 <1), severe comorbidity,

	or poor general physical/mental health.
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Range of means: 56.1 to 56.9. Gender (M:F): 90:30. Ethnicity: unclear
Further population details	1. CHADSVASC: <2 (mean <1). 2. Heart failure: No HF (most low NYHA).
Extra comments	RF pt to pt/ RF ME: CHADSVASC 0.63/0.96; LVEF >55% 75%/79%; LA diam 41.2mm/39.8mm; failed AADs 2/1; NYHA class 0 or I: 96%/91%
Indirectness of population	No indirectness
Interventions	(n=59) Intervention 1: Radiofrequency catheter ablation - point by point - RF point by point. Standard open irrigated catheters of any brand with a 3.5- to 4.0-mm tip were used. Power was set a 43°C with a maximum output of 30 W, with a flow of 17 mL/min. Applications lasted 60 s in case of point-by-point ablation or were continuous in case of a dragging technique. Nonfluoroscopic catheter visualization was performed with CARTO (Biosense Webster, Diamond Bar, CA) or NavX (St.Jude, Minneapolis, MN) by constructing a 3D electroanatomic map of the LA and PVs. The PVs were mapped by using any brand of a decapolar circular mapping catheter.. Duration Single procedure. Concurrent medication/care: All procedures were performed under intravenous heparin, with target activated clotting time of >250 s during the procedure. Patients maintained continuous vitamin K antagonist with therapeutic international normalized ratio (INR) levels or were bridged with low-molecular weight heparin if INR was subtherapeutic. LA access was obtained either through a patent foramen ovale or standard transseptal puncture per the Brockenbrough technique. Biplane or monoplane fluoroscopy was used to visualize catheter introduction and manipulation. A standard coronary sinus catheter was used for pacing maneuvers to verify PVI and pacing in case of bradycardia. Postprocedural patient management was per hospital standard. All patients (re)started vitamin K antagonist with bridging low-molecular weight heparin until INR >2.0 and for at least the first 3 months after the procedure. Indirectness: No indirectness (n=61) Intervention 2: Radiofrequency catheter ablation - multielectrode - RF multielectrode. A 25-mm diameter, decapolar catheter with platinum 3-mm electrodes with 3-mm spacing (PVAC; Ablation Frontiers/Medtronic Inc, Carlsbad CA) was used with the GENius Generator version 14 (Ablation Frontiers/Medtronic Inc). The decapolar multielectrode catheter is positioned around each PV, with a guidewire placed within the target PV for positioning. Radiofrequency applications are then delivered during 60 s, with a target temperature of 60°C, and maximum power output of 8 W or 9 W (in 4:1 and 2:1 energy modes, respectively). Electrodes failing to reach target temperature, or with power <3 W were deselected. To

	avoid overheating, electrode 1 or 10 were disabled if within close proximity. Duration Single procedure. Concurrent medication/care: All procedures were performed under intravenous heparin, with target activated clotting time of >250 s during the procedure. Patients maintained continuous vitamin K antagonist with therapeutic international normalized ratio (INR) levels or were bridged with low-molecular weight heparin if INR was subtherapeutic. LA access was obtained either through a patent foramen ovale or standard transseptal puncture per the Brockenbrough technique. Biplane or monoplane fluoroscopy was used to visualize catheter introduction and manipulation. A standard coronary sinus catheter was used for pacing maneuvers to verify PVI and pacing in case of bradycardia. Postprocedural patient management was per hospital standard. All patients (re)started vitamin K antagonist with bridging low-molecular weight heparin until INR >2.0 and for at least the first 3 months after the procedure.. Indirectness: No indirectness
Funding	Study funded by industry (Medtronic)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RF POINT BY POINT versus RF MULTIELECTRODE

Protocol outcome 1: Quality of life
- Actual outcome for paroxysmal: AF symptoms severity QoL score at 12 months; Group 1: mean 6.6 (SD 3.5); n=58, Group 2: mean 6.5 (SD 2.6); n=59;
Comments: RF pt to pt was 13.2 at baseline but MEA was 12.2 at baseline. Thus bias favouring RF MEA. However the authors performed a linear mixed model that adjusted for baseline and did not observe a difference between groups (p=0.83). They did not provide adjusted results as far as known.
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1 (unclear); Group 2 Number missing: 2 (unclear)

Protocol outcome 2: Length of stay
- Actual outcome for paroxysmal: length of hospital stay at 12 months; Group 1: mean 1 (SD 1); n=58, Group 2: mean 1 (SD 0); n=59
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1 (unclear); Group 2 Number missing: 2 (unclear)

Protocol outcome 3: Stroke and systemic embolism
- Actual outcome for paroxysmal: stroke at 12 months; Group 1: 0/58, Group 2: 0/59
Risk of bias: All domain – very high, Selection - Low, Blinding - High, Incomplete outcome data - high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1 (unclear); Group 2 Number missing: 2 (unclear)

Protocol outcome 4: Recurrence of symptomatic AF
- Actual outcome for paroxysmal: Recurrent AF requiring AADs (almost certainly symptomatic) at 12 months; Group 1: 11/58, Group 2: 14/59
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

- Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1 (unclear); Group 2 Number missing: 2 (unclear) Protocol outcome 5: Serious Adverse Events - Actual outcome for paroxysmal: Severe AEs at 12 months; Group 1: 0/58, Group 2: 0/59 Risk of bias: All domain – Very high, Selection - Low, Blinding - High, Incomplete outcome data - high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1 (unclear); Group 2 Number missing: 2 (unclear)	
Protocol outcomes not reported by the study	Mortality ; Redo of procedure ; HF or exacerbation of HF ; Hospitalisation

Study	NCT00678340 trial: Mccready 2014[153]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=188)
Countries and setting	Conducted in United Kingdom; Setting: unclear
Line of therapy	1st line
Duration of study	Follow up (post intervention): 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	paroxysmal
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with paroxysmal AF; failed at least one AAD; listed for ablation
Exclusion criteria	patient objection; prior ablation; LA diam >60mm; mechanical prosthetic vales; hypertrophic cardiomyopathy; contraindications to OACs; pregnancy
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Range of means: 58 to 62. Gender (M:F): 58:36. Ethnicity: Unclear
Further population details	1. CHADSVASC: <2 (mean was 1.19). 2. Heart failure: No HF (mean LA size 38mm and LVEF mean was 63).
Extra comments	Point by point/multielectrode: hypertension 28%/24%; DM 3%/6%; mean LA size 39/38mm; TIA or CVA 2.1%/3.2%; CHADSVASC 54/94 in each group were <2; amiodarone 11.7%/16%; sotalol 21%/22%; Beta blockers 53%/57%
Indirectness of population	No indirectness

Interventions	(n=94) Intervention 1: Radiofrequency catheter ablation - point by point - RF point by point. Double trans-septal puncture performed using SL1 and Aglis guide sheath and 3D geometry created using CARTO or NAVX mkapping system. Antral point by point circumferential ablation around ipsilateral PVs, with distance 0.5 to 1cm from ostia using 4mm open tip irrigated catheter. Maximum power set at 30-35 W. Duration Single procedure. Concurrent medication/care: 14/94 continued warfarin for the duration of the procedure. remained stopped warfarin 3 days pre-procedure. Indirectness: No indirectness (n=94) Intervention 2: Radiofrequency catheter ablation - multielectrode - RF multielectrode. Single trans-septal puncture performed using SL1 sheath. Circular decapolar 9Ff bidirectional PVAC catheter advanced over a 0.032 in wire, selectively placed in each PV or PV branch. 8W maximum power; Delivered RF in a combination of one or more of the 5 bipolar channels.. Duration single procedure. Concurrent medication/care: 19/94 continued warfarin.. Indirectness: No indirectness
Funding	Academic or government funding (UCLH Biomedicine NIHR; Glenfield University Hospital, Leicester University NIHR)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RF POINT BY POINT versus RF MULTIELECTRODE

Protocol outcome 1: Stroke and systemic embolism
- Actual outcome for paroxysmal: Strokes at 12 months; Group 1: 0/91, Group 2: 2/92
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: unclear (3 lost in total but to which groups is not known); Group 2 Number missing: unclear (3 lost in total but to which groups is not known)

Protocol outcome 2: Recurrence of symptomatic AF
- Actual outcome for paroxysmal: recurrence of symptomatic AF at 12 months; Group 1: 23/91, Group 2: 24/92
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: unclear (3 lost in total but to which groups is not known); Group 2 Number missing: unclear (3 lost in total but to which groups is not known)

Protocol outcome 3: Redo of procedure
- Actual outcome for paroxysmal: Re-do of procedure at 12 months; Group 1: 23/91, Group 2: 24/92
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: unclear (3 lost in total but to which groups is not known); Group 2 Number

missing: unclear (3 lost in total but to which groups is not known) Protocol outcome 4: Serious Adverse Events - Actual outcome for paroxysmal: serious adverse events at 12 months; Group 1: 4/91, Group 2: 1/92; Risk of bias: All domain - high, Selection - Low, Blinding - Low, Incomplete outcome data - high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: unclear (3 lost in total but to which groups is not known); Group 2 Number missing: unclear (3 lost in total but to which groups is not known)	
Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; Mortality ; HF or exacerbation of HF ; Length of stay

Study	NCT01456000 trial: Dukkipati 2015[70]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=353)
Countries and setting	Conducted in USA; Setting: Clinics in USA
Line of therapy	1st line
Duration of study	Follow up (post intervention): 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	paroxysmal
Subgroup analysis within study	Not applicable
Inclusion criteria	2 or more symptomatic AF episodes of at least 1 min within past 6/12; 1 documented AF episode in past 12 months; refractory or intolerant to AADs
Exclusion criteria	PV size >35mm; LA thrombus; LA diam >50mm; LVEF <30%; prev ablation; NYHA III or IV; MI in previous 60 days; unstable angina; cardiac surgery in previous 3 months; CABG in previous 6 months; cardiac valve surgery; thromoembolic event in past 3 months; uncontrolled bleeding; active infection; atrial myoma; severe pulmonary disease; or GI bleeding; previous valvular procedure; presence of implantable cardioverter defibrillator; pregnancy, lactating or not using birth control.
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Range of means: 59.7 to 60.1. Gender (M:F): 227:115. Ethnicity: 332 white, 5 black, 3 Asian, 2 other
Further population details	1. CHADSVASC: Not stated / Unclear 2. Heart failure: No HF (<5% with HF).
Extra comments	Laser/point by point RF; hypertension 59.4%/58.1%; CAD 21.2%/20.3%; MI 4.1%/4.1%; CABG 2.9%/4.1%;

	CHF 5.3%/2.3%; DM 15.3%/9.9%; LA diam 4/4cm; AA meds class I 49.4%/58.7%; class II 50.6%/47.1%; Class III 57.6%/57.6%
Indirectness of population	No indirectness
Interventions	(n=178) Intervention 1: Laser catheter ablation - laser ablation. Laser ablation performed with VGLB system, a variable-diameter compliant balloon with a flexible tip that is delivered through a 12-F deflectable sheath. Includes endoscope allowing real-time visualisation. . Duration single procedure. Concurrent medication/care: Anaesthesia depended on site, with most using GA. IV heparin administered. Intracardiac echocardiography used. . Indirectness: No indirectness (n=175) Intervention 2: Radiofrequency catheter ablation - point by point - RF point by point. Ablation using irrigated RFA catheter and CARTO electroanatomic mapping system. Circumferential ablation used. Additional ablation allowed at investigator discretion, including linear lesions, ablation of electrogram fractionation and cavotricuspid isthmus ablation. . Duration single procedure. Concurrent medication/care: Anaesthesia usually GA (depended on site). IV heparin and intracardiac echocardiography used.. Indirectness: No indirectness
Funding	Equipment / drugs provided by industry (CardioFocus Inc.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LASER ABLATION versus RF POINT BY POINT

Protocol outcome 1: Mortality
- Actual outcome for paroxysmal: death at 12 months; Group 1: 1/170, Group 2: 0/172; Comments: The single death was not classified as a primary adverse event.
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 11 (8 treatment not started, 1 lost to follow up, 1 adverse event, 1 withdrew consent; Group 2 Number missing: 8 (3 treatment not started, 2 lost to FU, 1 adverse event, 2 withdrew consent)

Protocol outcome 2: Stroke and systemic embolism
- Actual outcome for paroxysmal: stroke/TIA at 12 months; Group 1: 2/170, Group 2: 1/172
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 11 (8 treatment not started, 1 lost to follow up, 1 adverse event, 1 withdrew consent; Group 2 Number missing: 8 (3 treatment not started, 2 lost to FU, 1 adverse event, 2 withdrew consent)

Protocol outcome 3: Recurrence of symptomatic AF - Actual outcome for paroxysmal: 12 month incidence of symptomatic AF at 12 months; Group 1: 61/167, Group 2: 60/166 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 11 (8 treatment not started, 1 lost to follow up, 1 adverse event, 1 withdrew consent; Group 2 Number missing: 8 (3 treatment not started, 2 lost to FU, 1 adverse event, 2 withdrew consent) Protocol outcome 4: Serious Adverse Events - Actual outcome for paroxysmal: primary adverse event (definitions only include severe AEs) at 12 months; Group 1: 8/170, Group 2: 5/172 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 11 (8 treatment not started, 1 lost to follow up, 1 adverse event, 1 withdrew consent; Group 2 Number missing: 8 (3 treatment not started, 2 lost to FU, 1 adverse event, 2 withdrew consent)	
Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; Redo of procedure ; HF or exacerbation of HF ; Length of stay

Study	NCT01504451 trial: Sugihara 2018[235]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=73)
Countries and setting	Conducted in United Kingdom; Setting: Tertiary arrhythmia centre
Line of therapy	1st line
Duration of study	Follow up (post intervention): one year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	paroxysmal
Subgroup analysis within study	Not applicable
Inclusion criteria	Age >18; symptomatic paroxysmal AF suitable for ablation
Exclusion criteria	Prior cardiac or thoracic surgery; inability to undergo GA for AF ablation; pregnancy; cardiac rhythm disorders other than AF; presence of pre-existing permanent pacemakers or implantable loop recorders that did not allow for continuous monitoring of AF occurence, or were not MRI safe.
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Range of means: 61-67. Gender (M:F): 31:42. Ethnicity: unclear
Further population details	1. CHADSVASC: >=2 (most around 2). 2. Heart failure: Not stated / Unclear
Extra comments	PVAC/nMARQ/Surgery: prior ablation 16%/16%/16%; hypertension 48%/60%/43%; hyperlipidemia 32%/32%/22%; DM 16%/8%/4%; prior CVA 4%/0%/0%; prior TIA 16%/0/4%; hypothyroidism 16%/125/13%; CAD 12%/20%/9%; median CHADSVASC 2/2/1. The PVAC and nMARQ groups were both RF multielectrode treatments and so their results have been combined

Indirectness of population	No indirectness
Interventions	(n=50) Intervention 1: Radiofrequency catheter ablation - multielectrode - RF multielectrode. Two ablation methods used - PVAC and nMARQ. Both multielectrode and so although these were placed in separate groups in the study they are combined in this review (as defined in the protocol). . Duration single procedure. Concurrent medication/care: Bolus of unfractionated heparin; anticoagulation continued throughout procedure. Indirectness: No indirectness (n=23) Intervention 2: Thorascopic surgical ablation. PV isolation achieved by epicardial ablation using a bipolar RF clamp.. Duration single procedure. Concurrent medication/care: 6 weeks of OACs pre-procedure and then OACs stopped prior to procedure without bridging. OACs reinstated immediately after procedure. General anaesthetic used. . Indirectness: No indirectness
Funding	Academic or government funding (Eastbourne Cardiology Research Charity Fund)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RF MULTIELECTRODE versus THORASCOPIC SURGICAL ABLATION

Protocol outcome 1: Length of stay
- Actual outcome for paroxysmal: mean duration of hospital admission at 1 year; ;
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Mortality
- Actual outcome for paroxysmal: Death at 1 year; Group 1: 0/49, Group 2: 1/20
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Recurrence of symptomatic AF
- Actual outcome for paroxysmal: Number of patients requiring AADs after blanking period (in text the paper states that such patients had symptomatic recurrence) at 1 year; Group 1: 14/49, Group 2: 0/20
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Redo of procedure
- Actual outcome for paroxysmal: Number of patients requiring repeat ablation at 1 year; Group 1: 13/49, Group 2: 0/20

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 5: Serious Adverse Events - Actual outcome for paroxysmal: serious adverse events at 1 year; Group 1: 0/49, Group 2: 6/20; Comments: Did not count death as serious AE Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Stroke and systemic embolism ; HF or exacerbation of HF ; Hospitalisation

Study	NCT01863472 trial: Schmidt 2017[221]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=152)
Countries and setting	Conducted in Multiple countries; Setting:
Line of therapy	1st line
Duration of study	Follow up (post intervention): 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	persistent <1 year
Subgroup analysis within study	Not applicable
Inclusion criteria	symptomatic persistent AF refractory to at least 1 AAD including beta blockers class 1-111; episode duration of >7 days and <1 year; 18-80 years old; LVEF <50mm; LVEF >45%
Exclusion criteria	Previous PVI; ineligible for OACs; intracardiac thrombus; moderate or severe mitral valve disease
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Range of means: 65-66. Gender (M:F): 85:73. Ethnicity: unclear
Further population details	1. CHADSVASC: Not stated / Unclear 2. Heart failure: No HF (mean LVEF 61%).
Extra comments	laser/point by point: previous cardioversion 91%/89%; CAD 22%/15%; hypertension 71%/74%; MI 10%/3%; PAD 5%/6%; mDM 9%/11%; history of stroke 3%/3%; LVEF 61%/61%; AAD class I 15%/14%; class III 25%/26%
Indirectness of population	No indirectness

Interventions	(n=75) Intervention 1: Laser catheter ablation - laser ablation. Laser energy deployed in point by point fashion via 12F steerable sheath. Energy between 5.5 and 12W. Energy applied for 2-30 seconds respectively. . Duration single procedure. Concurrent medication/care: Deep sedation with boluses of midazolam and fentanyl followed by continuous infusion of propofol. Unfractionated heparin administered. PV angiographies performed for visualisation. Indirectness: No indirectness (n=77) Intervention 2: Radiofrequency catheter ablation - point by point - RF point by point. After flouroscopic identification of LA/PV junction, wide area circumferential ablation around PVs performed with point by point method. Energy was 25-40W.. Duration single procedure. Concurrent medication/care: Deep sedation; unfractionated heparin; PV angiography applied. Indirectness: No indirectness
Funding	Equipment / drugs provided by industry (CardioFocus)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LASER ABLATION versus RF POINT BY POINT

Protocol outcome 1: Mortality
- Actual outcome for persistent <1 year: death at 12 months; Group 1: 0/68, Group 2: 0/66
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5 (lost to follow up); Group 2 Number missing: 6 (lost to follow up)

Protocol outcome 2: Stroke and systemic embolism
- Actual outcome for persistent <1 year: stroke at 12 months; Group 1: 3/68, Group 2: 0/66
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5 (lost to follow up); Group 2 Number missing: 6 (lost to follow up)

Protocol outcome 3: Recurrence of symptomatic AF
- Actual outcome for persistent <1 year: recurrence of AF at 12 months; Group 1: 19/66, Group 2: 19/62
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Not symptomatic AF; Group 1 Number missing: 7 (lost to follow up); Group 2 Number missing: 10 (lost to follow up)

Protocol outcome 4: Redo of procedure
- Actual outcome for persistent <1 year: redo of procedure at 12 months; Group 1: 8/68, Group 2: 9/66
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 5 (lost to follow up); Group 2 Number missing: 6 (lost to follow up)

Protocol outcome 5: Serious Adverse Events - Actual outcome for persistent <1 year: complications (include only serious AEs) at 12 months; Group 1: 2/68, Group 2: 3/66 ; laser 1 false aneurysm, 1 MI (stroke and symptomatic phrenic nerve palsy not counted); RF: 2 false aneurysm, 1 MI Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5 (lost to follow up); Group 2 Number missing: 6 (lost to follow up)	
Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; HF or exacerbation of HF ; Length of stay

Study	Podd, 2015 trial: Podd 2015[200]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=50)
Countries and setting	Conducted in United Kingdom
Line of therapy	1st line
Duration of study	Follow up (post intervention): 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	paroxysmal
Subgroup analysis within study	Not applicable
Inclusion criteria	Drug refractory symptomatic paroxysmal AF; class IA indication
Exclusion criteria	pregnancy; unstable angina or MI in past 2 months; NYHA class III or IV HF; severe valvar dysfunction; previous left atrial ablation
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Range of means: 66.5-68.4. Gender (M:F): 22:28. Ethnicity: unclear
Further population details	1. CHADSVASC: <2 (mean 1.8). 2. Heart failure: No HF (HF excluded).
Extra comments	pt to point/multielectrode: hypertension 36%/48%; COPD or asthma 12%/12%; IHD 8%/4%; previous MI 0/4%; previous stroke/TIA 4%/4%; DM 4%/4%; AAds: 68%/60%; LA daim 40mm/37mm; CHADSVASC 1.8/1.8

Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Radiofrequency catheter ablation - point by point - RF point by point. Irrigated tip RF ablation catheter used with CARTO3 navigation and fluoroscopy; wide area circumferential ablation performed at a power of 25-35 . Duration Single procedure. Concurrent medication/care: All had implantable cardiac monitor or dual chamber PPM inserted at least 6 weeks before ablation; Ablation done under conscious sedation; all on uninterupted warfarin therapy (INT 2-3); IV heparin administered; all AADs stopped after ablation (n=25) Intervention 2: Radiofrequency catheter ablation - multielectrode - RF multielectrode. PVAC used in conjunction with the multichannel RF generator. Energy delivered at a maximum of 10 to generate a target temperature of 60C. . Duration Single procedure. Concurrent medication/care: All had implantable cardiac monitor or dual chamber PPM inserted at least 6 weeks before ablation; Ablation done under conscious sedation; all on uninterrupted warfarin therapy (INR 2-3); IV heparin administered; AADs stopped after ablation. Indirectness: No indirectness
Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RF POINT BY POINT versus RF MULTIELECTRODE

Protocol outcome 1: Quality of life
- Actual outcome for paroxysmal: improvement in SF 36 scores at 12 months; Group 1: mean 6.6 Units on a 100 point scale (SD 13); n=25, Group 2: mean 10.6 Units on a 100 point scale (SD 15.1); n=25; SF36 0-100 Top=High is good outcome
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Mortality
- Actual outcome for paroxysmal: procedure related death at 12 months; Group 1: 0/25, Group 2: 0/25
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Stroke and systemic embolism
- Actual outcome for paroxysmal: stroke/TIA at 12 months; Group 1: 0/25, Group 2: 0/25
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Recurrence of symptomatic AF - Actual outcome for paroxysmal: Recurrent symptomatic AF at 12 months; Group 1: 9/25, Group 2: 7/25 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 5: Redo of procedure - Actual outcome for paroxysmal: Redo of ablation at 12 months; Group 1: 0/25, Group 2: 0/25 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 6: Serious Adverse Events - Actual outcome for paroxysmal: major complications at 12 months; Group 1: 0/25, Group 2: 1/25; Comments: Cardiac tamponade that required additional 24 hr stay but no long term sequelae. Counted as a serious complication by reviewer. Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Hospitalisation ; HF or exacerbation of HF ; Length of stay

Study	POKUSHALOV, 2013 trial: Pokushalov 2013[201]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=80)
Countries and setting	Conducted in Russia
Line of therapy	1st line
Duration of study	Follow up (post intervention): 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	paroxysmal
Subgroup analysis within study	Not applicable
Inclusion criteria	Symptomatic paroxysmal AF; previous failed first RF ablation procedure (recurrences after 3 month blanking period).
Exclusion criteria	CHF; LVEF <35%; LA diam >60mm
Recruitment/selection of patients	Consecutive
Age, gender and ethnicity	Age - Mean (SD): 56. Gender (M:F): 64:16. Ethnicity: unclear
Further population details	1. CHADSVASC: Not stated / Unclear 2. Heart failure: No HF (CHF exclusion criterion).
Extra comments	Cryo/RF pt pt: hypertension 15%/17%; DM 5%/7%; prior stroke 5%/3%; LVEF 58/57; LA diam 46mm/48mm
Indirectness of population	No indirectness

Interventions	(n=40) Intervention 1: Radiofrequency catheter ablation - point by point - RF point by point. Navistar Thermocool irrigated catheter used to deliver 35W 0.5cm away from the PV ostia and anterior wall, reduced to 30W 1cm away from the PV ostia at the posterior wall. Duration single procedure. Concurrent medication/care: All patients underwent transesophageal echocardiogram before the procedure in order to exclude left atrium (LA) thrombus. The LA and PVs were explored through a transseptal approach. The PVs were continuously assessed for isolation using the Lasso catheter. All had implanted cardiac monitor. All kept on AADs until ablation and immediately after ablation kept on drugs for blanking period. After 3 months AADs stopped. Indirectness: No indirectness (n=40) Intervention 2: Cryoballon catheter ablation - Cryoballoon. 28mm balloon (Arctic Front) introduced into PV ostium. Cryoablation applied for 300 seconds at least twice in each vein. Right phrenic nerve continually stimulated by additional quadripolar catheter in SVC and if diaphragmatic movements stopped treatment curtailed. . Duration single procedure. Concurrent medication/care: All patients underwent transesophageal echocardiogram before the procedure in order to exclude left atrium (LA) thrombus. The LA and PVs were explored through a transseptal approach. The PVs were continuously assessed for isolation using the Lasso catheter. All had implanted cardiac monitor. All kept on AADs until ablation and immediately after ablation kept on drugs for blanking period. After 3 months AADs stopped.. Indirectness: No indirectness
Funding	Principal author funded by industry

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RF POINT BY POINT versus CRYOBALLOON

Protocol outcome 1: Mortality
- Actual outcome for paroxysmal: death at 1 year; Group 1: 0/40, Group 2: 0/40
Risk of bias: All domain - --, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Stroke and systemic embolism
- Actual outcome for paroxysmal: stroke at 1 year; Group 1: 0/40, Group 2: 0/40
Risk of bias: All domain - --, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Recurrence of symptomatic AF
- Actual outcome for paroxysmal: Recurrence of AF at 1 year; Group 1: 17/40, Group 2: 23/40; Comments: The paper also reported how many had got recurrence of AF symptoms but this was 'throughout' follow up, which presumably included the blanking period.

Risk of bias: All domain - --, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Not symptomatic; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 4: Redo of procedure - Actual outcome for paroxysmal: Redo at 1 year; Group 1: 7/40, Group 2: 12/40 Risk of bias: All domain - --, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 5: Serious Adverse Events - Actual outcome for paroxysmal: serious complications at 1 year; Group 1: 0/40, Group 2: 0/40; Comments: 3 in cryo group had phrenic nerve palsy but all recovered in 1 week. Not regarded as major complication by reviewer. Risk of bias: All domain - --, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; HF or exacerbation of HF ; Length of stay

Study	POKUSHALOV, 2013 trial: Pokushalov 2013[203]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=64)
Countries and setting	Conducted in Russia
Line of therapy	1st line
Duration of study	Follow up (post intervention): 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Mixed (<75% in any category)/unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with a history of symptomatic PAF/PersAF after a previous failed first RF ablation procedure were eligible for this study
Exclusion criteria	Patients with congestive heart failure, LA thrombus, LV ejection fraction <35%, left atrial diameter >65 mm, prior thoracotomy, prior cardiac surgery, and elevated hemidiaphragm were excluded from the study.
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Range of means: 56-57. Gender (M:F): 48:16. Ethnicity: Unclear
Further population details	1. CHADSVASC: <2 (CHADS2 was 0.6 so highly likely that CHADSVASC <2). 2. Heart failure: No HF (LVEF 55%/57%).
Extra comments	Thoracotomy/RF pt to pt: hypertension 40%/34%; DM 9%/12%; prior stroke 9%/6%; LVEF 55%/57%; LAD 46mm/45mm; Prior AADs 1.7/1.6; CHADS2: 0.6/0.6

Indirectness of population	--
Interventions	(n=32) Intervention 1: Radiofrequency catheter ablation - point by point - RF point by point. RF energy was delivered at 43 ◦C, 35W, 0.5 cm away from the PV ostia at the anterior wall, and was reduced to 43 ◦C, 30W, 1 cm away from the PV ostia at the posterior wall, with a saline irrigation rate of 17 mL/min. Each lesion was ablated continuously until the local potential amplitude decreased by>80% or RF energy deliveries exceeded 40 seconds. The endpoint of was complete reisolation; this was confirmed when Lasso catheter mapping showed the disappearance of all PV potentials or the dissociation of PV potentials from LA activity. In all patients with PersAF additional RF ablation lines were created by connecting the left inferior PV to the mitral annulus (mitral isthmus) and the roof of the LA between the 2 superior PVs. In the case of registration or induction of typical atrial flutter, the cavotricuspid isthmus was ablated. Bidirectional conduction block across the lines was assessed in all patients by differential pacing.. Duration Single procedure. Concurrent medication/care: All patients were kept on antiarrhythmic drug(AAD)therapy before ablation. After the procedure, all patients were treated with AAD (propafenone or flecainide) for 6 weeks after PVI (amiodarone was excluded by protocol and discontinued at least 3 months before ablation); these drugs were subsequently withdrawn, regardless of the cardiac rhythm, in order to prevent their influence after the blanking period. In both treatment groups, electric or chemical cardioversion was allowed during the 3-month blanking period.. Indirectness: No indirectness (n=32) Intervention 2: Thorascopic surgical ablation. Patients were treated with video-assisted thoracoscopy under general anesthesia, according to a previously described protocol.8,9 In brief, PVI was performed from the epicardial side with a bipolar RF ablation clamp (AtriCure, Inc.,West Chester, OH, USA). At least 2 overlapping applications around each of the ipsilateral veins were made, and isolation was confirmed by the absence of PV potentials and exit block during pacing. In addition to PVI, the bilateral epicardial ganglia were found by high-frequency stimulation and ablated, as confirmed by the absence of a vagal response after ablation. Finally, additional lines were made to create a posterior box lesion. Sensing and pacing maneuvers verified isolation of the posterior box. In all patients, the LA appendage was removed by stapling and then cutting. Duration Single procedure. Concurrent medication/care: All patients were kept on antiarrhythmic drug (AAD)therapy before ablation. After the procedure, all patients were treated with AAD (propafenone or flecainide) for 6 weeks after PVI (amiodarone was excluded by protocol and discontinued at least 3 months before ablation); these drugs were subsequently withdrawn, regardless of the cardiac rhythm, in order to prevent their influence after the blanking period. In both treatment groups, electric or chemical cardioversion was allowed during the 3-month blanking period. . Indirectness: No indirectness

Funding	Principal author funded by industry
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RF POINT BY POINT versus THORASCOPIC SURGICAL ABLATION Protocol outcome 1: Length of stay - Actual outcome for Mixed (<75% in any category)/unclear: duration of hospitalization at 12 months; Group 1: mean 2.4 (SD 0.7); n=32, Group 2: mean 5.2 (SD 1.3); n=32 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Stroke and systemic embolism - Actual outcome for Mixed (<75% in any category)/unclear: TIA/Stroke at 12 months; Group 1: 1/32, Group 2: 0/32 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Recurrence of symptomatic AF - Actual outcome for Mixed (<75% in any category)/unclear: Recurrence of AF requiring AADs at 12 months; Group 1: 17/32, Group 2: 6/32 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Not symptomatic; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 4: Redo of procedure - Actual outcome for Mixed (<75% in any category)/unclear: Redo of procedure at 12 months; Group 1: 7/32, Group 2: 1/32 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 5: Serious Adverse Events - Actual outcome for Mixed (<75% in any category)/unclear: Serious AEs at 12 months; Group 1: 0/32, Group 2: 7/32; Comments: Serious AEs included pneumothorax, hemothorax, pericardial effusion/tamponade. Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Mortality ; HF or exacerbation of HF ; Hospitalisation

Study	POKUSHALOV, 2013 trial: Pokushalov 2013[202]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=154)
Countries and setting	Conducted in Multiple countries
Line of therapy	1st line
Duration of study	Follow up (post intervention): 3 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	paroxysmal
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with a history of symptomatic PAF eligible for AAD therapy or reablation after a previous failed initial radio frequency ablation (RFA) procedure involving only PVI were eligible for this study
Exclusion criteria	Patients with persistent AF or atrial flutter, inability to tolerate any AAD, amiodarone therapy within 3 months before the ablation procedure, congestive heart failure, left ventricular ejection fraction <35%, or left atrial (LA) diameter >60 mm were excluded
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Range of means: 56-57. Gender (M:F): 117:37. Ethnicity: unclear
Further population details	1. CHADSVASC: <2 (CHADS2 0.6). 2. Heart failure: No HF (LVEF 57%).
Extra comments	RF/AADs: hypertension 31%/38%; DM 12%/9%; prior stroke 6%/8%; LVEF%: 57/58; LAD 45mm/46mm; Prior AADs 1.4/1.6; CAD 10%/13%; CHADS2 0.6/0.6

Indirectness of population	No indirectness
Interventions	(n=77) Intervention 1: Radiofrequency catheter ablation - point by point - RF point by point. Reisolation of the PVs was performed by identifying the breakthrough sites guided by the Lasso recordings and on the mapping catheter (NaviStar ThermoCool, Biosense-Webster Inc, Diamond Bar, CA). Radio frequency energy was delivered at 43°C, 35 W, 0.5 cm away from the PV ostia at the anterior wall and was reduced to 43°C, 30 W, 1 cm away from the PV ostia at the posterior wall, with a saline irrigation rate of 17 mL/min. Each lesion was ablated continuously until the local potential amplitude decreased by >80% or radiofrequency energy delivery exceeded 40 s. The end point of ablation was complete PVI; this was confirmed when Lasso catheter mapping showed the disappearance of all PV potentials or the dissociation of PV potentials from LA activity. For patients with induced LA flutter, additional RFA lines were created by connecting the left inferior PV to the mitral annulus (mitral isthmus) and the roof of the LA between the 2 superior PVs, depending on the mechanism of induced flutter. In the case of registration or induction of typical atrial flutter, the cavotricuspid isthmus was ablated. Bidirectional conduction block across the lines was assessed in all patients by differential pacing.. Duration Single procedure. Concurrent medication/care: All patients underwent transesophageal echocardiogram before the procedure to exclude LA thrombus. The LA and pulmonary veins (PVs) were explored through a transseptal approach. The PVs were continuously assessed for isolation using the Lasso catheter (Biosense-Webster Inc, Diamond Bar, CA). Indirectness: No indirectness (n=77) Intervention 2: usual care - medical therapy. In the drug therapy (control) group, recurrent episodes were pharmacologically managed by conventional AAD therapy (propafenone, 450–900 mg/d; flecainide, 200–400 mg/d; or sotalol, 160–320 mg/d) according to AF management guidelines. Class 1C drugs were recommended as first-line agents for most patients in the absence of structural heart disease. Sotalol was recommended as a first-line agent for patients with coronary artery disease. The final choice of agent and dosage was left to the discretion of the treating electrophysiologist. In the case of AAD therapy failure or intolerable side effects, catheter ablation was offered.. Duration unclear. Concurrent medication/care: None. Indirectness: No indirectness
Funding	Other (One author employed by industry)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RF POINT BY POINT versus MEDICAL THERAPY

Protocol outcome 1: Recurrence of symptomatic AF
- Actual outcome for paroxysmal: Recurrence of AF at 36 months; Group 1: 32/77, Group 2: 68/77
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low,

Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Not symptomatic AF; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Serious Adverse Events - Actual outcome for paroxysmal: Serious AEs at 36 months; Group 1: 2/77, Group 2: 1/77 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; Mortality ; Stroke and systemic embolism ; Redo of procedure ; HF or exacerbation of HF ; Length of stay

Study	RAAFT-2 trial: Morillo 2014[162]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=127)
Countries and setting	Conducted in Multiple countries
Line of therapy	1st line
Duration of study	Follow up (post intervention): 24 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	paroxysmal
Subgroup analysis within study	Not applicable
Inclusion criteria	Eligible patients had a history of paroxysmal AF. Patients were enrolled if they were older than 18 and no older than 75 years; were symptomatic with recurrent paroxysmal AF lasting more than 30 seconds (≤4 episodes within the prior 6months); experienced at least 1 episode that was documented by surface ECG, 6months before randomization; and had no previous antiarrhythmic drug treatment.
Exclusion criteria	Documented left ventricular ejection fraction of lessthan40%;had left atrial diameter larger than 5.5 cm; had moderate to severe left ventricular hypertrophy (wall thickness >1.5 cm), valvular disease, coronary artery disease, or postcardiac surgery within 6 months; had undergone a left heart ablation procedure, either by surgery or by radiofrequency catheter ablation for AF; or had a complete contraindication for the use of heparin, warfarin, or both
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Range of means: 54.3-56.3. Gender (M:F): 96:31. Ethnicity: unclear

Further population details	1. CHADSVASC: <2 (CHADS 0.7). 2. Heart failure: No HF (<3% with HF).
Extra comments	RF/med: paroxysmal 98.5%/96.7%; hypertension 42.4%/41%; DM 1.5%/6.6%; stroke or TIA 4.6%/6.6%; MI or CAD 9.1%/3.3%; HF 3%/1.6%; CHADS2 <2 93.9%/88%; LVEF 61.4/60.8;
Indirectness of population	No indirectness
Interventions	(n=66) Intervention 1: Radiofrequency catheter ablation - point by point - RF point by point. Patients randomized to ablation underwent circumferential isolation of the pulmonary veins with confirmation of entrance block into each vein. Selection of ablation catheter, power and irrigation settings, and use of navigation systems were left to the discretion of the investigator. Additional ablation lesions including linear lesions in the left atrium, targeting of fractionated electrogram regions, ganglionic plexi, superior vena cava isolation, and cavotricuspid isthmus ablation were also allowed at investigator discretion.. Duration Single procedure. Concurrent medication/care: All patients received oral anticoagulation targeting an international normalized ratio of 2.0 or higher for at least 3weeks or received low-molecular-weight heparin for at least 1week before ablation and transesophageal echocardiogram was performed prior to the procedure.. Indirectness: No indirectness (n=61) Intervention 2: usual care - medical therapy. Patients randomized to the antiarrhythmic drug group were administered medications approved for treatment of AF by the regulatory bodies of each participating country. The selection of antiarrhythmic drugs was left to the discretion of the investigator, and dosages were based on guidelines. Drug dosages titrated during the 90-day blanking period were maintained throughout the study. . Duration Unclear. Concurrent medication/care: Patients in the antiarrhythmic drug group were allowed to cross-over and to undergo ablation after 90days if treatment had failed, which was defined as drug discontinuation due to intolerance, adverse events, or inefficacy.. Indirectness: No indirectness
Funding	Study funded by industry (Biosense Webster)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RF POINT BY POINT versus MEDICAL THERAPY

Protocol outcome 1: Quality of life
- Actual outcome for paroxysmal: EQ5D at 1 year; ;
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Mortality - Actual outcome for paroxysmal: death at 1 year; Group 1: 0/66, Group 2: 0/61 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Stroke and systemic embolism - Actual outcome for paroxysmal: Stroke/TIA at 1 year; Group 1: 0/66, Group 2: 0/61 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 4: Recurrence of symptomatic AF - Actual outcome for paroxysmal: Recurrent symptomatic AF at 1 year; Group 1: 27/66, Group 2: 35/61 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 5: Serious Adverse Events - Actual outcome for paroxysmal: serious AEs at 1 year; Group 1: 6/66, Group 2: 3/61 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Hospitalisation ; Redo of procedure ; HF or exacerbation of HF ; Length of stay

Study	RATISBONA trial: Ucer 2018[245]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=50)
Countries and setting	Conducted in Germany
Line of therapy	1st line
Duration of study	Not clear:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	paroxysmal
Subgroup analysis within study	Not applicable
Inclusion criteria	paroxysmal AF; symptomatic AF
Exclusion criteria	Asthma; known allergy to adenosine; LA thrombus; LA diam >55mm; LVEF <35%; previous LA ablation for AF; NYHA class IV symptoms; MI in past 60 days; unstable angina; history of cardiac valve surgery; uncontrolled bleeding; active infection; severe pulmonary disease
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Range of means: 29.7 o 65.3. Gender (M:F): 25:25. Ethnicity: unclear
Further population details	1. CHADSVASC: Not stated / Unclear (no data). 2. Heart failure: No HF (HF largely excluded).
Extra comments	laser/RF: hypertension 84%/76%; DM 24%/20%; CAD 24%/28%; MI 16%/16%; CABG 0/8%; CHF 16%/12%; stroke or TIA 12%/16%; LA diam 41.3/44.8mm; LVEF 60.9%/60.6%; AADs (class I or III): 40%/32%; EHRA 3 or above 76%/52%

Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Laser catheter ablation - laser ablation. Visually guided laser balloon with 15F steerable sheath. Maximal power of 12W for 20 seconds. Balloon inflated aiming to completely occlude the PV ostium. Duration single procedure. Concurrent medication/care: continued OACs. Sedation with propofol and midazolam with fentanyl boluses. GA used only in patients with sleep apnoea syndrome and those preferring it. Cardioversion used prior to procedure if not in sinus rhythm pre-ablation. Indirectness: No indirectness (n=25) Intervention 2: Radiofrequency catheter ablation - point by point - RF point by point. 3.5 mm mapping/ablation catheter (thermocool point by point) placed in LA. RF ablation around PV ostiaa dn at acrina between ipsilateral PVs. RF energy titrated from 30W at posterior wall to 40W for 30 seconds at the anterior wall.. Duration single procedure. Concurrent medication/care: continued OACs. Sedation with propofol and midazolam with fentanyl boluses. GA used only in patients with sleep apnoea syndrome and those preferring it. Cardioversion used prior to procedure if not in sinus rhythm pre-ablation.. Indirectness: No indirectness
Funding	Study funded by industry (CardioFocus)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LASER ABLATION versus RF POINT BY POINT

Protocol outcome 1: Serious Adverse Events
- Actual outcome for paroxysmal: Complications at unclear; Group 1: 1/25, Group 2: 1/25; Comments: Unclear results. Pericardial tamponade occurred in RF group, but due to diagnostic catheter. 4 weeks later a successful PVI with RF performed. Classified in paper as procedure but not device related complication. Laser complication was need for later atrial septal closure after failure of atrial septal puncture site. I have kept both as AEs for this analysis. Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; Mortality ; Stroke and systemic embolism ; Recurrence of symptomatic AF ; Redo of procedure ; HF or exacerbation of HF ; Length of stay

Study	SARA study, 2014 trial: Mont 2014[160]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=146)
Countries and setting	Conducted in Spain
Line of therapy	1st line
Duration of study	Follow up (post intervention): 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	persistent <1 year
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with symptomatic persistent AF7 (>7or,<7days requiring electrical or pharmacological cardioversion) refractory to at least one class I or class III antiarrhythmic drug were recruited.
Exclusion criteria	Age,18 or.70 years, long-standing persistent AF(.1 year of continuous AF), first episode ofAF, hyper- or hypothyroidism, hypertrophic cardiomyopathy, implanted pacemaker or defibrillator, moderate or severe mitral disease or mitral prosthesis, left ventricular ejection fraction <30%, left atrial diameter .50 mm, prior ablation procedure, contraindication for oral anticoagulation, left atrial thrombus, active infection or sepsis, pregnancy, unstable angina, acute myocardial infarction during previous 3 months, life expectation,12 months, current participation in another clinical trial, mental disease or inability to give informed consent, or disease contraindicating ablation or ADT.
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Mean (SD): 55(9). Gender (M:F): 113:33. Ethnicity: unclear
Further population details	1. CHADSVASC: Not stated / Unclear 2. Heart failure: No HF (Most NYHA class I).

Extra comments	RF/medical: TIA: 1%/2.1%; CVA 3.1%/2.1%; PE 3.1%/2.1%; Ischaemic cardiopathy 3.1%/2.1%; LA size 41.3/42.7; LVEF 61.1%/60.8%; NYHA Class I 74.5%/81.2%
Indirectness of population	No indirectness
Interventions	(n=98) Intervention 1: Radiofrequency catheter ablation - point by point - RF point by point. Wide encircling pulmonary vein ablation was performed using radiofrequency energy (cooled-tip catheter) assisted by a circular multipolar catheter. The endpoint was the absence or dissociation of a local electrograminside the entire surrounded region together with exit block by pacing within the pulmonary vein ostia. Additional ablation lines or ablation of complex fractioned electrograms were performed according to each hospital's protocol. When lines at the roof of the left atrium (connecting both superior pulmonary veins) or at the mitral isthmus (mitral annulus to the ostium of the left inferior pulmonary vein) were deployed, complete bidirectional conduction block was required. The endpoint for complex fractionated atrial electrogramablation was the complete abatement of potentials at these sites.. Duration Single procedure. Concurrent medication/care: Pre- and postprocedural oral anticoagulation (international normalized ratio between 2 and 3) was required for at least 1 month before and after CA. Antiarrhythmic drugs were discontinued ≥5 half-life periods (or ≥1 week for amiodarone) before ablation; antiarrhythmics were re-initiated immediately after CA for the 3-month blanking period. Transoesophageal echocardiography was performed in all patients before CA to exclude the presence of left atrial thrombus. After trans- septal puncture to gain LA access, a bolus of heparin was administered (5000–6000 IU, according to patient weight), followed by additional boluses to maintain an activated clotting time of 250–300 s. A 3D map was constructed using an electroanatomic mapping system. Computed tomographyor magnetic resonance images were integrated into the navigation system to improve LA anatomic reconstruction. (n=48) Intervention 2: usual care - medical therapy. Patients were treated depending on physician's choice and according to current guidelines.3 Discontinuation of the antiarrhythmic treatment was not required before inclusion in theADTgroup. Class III drugs (amiodarone) were recommended for patients with structural cardiomyopathy and class Ic (flecainide) plus diltiazem or b-blockers otherwise. There was not a predefined protocol on the use of ADT during the blanking period.. Duration Unclear. Concurrent medication/care: None
Funding	Study funded by industry (Medtronic and Biosense Webster)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RF POINT BY POINT versus MEDICAL THERAPY	

Protocol outcome 1: Quality of life
- Actual outcome for persistent <1 year: AF-QoL at 1 year; MD; +3.8 (95%CI -5.2 to 12.8, Comments: Adjusted for baseline values);
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Hospitalisation
- Actual outcome for persistent <1 year: hospitalization related to arrhythmia at 1 year; Group 1: 2/98, Group 2: 3/48
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Mortality
- Actual outcome for persistent <1 year: Mortality at 1 year;
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Stroke and systemic embolism
- Actual outcome for persistent <1 year: Stroke/TIA at 1 year;
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 5: Recurrence of symptomatic AF
- Actual outcome for persistent <1 year: Recurrence of AF at 1 year; Group 1: 39/98, Group 2: 34/48
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Not symptomatic; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 6: Redo of procedure
- Actual outcome for persistent <1 year: Reablation at 1 year; Group 1: 5/98, Group 2: 0/48
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 7: Serious Adverse Events
- Actual outcome for persistent <1 year: Serious complications at 1 year; Group 1: 5/98, Group 2: 1/48; Comments: For ablation: 2 pericarditis, 1 pericardial effusion, 1 renal hematoma, 1 symptomatic pulm vein stenosis requiring stenting (not including 3 vasc access complications)
For med: 1 flecanaide intoxication (not inc 1 minor vasc access complication)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

HF or exacerbation of HF ; Length of stay

Protocol outcomes not reported by the study

Study	SCHMIDT, 2013 trial: Schmidt 2013[220]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=99)
Countries and setting	Conducted in Germany
Line of therapy	1st line
Duration of study	Follow up (post intervention): 1-2 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	paroxysmal
Subgroup analysis within study	Not applicable
Inclusion criteria	Drug-refractory paroxysmal AF; indications for catheter ablation
Exclusion criteria	LA diam >50mm; LVEF <45%; contraindications for MRI scanning; tsage III renal failure; intracardiac thrombus; CHADS >3
Age, gender and ethnicity	Age - Mean (SD): 65(9). Gender (M:F): not reported. Ethnicity: unclear
Further population details	1. CHADSVASC: >=2 (median 2 so definitely more 2 and above than below.). 2. Heart failure: No HF (mean LVEF 59%).
Extra comments	LA diam 40mm; hypertension 73%; mean LVEF 59%; DM 6%; Stroke/TIA 7%; CAD 18%; median CHADSVASC 2(1-3)
Indirectness of population	No indirectness
Interventions	(n=33) Intervention 1: Radiofrequency catheter ablation - point by point - RF point by point. After a 3D

	reconstruction of the left atrium circumferential PVI was performed aiming at isolating the ipsilateral PV pairs by a single circular ablation line. A circular mapping catheter positioned in the respective PV confirmed electrical PVI. Irrigated ablations were performed with a maximum power of 40 W, a cut-off temperature of 43◦C, and a flush-rate of 17–25 mL/min. No additional substrate modification was performed. Duration single procedure. Concurrent medication/care: Ablation procedures were performed under conscious sedation with boluses of midazolam and fentanyl followed by a continuous infusion of propofol. After positioning of a 7 F and a 6 F octapolar catheter in the coronary sinus and at the His region, transseptal puncture was performed using the modified Brockenbrough technique. One (for CB and LB) or 2 (for RFC) 8.5 F sheaths (SL1; St. Jude Medical, Minneapolis,MN, USA) were advanced into the LA. Unfractionated heparin (100 IU/kg body weight) was administered immediately after the first transseptal puncture and repeatedly injected aiming at an activated clotting time >250 seconds throughout the procedure. The transseptal sheaths were flushed with heparinized saline using a syringe pump at a rate of 10 mL/h (RFC), 20 mL/h (CB) or with a pressure bag (LB) ensuring continuous flushing. Selective PVangiographies in a right anterior oblique 30◦ and left anterior oblique 40◦ projection were performed to assess PV anatomy and to position a circular mapping catheter (LASSOTM, Biosense Webster, Diamond Bar, CA, USA) at the PV ostium to record baseline PV potentials. Then, the transseptal sheath was exchanged with a 12Fsteerable sheath (FlexCathTM, Medtronic or a 12 F steerable sheath, CardioFocus). During ablation at the right superior pulmonary vein, diaphragmatic function was monitored by continuous pacing of the right phrenic nerve with a 6Fdiagnostic catheter positioned in the superior vena cava.. Indirectness: No indirectness (n=33) Intervention 2: Cryoballon catheter ablation - Cryoballoon. For all CB procedures, exclusively the 28 mm balloon was used. It was navigated to the individual PV by the steerable sheath and the use of a guide-wire (Amplatz StiffWire,Cook Medical Inc., Bloomington, IN, USA) or a multipolar circumferential mapping catheter (AchieveTM, Medtronic) advanced via the central lumen of the CB catheter. After obtaining optimal PV occlusion, confirmed by occlusion angiograms, cryothermal energy was deployed for 300 seconds. In the case of residual PV conduction, cryothermal energy was repeatedly administered after CB repositioning until complete electrical PVI. After obtaining PVI a single bonus application was delivered for another 300 seconds at each individual PV.. Duration single procedure. Concurrent medication/care: Ablation procedures were performed under conscious sedation with boluses of midazolam and fentanyl followed by a continuous infusion of propofol. After positioning of a 7 F and a 6 F octapolar catheter in the coronary sinus and at the His region, transseptal puncture was performed using the modified Brockenbrough technique. One (for CB and LB) or 2 (for RFC) 8.5 F sheaths (SL1; St. Jude Medical, Minneapolis,MN, USA) were advanced into the LA. Unfractionated heparin (100 IU/kg body weight) was administered immediately after the first transseptal puncture and repeatedly injected aiming at an activated clotting time >250 seconds throughout the procedure. The transseptal sheaths were flushed with heparinized saline using a syringe pump at a rate of 10 mL/h (RFC), 20 mL/h (CB) or with a pressure bag (LB) ensuring continuous flushing. Selective PVangiographies in a right anterior oblique 30◦ and left anterior oblique 40◦ projection were performed to assess PV anatomy and to position a circular mapping catheter (LASSOTM, Biosense Webster, Diamond Bar, CA, USA) at the PV

	ostium to record baseline PV potentials. Then, the transseptal sheath was exchanged with a 12Fsteerable sheath (FlexCathTM, Medtronic or a 12 F steerable sheath, CardioFocus). During ablation at the right superior pulmonary vein, diaphragmatic function was monitored by continuous pacing of the right phrenic nerve with a 6Fdiagnostic catheter positioned in the superior vena cava. Indirectness: No indirectness (n=33) Intervention 3: Laser catheter ablation - laser ablation. The LB was navigated to the individual PV by the steerable sheath and inflated to obtain optimal PV occlusion. Laser energy was deployed in a point-by-point fashion, thereby covering 30◦ of a circle with each ablation lesion. The energy level was titrated according to the degree of tissue exposure between 5.5 W and 12 W. Energy was applied for 20 or 30 secs. After complete visually guided circular ablation the PVs were remapped using the circular mapping catheter. In the case of residual LA to PV conduction, additional ablation was carried out using the LB according to the activation sequence in the circular mapping catheter as recently described. Duration single procedure. Concurrent medication/care: Ablation procedures were performed under conscious sedation with boluses of midazolam and fentanyl followed by a continuous infusion of propofol. After positioning of a 7 F and a 6 F octapolar catheter in the coronary sinus and at the His region, transseptal puncture was performed using the modified Brockenbrough technique. One (for CB and LB) or 2 (for RFC) 8.5 F sheaths (SL1; St. Jude Medical, Minneapolis, MN, USA) were advanced into the LA. Unfractionated heparin (100 IU/kg body weight) was administered immediately after the first transseptal puncture and repeatedly injected aiming at an activated clotting time >250 seconds throughout the procedure. The transseptal sheaths were flushed with heparinized saline using a syringe pump at a rate of 10 mL/h (RFC), 20 mL/h (CB) or with a pressure bag (LB) ensuring continuous flushing. Selective PVangiographies in a right anterior oblique 30◦ and left anterior oblique 40◦ projection were performed to assess PV anatomy and to position a circular mapping catheter (LASSOTM, Biosense Webster, Diamond Bar, CA, USA) at the PV ostium to record baseline PV potentials. Then, the transseptal sheath was exchanged with a 12Fsteerable sheath (FlexCathTM, Medtronic or a 12 F steerable sheath, CardioFocus). During ablation at the right superior pulmonary vein, diaphragmatic function was monitored by continuous pacing of the right phrenic nerve with a 6Fdiagnostic catheter positioned in the superior vena cava. Indirectness: No indirectness
Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RF POINT BY POINT versus CRYOBALLOON

Protocol outcome 1: Stroke and systemic embolism
- Actual outcome for paroxysmal: asymptomatic cerebral lesions observed on MRI at 1-2 days; Group 1: 8/33, Group 2: 6/33
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Not symptomatic - but a manifestation of a thromboembolic event

	nevertheless; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Serious Adverse Events - Actual outcome for paroxysmal: major procedural complications at 1-2 days; Group 1: 0/33, Group 2: 0/33 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RF POINT BY POINT versus LASER ABLATION Protocol outcome 1: Stroke and systemic embolism - Actual outcome for paroxysmal: asymptomatic cerebral lesions observed on MRI at 1-2 days; Group 1: 8/33, Group 2: 8/33 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Not symptomatic - but a manifestation of a thromboembolic event nevertheless; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Serious Adverse Events - Actual outcome for paroxysmal: major procedural complications at 1-2 days; Group 1: 0/33, Group 2: 0/33 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CRYOBALLOON versus LASER ABLATION Protocol outcome 1: Stroke and systemic embolism - Actual outcome for paroxysmal: asymptomatic cerebral lesions observed on MRI at 1-2 days; Group 1: 6/33, Group 2: 8/33 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Not symptomatic - but a manifestation of a thromboembolic event nevertheless; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Serious Adverse Events - Actual outcome for paroxysmal: major procedural complications at 1-2 days; Group 1: 0/33, Group 2: 0/33 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0
Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; Mortality ; Recurrence of symptomatic AF ; Redo of procedure ; HF or exacerbation of HF ; Length of stay

Study	STOP AF trial: Packer 2013[183]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=245)
Countries and setting	Conducted in USA
Line of therapy	1st line
Duration of study	Follow up (post intervention): 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	paroxysmal
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with >2 episodes of PAF in 2 months prior to randomisation; at least 1 membrane active drug failure
Exclusion criteria	LA>50mm; LVEF <40%; NYHA clas III or IV; CAD; Stroke or TIA in previous 6 months; previous LA ablation/surgery for AF; prosthetic heart valves; amiodarone therapy in previous 3 months; >2 cardioversions within 2 years; implantable rhythm device
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Mean (SD): 57(9). Gender (M:F): 189:56. Ethnicity: unclear
Further population details	1. CHADSVASC: <2 (CHADS2 0.6). 2. Heart failure: No HF (NYHA class III or IV excluded).
Extra comments	Hypertension 42.4%; DM 7.3%; CAD 8.6%; LA diam 41mm; LVEF% 60; NYHA none or I 93.5%; CHADS2: 0.6; overall SF36 71(17); 99.6% >1 AAD used;
Indirectness of population	No indirectness

Interventions	(n=163) Intervention 1: Cryoballon catheter ablation - Cryoballoon. 23 or 28mm Arctic Front cryoballoon catheter used for ablation. 240 second deliveries to 4 major PVs.. Duration single procedure. Concurrent medication/care: Patients received heparin, with activated clotting time of >300 seconds. Indirectness: No indirectness (n=82) Intervention 2: usual care - medical therapy. Flecainide, propafenone or sotalol if they had not previously experienced failure with these drugs.. Duration unclear. Concurrent medication/care: If necessary a change to one of the other 3 drugs was allowed. Once stabilised the drug therapy was maintained throughout the study. Indirectness: No indirectness
Funding	Study funded by industry (Medtronic)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CRYOBALLOON versus MEDICAL THERAPY Protocol outcome 1: Mortality - Actual outcome for paroxysmal: Death at 12 months; Group 1: 1/163, Group 2: 0/82 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 3 (loss to follow up) - Actual outcome for paroxysmal: Stroke/TIA at 12 months; Group 1: 7/163, Group 2: 0/82 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 3 (loss to follow up) Protocol outcome 2: Recurrence of symptomatic AF - Actual outcome for paroxysmal: Recurrence of AF at 12 months; Group 1: 49/163, Group 2: 76/82 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: not symptomatic; Group 1 Number missing: 0; Group 2 Number missing: 3 (loss to follow up) NOT USED AS DATA FLAWED BY CROSS-OVER (and therefore designation of recurrence) prior to end of 3 months Protocol outcome 3: Serious Adverse Events - Actual outcome for paroxysmal: serious AEs at 12 months; DATA NOT USED AS BIASED TOWARDS CRYOTHERAPY AEs	
Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; Stroke and systemic embolism ; Redo of procedure ; HF or exacerbation of HF ; Length of stay

Study	The Cryo Versus RF Trial: Hunter 2015[13, 92]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=158 (79 from combined RF/cryo group not included as off protocol))
Countries and setting	Conducted in United Kingdom; Setting: St Barts Hospital
Line of therapy	1st line
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	paroxysmal
Subgroup analysis within study	Not applicable
Inclusion criteria	symptomatic paroxysmal AF refractory to >1 AAD
Exclusion criteria	Persistent AF; potentially reversible cause of AF; contraindications to ablation; severe valvular heart disease; prior LA ablation
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Range of means: 56-61. Gender (M:F): 103:55. Ethnicity: Unclear
Further population details	1. CHADSVASC: Not stated / Unclear (no data). 2. Heart failure: No HF (<7% with cardiac failure).
Extra comments	RF/cryo: hypertension 30%/35%; DM 6%/5%; IHD 8%/8%; prior stroke or TIA 8%/9%; LA diam 43mm/42mm; cardiac failure 5%/9%; AADs failed 2.3(1.1)/2.4(1); failed amiodarone 13%/9%.
Indirectness of population	No indirectness

Interventions	(n=79) Intervention 1: Radiofrequency catheter ablation - point by point - RF point by point. Ablation delivered by an irrigated 3.5mm ablation catheter guided by CARTO3, with lesions placed 1-2cm outside PV ostia to isolate them in ipsilateral pairs. power limited to 30W.. Duration single procedure. Concurrent medication/care: Transesophageal echo immediately pre-procedure. Procedures performed on OACs under moderate sedation. Boluses of heparin used. . Indirectness: No indirectness (n=79) Intervention 2: Cryoballon catheter ablation - Cryoballoon. 12F Flex Cath sheath used. Cryoablation of all PVs performed using first generation cryoballoon (Arctic Front). Choice of balloon size 923 or 28mm) at discretion of operator. At least 2 5 min freezes performed at each PV ostium. temperatures of < -40C considered adequate. Duration Single procedure. Concurrent medication/care: Transesophageal echo immediately pre-procedure. Procedures performed on OACs under moderate sedation. Boluses of heparin used. . Indirectness: No indirectness
Funding	Study funded by industry (Investigator-initiated study that was part-funded by Medtronic. No input from industry in terms of data collection, analysis and writing.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RF POINT BY POINT versus CRYOBALLOON

Protocol outcome 1: Mortality
- Actual outcome for paroxysmal: death at >24 months; Group 1: 1/67, Group 2: 2/67
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 12 (1 withdrew after contraindications, 10 lost to FU); Group 2 Number missing: 1 (1 asymptomatic after drug therapy, 11 lost to FU)

Protocol outcome 2: Recurrence of symptomatic AF
- Actual outcome for paroxysmal: recurrence of AF (symptomatic or not) at 12 months; Group 1: 41/77, Group 2: 26/78
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Not defined as symptomatic only; Group 1 Number missing: 2 (withdrew after contraindications); Group 2 Number missing: 1 (asymptomatic after drug therapy)

- Actual outcome for paroxysmal: recurrence of AF (symptomatic or not) at 60 months; Group 1: 56/67, Group 2: 42/67
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Not defined as symptomatic only; Group 1 Number missing: 12 (1 withdrew after contraindications, 10 lost to FU); Group 2 Number missing: 1 (1 asymptomatic after drug therapy, 11 lost to FU)

Protocol outcome 3: Redo of procedure - Actual outcome for paroxysmal: repeat ablation at 12 months; Group 1: 16/77, Group 2: 15/78 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2 (withdrew after contraindications); Group 2 Number missing: 1 (asymptomatic after drug therapy) - Actual outcome for paroxysmal: repeat ablation at 60 months; Group 1: 36/67, Group 2: 33/67 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Not defined as symptomatic only; Group 1 Number missing: 12 (1 withdrew after contraindications, 10 lost to FU); Group 2 Number missing: 1 (1 asymptomatic after drug therapy, 11 lost to FU) Protocol outcome 4: Serious Adverse Events - Actual outcome for paroxysmal: Major complications at 12 months; Group 1: 2/77, Group 2: 4/78 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 2 (withdrew after contraindications); Group 2 Number missing: 1 (asymptomatic after drug therapy)	
Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; Stroke and systemic embolism ; HF or exacerbation of HF ; Length of stay

Study	TSE, 2005 trial: Tse 2005[242]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=30)
Countries and setting	Conducted in Hong Kong (China)
Line of therapy	1st line
Duration of study	Not clear:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	paroxysmal
Subgroup analysis within study	Not applicable
Inclusion criteria	Symptomatic paroxysmal AF selected to undergo catheter ablation procedure
Exclusion criteria	CHF; DM; prior stroke or SE; prior CAD and MI; valvular heart disease; malignancy; renal impairment or hepatic dysfunction; active infection/inflammation; ejection fraction <45%; LAD >50mm; previous ablation procedures; AF episodes lasting >48 hours prior to procedure
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Range of means: 51-53. Gender (M:F): 23:7. Ethnicity: unclear
Further population details	1. CHADSVASC: Not stated / Unclear 2. Heart failure: No HF (HF exclusion criterion).
Extra comments	RF/cryo: LVEF: 56/58; LA diam 38/40; CV diseases 20%/20%; hypertension 13.3%/20%; CAD 6.7%/0
Indirectness of population	No indirectness

Interventions	(n=15) Intervention 1: Radiofrequency catheter ablation - point by point - RF point by point. 4mm tip deflectable catheter inserted into LA through an 8F sheath, delivering 35W for 60-90 seconds at each target site (ostial PVs). Duration Single procedure. Concurrent medication/care: OACs given for at least 4 weeks to achieve INR 2-3, and stopped 2-3 days before ablation Decapolar mapping catheter used. All via femoral veins. IV heparin used.. Indirectness: No indirectness (n=15) Intervention 2: Cryoballon catheter ablation - Cryoballoon. Given with 6.5mm tip 10F cryoballoon catheter. At each target site 2.5 minutes of cryoablation delivered twice at a target tip temperature of <-70 degrees C. Duration Single procedure. Concurrent medication/care: OACs given for at least 4 weeks to achieve INR 2-3, and stopped 2-3 days before ablation Decapolar mapping catheter used. All via femoral veins. IV heparin used.. Indirectness: No indirectness
Funding	Principal author funded by industry
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RF POINT BY POINT versus CRYOBALLOON Protocol outcome 1: Stroke and systemic embolism - Actual outcome for paroxysmal: Thromboembolic complications at Unclear; Group 1: 0/15, Group 2: 0/15 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; Mortality ; Recurrence of symptomatic AF ; Redo of procedure ; HF or exacerbation of HF ; Serious Adverse Events ; Length of stay

Study	Wang, 2014 trial: Wang 2014[256]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=138)
Countries and setting	Conducted in China; Setting:
Line of therapy	1st line
Duration of study	Follow up (post intervention): 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	paroxysmal
Subgroup analysis within study	Not applicable
Inclusion criteria	paroxysmal AF; indication for ablation; preference for minimal invasive surgery
Exclusion criteria	unstable angina; shock; cardiac failure; indication for other surgical procedures; hyperthyroidism
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Range of means: 51-52. Gender (M:F): 84:54. Ethnicity: unclear
Further population details	1. CHADSVASC: Not stated / Unclear 2. Heart failure: No HF (HF exclusion criterion).
Extra comments	Thoracoscopy/RF: hypertension 39%/37.5%; Stroke 10.6%/6.9%; DM 13.6%/15.3%; LA diam 45/47mm; LVEF 64/65
Indirectness of population	No indirectness

Interventions	(n=72) Intervention 1: Radiofrequency catheter ablation - point by point - RF point by point. Point by point RF navigated via CARTO 3D mapping system. ablation was 0.5 to 1cm outside the pulmonary vein outlet. Default power 30-40W. Duration Single procedure. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=66) Intervention 2: Thorascopic surgical ablation. Video assisted thoracoscopy surgery performed on bilateral thorax under GA. Bipolar RF clamp and RF generator system used to obtain linear, transmural ablation lesions. Duration Single procedure. Concurrent medication/care: None reported. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RF POINT BY POINT versus THORASCOPIC SURGICAL ABLATION Protocol outcome 1: Recurrence of symptomatic AF - Actual outcome for paroxysmal: Recurrent AF at 1 year; DATA NOT USED AS DID NOT EXCLUDE EVENTS EARLY AFTER EBLATION	
Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; Mortality ; Stroke and systemic embolism ; Redo of procedure ; HF or exacerbation of HF ; Serious Adverse Events ; Length of stay

Study	Watanabe 2018 trial: Watanabe 2018[259]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=52)
Countries and setting	Conducted in Japan
Line of therapy	1st line
Duration of study	Follow up (post intervention): 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	paroxysmal
Subgroup analysis within study	Not applicable
Inclusion criteria	>18 years; scheduled for PV isolation for AAD refractory AF for first time; paroxysmal AF
Exclusion criteria	Renal insufficiency; common left PV trunk
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Range of means: 62-68. Gender (M:F): 36:14. Ethnicity: Unclear
Further population details	1. CHADSVASC: Not stated / Unclear 2. Heart failure: No HF (mean LVEF 58-63%; LA diam 39-42mm).
Extra comments	Cryo/RF: hypertension 64%/56%; DM 12%/20%; HF 8%/8%; previous stroke 4%/8%; LA diam 39mm/42mm; LVEF % 63/58
Indirectness of population	No indirectness

Interventions	(n=25) Intervention 1: Radiofrequency catheter ablation - point by point - RF point by point. 3.5mm tip irrigated catheter used. RF energy delivered with maximum power of 30W. Circumferential ablation lines created around left and right ipsilateral PVs guided by CARTO3.. Duration single procedure. Concurrent medication/care: Conscious sedation using dexmedotimidine. IV heparin administered. Decapolar catheter placed in coronary sinus in all patients. . Indirectness: No indirectness (n=25) Intervention 2: Cryoballon catheter ablation - Cryoballoon. Arctic Front Advance with 28mm size balloon, using 180sec freeze to each PV through the balloon. Duration Single procedure. Concurrent medication/care: Conscious sedation using dexmedotimidine. IV heparin administered. Decapolar catheter placed in coronary sinus in all patients. . Indirectness: No indirectness
Funding	No funding (None declared)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RF POINT BY POINT versus CRYOBALLOON Protocol outcome 1: Recurrence of symptomatic AF - Actual outcome for paroxysmal: Recurrence of AF at 12 months; DATA NOT USED AS UNCLEAR - 'use of AADs' provided, but cannot be used as proxy for recurrence, as patients allowed to use them even if no recurrence. Paper also gives number without AF but this is when AADs are being used. Protocol outcome 2: Serious Adverse Events - Actual outcome for paroxysmal: serious complications at 12 months; Group 1: 0/25, Group 2: 0/25 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 1 (lost to follow up); Group 2 Number missing: 1 (common L PV trunk)	
Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; Mortality ; Stroke and systemic embolism ; Redo of procedure ; HF or exacerbation of HF ; Length of stay

Study	Bin Waleed: Bin Waleed, 2019[25]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=58)
Countries and setting	Conducted in China
Line of therapy	1st line
Duration of study	Follow up (post intervention): 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	paroxysmal
Subgroup analysis within study	Not applicable
Inclusion criteria	Symptomatic AF; paroxysmal AF; scheduled for first-time catheter ablation
Exclusion criteria	Long-standing and persistent AF; acute cause of AF; HF; vascular diseases such as MI in past 3 months; inflammatory diseases; cancer; renal dysfunction (eGFR <30); LA diam >=55 mm; antiplatelet and NSAIDs within 1 month of enrolment into study
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Range of means: 61.2-62.4. Gender (M:F): 34:16. Ethnicity: Unclear
Further population details	1. CHADSVASC: <2 (>75% < 2) 2. Heart failure: No HF (HF exclusion criterion).
Extra comments	Cryo/RF: AF history (months) 42/24; hypertension 50%/57.7%; DM 12.5%/7.7%; stroke/TIA 17.2%/6.9%; mean CHADSVASC 1.5/1; DOACs 70.8%/69.2%; LA diam 36.5/36
Indirectness of population	No indirectness

Interventions	(n=29) Intervention 1: Radiofrequency catheter ablation - point by point - RF point by point. 3.5mm tip irrigated Navistar thermocool catheter used. RF energy delivered with maximum power of 35W. Contiguous circumferential ablation lines guided by Lasso. Duration single procedure. Concurrent medication/care: GA using midazolam and propofol. All treated with warfarin at INR >2 or DOAC for at least 3 weeks prior to ablation. Indirectness: No indirectness (n=29) Intervention 2: Cryoballon catheter ablation - Cryoballoon. Arctic Front Advance with 23-28mm size balloon depending on PV diameter, using 180-300sec freeze to each PV through the balloon. Duration Single procedure. Concurrent medication/care: GA using midazolam and propofol. All treated with warfarin at INR >2 or DOAC for at least 3 weeks prior to ablation. Indirectness: No indirectness
Funding	No funding (None declared)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RF POINT BY POINT versus CRYOBALLOON Protocol outcome 1: Recurrence of symptomatic AF - Actual outcome for paroxysmal: Recurrence of AF at 6 months; Group 1: 3/29, Group 2: 4/28 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Not stated as being symptomatic; Group 1 Number missing: 0; Group 2 Number missing: 1 (lost to follow up)	
Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; Mortality ; Stroke and systemic embolism ; Redo of procedure ; serious adverse events; HF or exacerbation of HF ; Length of stay

Study	**Kece, 2019[104]**

Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=70)
Countries and setting	Conducted in Holland
Line of therapy	1st line
Duration of study	Follow up (post intervention): 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	paroxysmal
Subgroup analysis within study	Not applicable
Inclusion criteria	Scheduled for first-time catheter ablation of paroxysmal drug-refractory AF
Exclusion criteria	Previous AF ablation; persistent AF; contraindications for MRI/inability to perform neuropsychological testing
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age – mean (SD): 61.0 (9). Gender (M:F): 43:27. Ethnicity: Unclear
Further population details	1. CHADSVASC: <2 mean 1.6(1.2)) 2. Heart failure: No HF (LVEF >55% for all; LA diameter 39/40mm).
Extra comments	RF ME/RF pt pt: hypertension 46%/51%; DM 6%/3%; stroke/TIA 17%/14%; mean CHADSVASC 1.6/1.6; antiplatelet drugs 9%/3%; LA diam 39/40
Indirectness of population	No indirectness
Interventions	(n=35) Intervention 1: PVAC Gold: RF multielectrode. Duty-cycled RF energy applications of 60s (Genius Generator software version 15.1; Medtronic) were delivered in a bipolar:unipolar ratio of either 4:1 (10 W) or 2:1 (8 W) until PVI was achieved. Duration single procedure.

	Concurrent medication/care: Patients were treated under deep sedation with propofol/remifentanil or conscious sedation with midazolam/fentanyl. After venous access, a dose of 5,000 IU of heparin was administered. All treated with VKAs on established INR ranges for at least 2 months before until 3 months after ablation. Indirectness: No indirectness (n=35) Intervention 2: RF point by point. 3.5mm tip irrigated Navistar thermocool catheter used. A point-by-point ablation around both ipsilateral veins was performed until PVI was achieved. RF power was set at 30 to 35 W with a flow rate of 17 to 20 ml/min and a maximum temperature of 43C. Duration single procedure. Concurrent medication/care: Patients were treated under deep sedation with propofol/remifentanil or conscious sedation with midazolam/fentanyl. After venous access, a dose of 5,000 IU of heparin was administered. All treated with VKAs on established INR ranges for at least 2 months before until 3 months after ablation. Indirectness: No indirectness
Funding	The department has unrestricted research and fellowship grants from Abbott, Boston Scientific, Medtronic and Biotronik. This research did not receive and specific grant from funding agencies in the public, commercial or not for profit sectors.

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RF POINT BY POINT versus RF multielectrode

Protocol outcome 1: Recurrence of symptomatic AF
- Actual outcome for paroxysmal: DATA NOTUSED: unclear if events occurred in blanking period

Protocol outcome 2: Serious adverse events
- Actual outcome for paroxysmal: adverse events at 12 months; Group 1: 1/35, Group 2: 1/35
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Not stated as being symptomatic; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Stroke and systemic embolism
- Actual outcome for paroxysmal: new asymptomatic cerebral embolisms at 3 months; Group 1: 2/35, Group 2: 8/35
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Not stated as being symptomatic; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; Mortality ; Redo of procedure ; HF or exacerbation of HF ; Length of stay

Study	**You: You, 2019[272]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=210)
Countries and setting	Conducted in China
Line of therapy	1st line
Duration of study	Follow up (post intervention): 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	paroxysmal
Subgroup analysis within study	Not applicable
Inclusion criteria	(1) ECG-confirmed PAF that occurred at least twice within 6 months before study enrollment; (2) occurrence of PAF remained despite application of class I and III antiarrhythmic drugs; and (3) <80 years old and agreed to receive catheter ablation treatment for PAF.
Exclusion criteria	(1) prior history of receiving catheter ablation for AF; (2) atrial thrombosis; (3) diagnosis of valvular heart disease (moderate and severe valvular stenosis, severe valvular regurgitation); (4) an LA dimension of >50 mm; (5) prior history of prosthetic heart valve replacement; (5) pregnancy; or (6) existing liver and kidney diseases, malignant tumors or hematological system diseases.
Recruitment/selection of patients	consecutive

Age, gender and ethnicity	Age - mean: 59.1. Gender (M:F): 122:88. Ethnicity: Unclear
Further population details	1. CHADSVASC: unclear 2. Heart failure: No HF (HF only in 7.1%).
Extra comments	Cryo/RF: hypertension 61%/54.3%; DM 15.7%/21.4%; HF 7.1%/7.1%
Indirectness of population	No indirectness
Interventions	(n=70) Intervention 1: Radiofrequency catheter ablation - point by point - RF point by point. Standardised RFCA procedure performed with a mapping catheter (Lasso) and 3d electro-anatomical mapping system (CARTO 3). Duration single procedure. Concurrent medication/care: Reconstructive CT images of the PV obtained before ablation. Indirectness: No indirectness (n=140) Intervention 2: Cryoballon catheter ablation - Cryoballoon. Arctic Front Advance with 23-28mm size balloon depending on PV diameter, using 180-240sec freeze to each PV through the balloon. Either standard cryoballoon [n=70], or cryoballoon applied with a 3D mapping [n=70] was applied (these n=70 groups have been combined to the n=120 group for this review). Duration single procedure. Concurrent medication/care: Reconstructive CT images of the PV obtained before ablation. Indirectness: No indirectness
Funding	No funding (None declared)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RF POINT BY POINT versus CRYOBALLOON Protocol outcome 1: Recurrence of symptomatic AF - Actual outcome for paroxysmal: Recurrence of AF at 12 months; DATA NOT USED – unclear if events occurred in blanking period Protocol outcome 1: Serious adverse events - Actual outcome for paroxysmal: adverse events perioperatively; Group 1: 2/70, Group 2: 3/140 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Not stated as being symptomatic; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; Mortality ; Stroke and systemic embolism ; Redo of procedure ; serious

adverse events; HF or exacerbation of HF ; Length of stay

Study	WAZNI, 2005 trial: Wazni 2005[260]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=70)
Countries and setting	Conducted in Multiple countries; Setting:
Line of therapy	1st line
Duration of study	Follow up (post intervention): 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	paroxysmal
Subgroup analysis within study	Not applicable
Inclusion criteria	Monthly symptomatic AF episodes for at least 3 months.
Exclusion criteria	Age younger than 18 years and older than 75 years, previous history of atrial flutter or AF ablation, previous history of open-heart surgery, previous treatment with antiarrhythmic drugs, and contraindication to long-term anticoagulation treatment.
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Range of means: 53-54. Gender (M:F): Not reported. Ethnicity: unclear
Further population details	1. CHADSVASC: Not stated / Unclear 2. Heart failure: No HF (LVEF >53%).
Extra comments	RF/meds: LA size 41mm/42mm; paroxysmal 97%/95%; structural heart disease and hypertension 25%/28%; LVEF 53%/54%; Use of beta blockers 57%/62%

Indirectness of population	No indirectness
Interventions	(n=33) Intervention 1: Radiofrequency catheter ablation - point by point - RF point by point. Radiofrequency energy was delivered by using an 8-mm tip ablation catheter. Radiofrequency ablation was performed wherever pulmonary vein potentials were recorded around the pulmonary vein antra. The end point of ablation was complete electrical disconnection of the pulmonary vein antrum from the left atrium.. Duration single procedure. Concurrent medication/care: Intravenous heparin was administered to achieve an activated clotting time of 350 to 400 seconds.. Indirectness: No indirectness (n=37) Intervention 2: usual care - medical therapy. dose/quantity, brand name, extra details. Duration unclear. Concurrent medication/care: The physician providing patient care chose the drug used in the antiarrhythmic drug study group. Each study centre was advised to use the maximum tolerable dose of each antiarrhythmic drug. An effort was made to use amiodarone only after the patient failed at least 2 antiarrhythmic drugs. The initiation of class I antiarrhythmic agents was conducted on an outpatient basis, while class III agents were administered in-hospital. The recommended medical regimen consisted of oral flecainide (100-150 mg) twice daily, propafenone (225-300 mg) 3 times daily, and sotalol (120-160mg)twice daily. For patients not already receiving warfarin, anticoagulation with warfarin was initiated and maintained throughout the study in all patients enrolled in the antiarrhythmic drug group with a target INR of 2-3. Indirectness: No indirectness
Funding	Study funded by industry (Acuson, a division of Siemens)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RF POINT BY POINT versus MEDICAL THERAPY

Protocol outcome 1: Quality of life
- Actual outcome for paroxysmal: SF36 (individual scales) at 1 year; ;
Risk of bias: All domain - --, Selection - High, Blinding - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 01; Group 2 Number missing: 02

Protocol outcome 2: Hospitalisation
- Actual outcome for paroxysmal: Hospitalisation at 1 year; Group 1: 3/32, Group 2: 19/35
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1 (lost to follow up); Group 2 Number missing: 2 (lost to follow up)

Protocol outcome 3: Stroke and systemic embolism

- Actual outcome for paroxysmal: Thrombolic events at 1 year; Group 1: 0/32, Group 2: 0/35 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1 (lost to follow up); Group 2 Number missing: 2 (lost to follow up) Protocol outcome 4: Recurrence of symptomatic AF - Actual outcome for paroxysmal: Recurrence of symptomatic AF at 1 year; Group 1: 4/32, Group 2: 22/35 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1 (lost to follow up); Group 2 Number missing: 2 (lost to follow up) Protocol outcome 5: Redo of procedure - Actual outcome for paroxysmal: Redo of RF (or new RF for medical group) at 1 year; Group 1: 4/32, Group 2: 18/35 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1 (lost to follow up); Group 2 Number missing: 2 (lost to follow up) Protocol outcome 6: Serious Adverse Events - Actual outcome for paroxysmal: serious AEs at 1 year; Group 1: 2/32, Group 2: 1/35; Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1 (lost to follow up); Group 2 Number missing: 2 (lost to follow up)	
Protocol outcomes not reported by the study	Mortality ; HF or exacerbation of HF ; Length of stay

Study (subsidiary papers)	WILBER, 2010 trial: Wilber 2010[261] (Reynolds 2010[211])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=167)
Countries and setting	Conducted in Multiple countries
Line of therapy	1st line
Duration of study	Follow up (post intervention): 9 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	paroxysmal
Subgroup analysis within study	Not applicable
Inclusion criteria	Enrolment required at least 3 symptomatic AF episodes (>=1episode verified by electrocardiogram) within the 6 months before randomization, and not responding to at least 1 antiarrhythmic drug (class I, class III, or atrioventricular nodal blocker)
Exclusion criteria	Exclusion criteria included patients with AF of more than 30 days in duration, age younger than 18 years, an ejection fraction of less than 40%, previous ablation for AF, documented left atrial thrombus, amiodarone therapy in the previous 6months,NewYork Heart Association class III (marked limitation in activity due to symptoms) or IV (severe limitations), myocardial infarction within the previous 2 months, coronary artery bypass graft procedure in the previous 6 months, thromboembolic event in the previous 12 months, severe pulmonary disease, a prior valvular cardiac surgical procedure, presence of an implanted cardioverter-defibrillator, contraindication to antiarrhythmic or anticoagulation medications, life expectancy of less than 12 months, and left atrial size of at least 50mmin the parasternal long axis view
Recruitment/selection of patients	Consecutive

Age, gender and ethnicity	Age - Range of means: 55.5 to 56.1. Gender (M:F): 111:56. Ethnicity: unclear
Further population details	1. CHADSVASC: Not stated / Unclear 2. Heart failure: No HF (Most NYHA class I).
Extra comments	Rf pt to pt/Medical: hypertension 48.6%/50%; DM 9.5%/12%; Structural heart disease 9.5%/15%; CVA or TIA 1.9%/5%; prior thromboembolic events 1.9%/3%; NYHA class I 87%/86%; LVEF 62.3%/62.7%; Failed AAD classes I/II: 1.3/1.2
Indirectness of population	No indirectness
Interventions	(n=106) Intervention 1: Radiofrequency catheter ablation - point by point - RF point by point. The ablation catheter (NaviStar ThermoCool Irrigated Tip Catheter; Biosense Webster, Diamond Bar, California) was introduced under fluoroscopic guidance, and the Carto Navigation System (Biosense Webster) was used to map and document the placement of radiofrequency lesions. The PVs were isolated by circumferential lesions. Additional ablation was allowed at investigator discretion and included left atrial linear lesions, ablation at sites with electrogram fractionation, and cavotricuspid isthmus ablation. Infusion of isoproterenol (□20 μg/min) was recommended post-ablation to confirm that all AF foci had been eliminated or isolated.. Duration Single procedure. Concurrent medication/care: For patients undergoing ablation, a computed tomography (CT) scan or magnetic resonance imaging (MRI) scan was required within 30 days before the procedure and at 3 months and 12 months after the procedure.. Indirectness: No indirectness (n=61) Intervention 2: usual care - medical therapy. Patients randomized to the ADT group received a not previously administered, Food and Drug Administration–approved medication for treating AF (dofetilide, flecainide, propafenone, sotalol, or quinidine). The choice of drug was at the discretion of the investigator. Dosages were based on recommendations from the American College of Cardiology/American Heart Association/European Society of Cardiology 2001 Practice Guidelines for Management of Patients With Atrial Fibrillation. The drug and dosage at the end of the titration period were then maintained throughout the study. Amiodarone was not allowed per study protocol. Patients in the ADT group were allowed to crossover and undergo an ablation procedure after 90 days of therapy if the treatment failed.. Duration unclear. Concurrent medication/care: None. Indirectness: No indirectness
Funding	Study funded by industry (Biosense Webster)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RF POINT BY POINT versus MEDICAL THERAPY

Protocol outcome 1: Quality of life
- Actual outcome for paroxysmal: SF36 mental at 3 months; MD; 6.9 (95%CI 2.6 to 11.2);
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3 (persistent AF, withdrew consent, insurance issue); Group 2 Number missing: 5 (withdrew consent)
- Actual outcome for paroxysmal: SF36 physical at 3 months; MD; 6.6 (95%CI 3.6 to 9.4);
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3 (persistent AF, withdrew consent, insurance issue); Group 2 Number missing: 5 (withdrew consent)
- Actual outcome for paroxysmal: SF36 physical at 9 months; Group 1: mean 6.1 (SD 8.15); n=99, Group 2: mean 0.2 (SD 21.89); n=17; Comments: Sds calculated from 95% CIs given in paper. Note that n for med group only 17 as a result of censoring of those who crossed over. Therefore this is a per-protocol analysis
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3 (persistent AF, withdrew consent, insurance issue); Group 2 Number missing: 5 (withdrew consent)
- Actual outcome for paroxysmal: SF36 mental at 9 months; Group 1: mean 7.6 (SD 4.95); n=99, Group 2: mean 1.4 (SD 11.79); n=17; Comments: See comments for physical score
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3 (persistent AF, withdrew consent, insurance issue); Group 2 Number missing: 5 (withdrew consent)

Protocol outcome 2: Recurrence of symptomatic AF
- Actual outcome for paroxysmal: Recurrence of symptomatic atrial arrhythmias at 9 months; Group 1: 31/103, Group 2: 45/56
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3 (persistent AF, withdrew consent, insurance issue); Group 2 Number missing: 5 (withdrew consent)

Protocol outcome 3: Serious Adverse Events
- Actual outcome for paroxysmal: Serious AEs at 9 months; Group 1: 4/103, Group 2: 2/57;
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3 (persistent AF, withdrew consent, insurance issue); Group 2 Number missing: 5 (withdrew consent)

Protocol outcome 4: Mortality

- Actual outcome for paroxysmal: Serious AEs at 9 months; Group 1: 1/103, Group 2: 0/57; Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3 (persistent AF, withdrew consent, insurance issue); Group 2 Number missing: 5 (withdrew consent)	
Protocol outcomes not reported by the study	Hospitalisation ; Mortality ; Stroke and systemic embolism ; Redo of procedure ; HF or exacerbation of HF ; Length of stay

Study	Xu, 2012 trial: Xu 2012[268]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=123)
Countries and setting	Conducted in China
Line of therapy	1st line
Duration of study	Follow up (post intervention): 12.7 months (mean)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	paroxysmal
Subgroup analysis within study	Not applicable
Inclusion criteria	Paroxysmal of persistent AF
Exclusion criteria	Not reported
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Range of means: 60.9 - 61.5. Gender (M:F): 80: 43. Ethnicity: Unclear
Further population details	1. CHADSVASC: Not stated / Unclear 2. Heart failure: Not stated / Unclear
Extra comments	RF/medical: hypertension 40.9%/35.1%; DM 12.1%/22.8%; Stroke 7.6%/10.5%; Paroxysmal 91%/88%; CHD 37.5%/49.1%; Hypertensive Cardiopathy 4.5%/7%; Valvular disease 4.5%/3.5%
Indirectness of population	Serious indirectness: 4% with valvular disease

Interventions	(n=66) Intervention 1: Radiofrequency catheter ablation - point by point - RF point by point. Contiguous applications of radiofrequency energy were delivered at a target temperature of 50–60□C and a maximal power output of 40–50 W. The endpoint of ablation was an 80% reduction in the amplitude of the electrogram or a total of 40 s of energy application. Additional ablation was performed in the outer pulmonary veins, where the local electrogram amplitude exceeded 0.2mV. If AF was still present at the end of circumferential pulmonary vein ablation, either amiodarone or transthoracic cardioversion was used to restore sinus rhythm.. Duration Single procedure. Concurrent medication/care: The right internal jugular vein or subclavian vein was punctured while patients were under local anesthesia (lidocaine). An electrode catheter was introduced into the coronary sinus to record left atrial electrical activity and pacing. The intra-atrial septum was punctured under X-ray guidance projected into a SWARTZ L1 and R0 expansion scabbard along the sheath pipe into the ablation catheter infused with a cold saline catheter (St. Jude, USA) and LASSO catheter (St. Jude, USA). Under X-ray guidance and the EnSite3000 noncontact mapping system, three-dimensional (3D) electro-anatomic maps were constructed. The left and right pulmonary veins were encircled, with additional lines in the posterior left atrium or roof and along the mitral isthmus for those who had atrial flutter. Indirectness: No indirectness (n=57) Intervention 2: usual care - medical therapy. Antiarrhythmic drug therapy. No information provided. Duration unclear. Concurrent medication/care: None. Indirectness: No indirectness
Funding	Funding not stated (Statement of no conflicts)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RF POINT BY POINT versus MEDICAL THERAPY

Protocol outcome 1: Quality of life
- Actual outcome for paroxysmal: SF 36 physical at 6 months; Group 1: mean 269.3 (SD 58.6); n=66, Group 2: mean 234.9 (SD 66.9); n=57
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for paroxysmal: SF 36 mental at 6 months; Group 1: mean 273.6 (SD 69.4); n=66, Group 2: mean 234.1 (SD 44.7); n=57
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Recurrence of symptomatic AF
DATA NOT USED: Unclear if events occurred in blanking period

Protocol outcomes not reported by the study	Hospitalisation ; Mortality ; Stroke and systemic embolism ; Redo of procedure ; HF or exacerbation of HF ; Serious Adverse Events ; Length of stay

Appendix E: Forest plots

PAROXYSMAL STRATUM

RF point by point versus cryoballoon [PAROXYSMAL STRATUM]

Figure 5: Health-related quality of life – SF12 mental

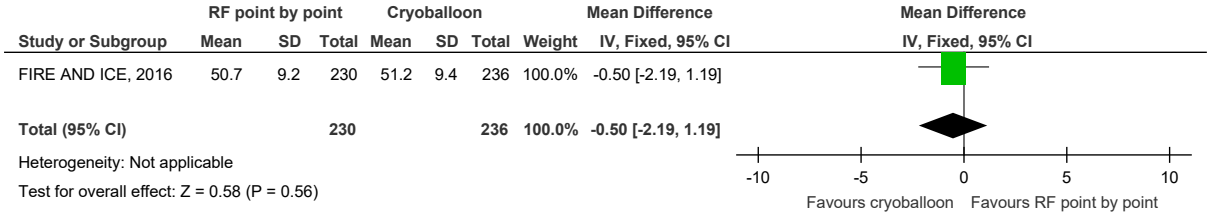


Figure 6: Health-related quality of life – SF12 physical

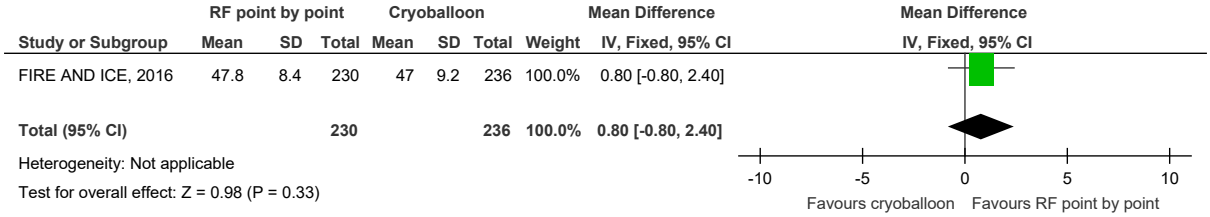


Figure 7: Health-related quality of life – EQ5D-3L

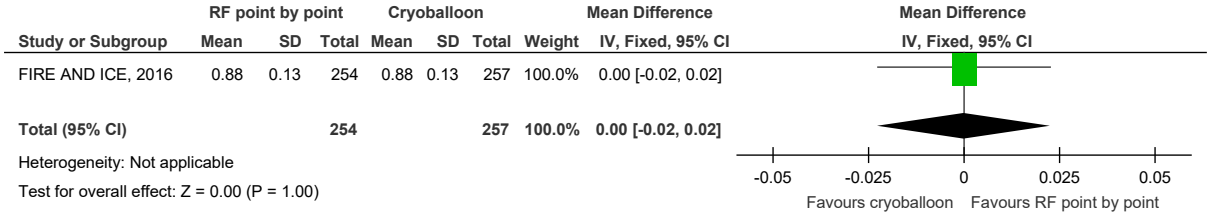
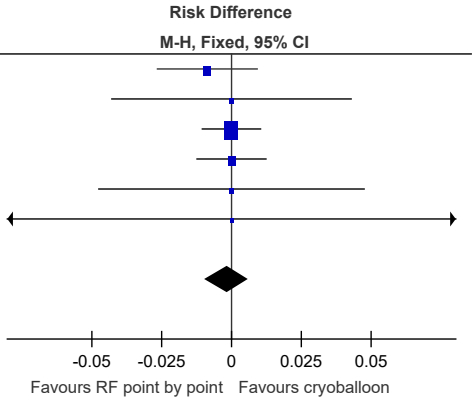


Figure 8: Stroke or thromboembolic complications

Study or Subgroup	RF point by point Events	Total	Cryoballoon Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
ANDRADE, 2020	0	115	2	231	19.5%	-0.01 [-0.03, 0.01]
DAVTYAN, 2018	0	44	0	45	5.7%	0.00 [-0.04, 0.04]
FIRE AND ICE, 2016	2	376	2	374	47.7%	-0.00 [-0.01, 0.01]
FREEZE, 2017	0	159	0	156	20.0%	0.00 [-0.01, 0.01]
POKUSHALOV, 2013	0	40	0	40	5.1%	0.00 [-0.05, 0.05]
TSE, 2005	0	15	0	15	1.9%	0.00 [-0.12, 0.12]
Total (95% CI)		**749**		**861**	**100.0%**	**-0.00 [-0.01, 0.01]**
Total events	2		4			

Heterogeneity: Chi² = 0.77, df = 5 (P = 0.98); I² = 0%

Test for overall effect: Z = 0.43 (P = 0.67)



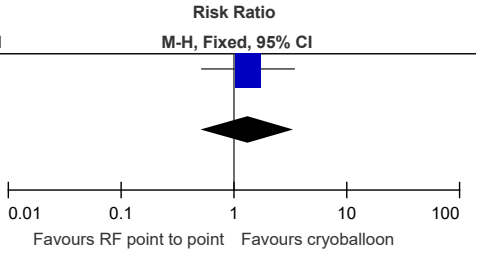
1

Figure 9: Asymptomatic cerebral lesions on MRI

Study or Subgroup	RF point by point Events	Total	Cryoballoon Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
SCHMIDT, 2013	8	33	6	33	100.0%	1.33 [0.52, 3.42]
Total (95% CI)		**33**		**33**	**100.0%**	**1.33 [0.52, 3.42]**
Total events	8		6			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.60 (P = 0.55)



2

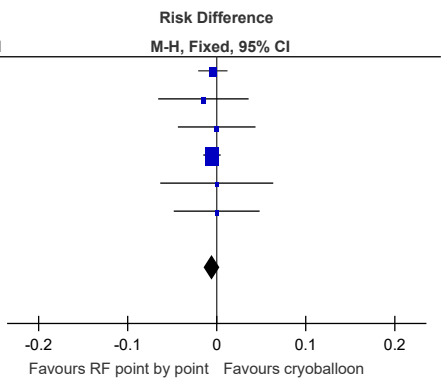
3

Figure 10: Mortality

Study or Subgroup	RF point by point Events	Total	Cryoballoon Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
ANDRADE, 2020	0	115	1	231	21.6%	-0.00 [-0.02, 0.01]
CRYO VERSUS RF TRIAL, 2015	1	67	2	67	9.4%	-0.01 [-0.06, 0.04]
DAVTYAN, 2018	0	44	0	45	6.3%	0.00 [-0.04, 0.04]
FIRE AND ICE, 2016	0	376	2	374	52.8%	-0.01 [-0.01, 0.00]
GUNARWARDINE, 2018	0	30	0	30	4.2%	0.00 [-0.06, 0.06]
POKUSHALOV, 2013	0	40	0	40	5.6%	0.00 [-0.05, 0.05]
Total (95% CI)		**672**		**787**	**100.0%**	**-0.01 [-0.01, 0.00]**
Total events	1		5			

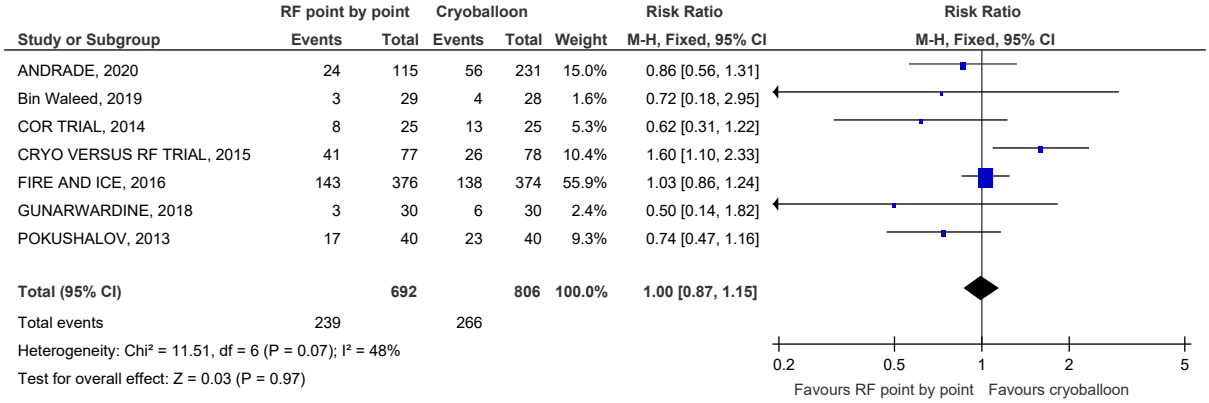
Heterogeneity: Chi² = 0.29, df = 5 (P = 1.00); I² = 0%

Test for overall effect: Z = 1.14 (P = 0.26)



4

Figure 11: Recurrent symptomatic AF (post blanking period)



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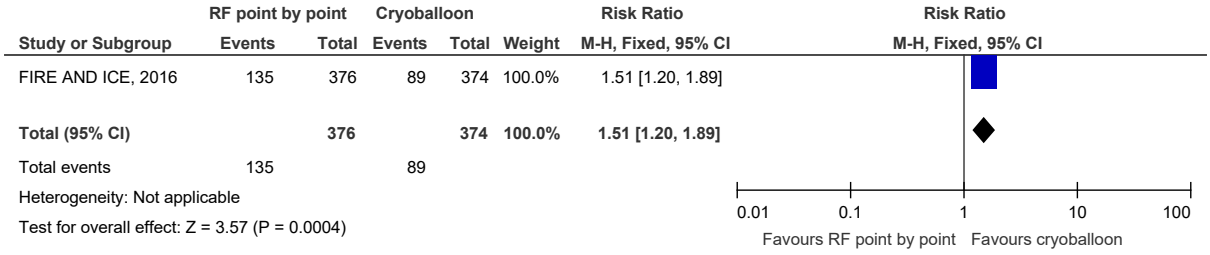
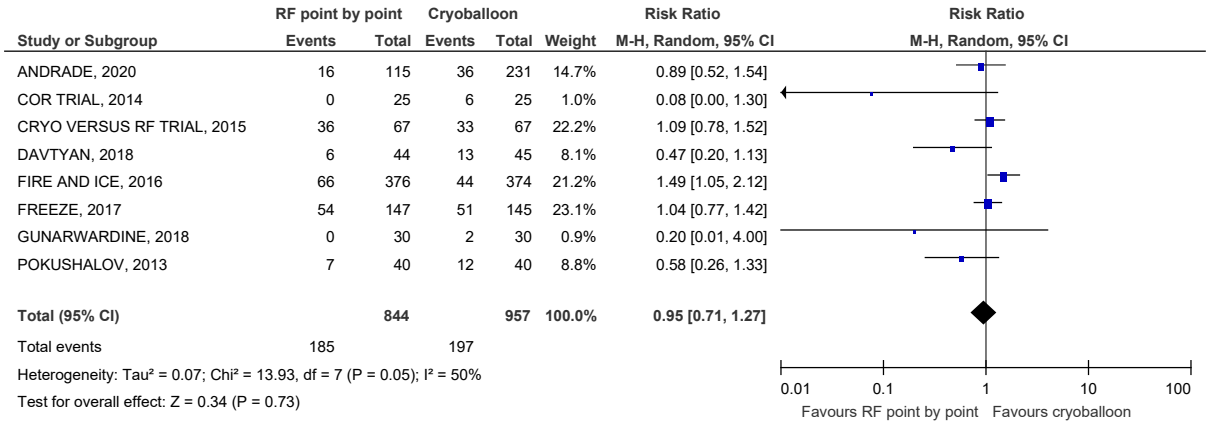
2

Figure 12: Hospitalisation with a primary diagnosis of AF



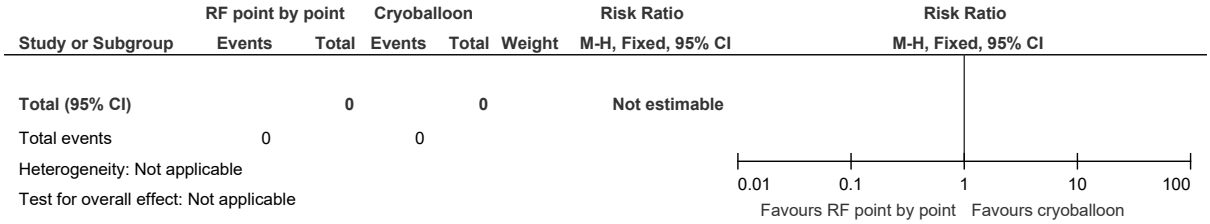
3

Figure 13: Redo of procedure



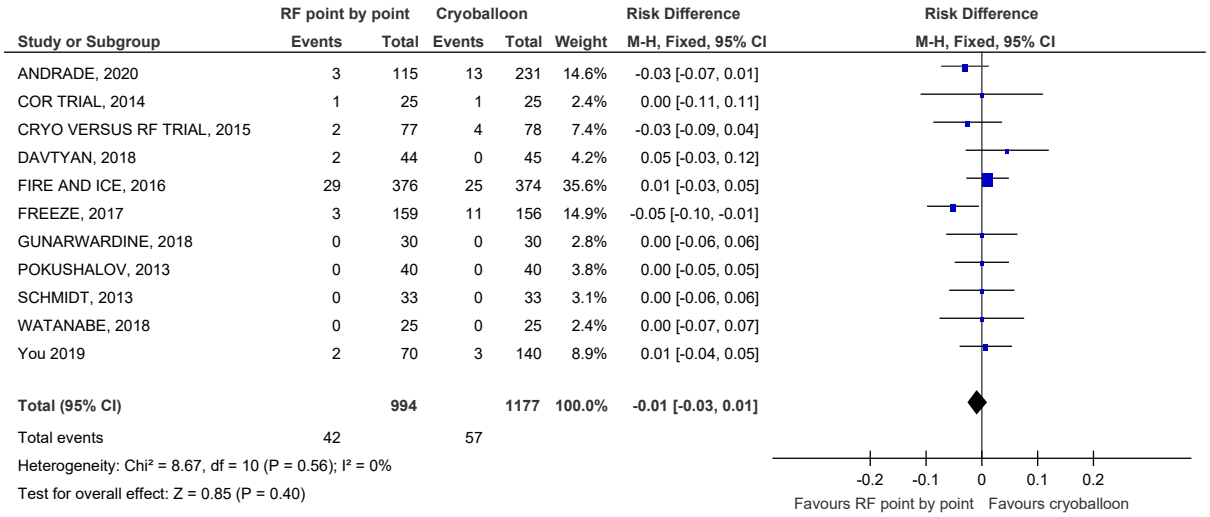
4

Figure 14: HF incidence or exacerbation



1

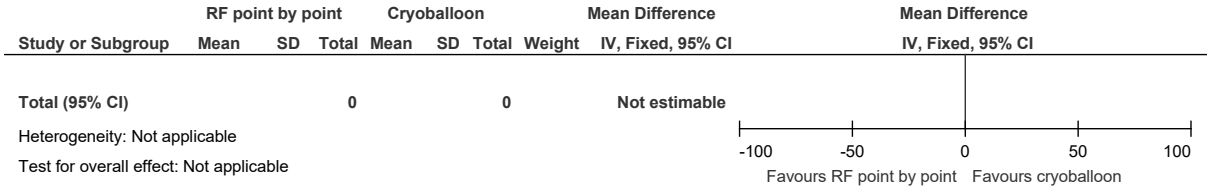
Figure 15: Serious AEs



2

3

Figure 16: Hospital length of stay

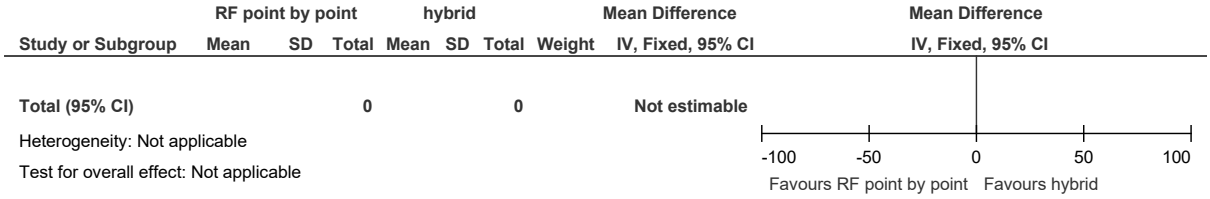


4

5

1 RF point by point versus hybrid [PAROXYSMAL STRATUM]

Figure 17: Health-related quality of life



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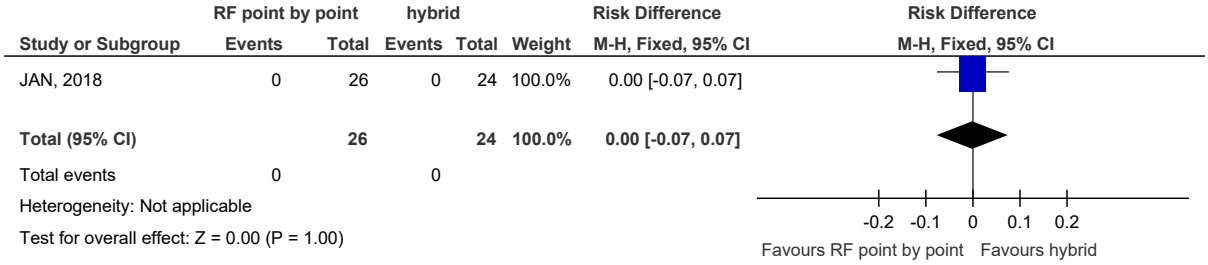
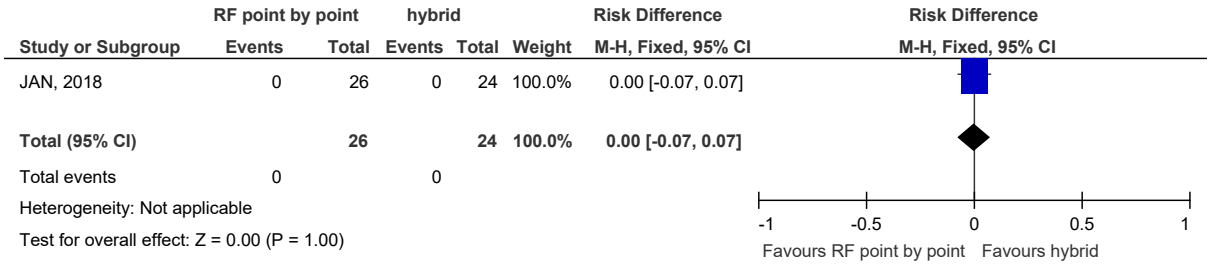
3

Figure 18: Stroke or thromboembolic complications



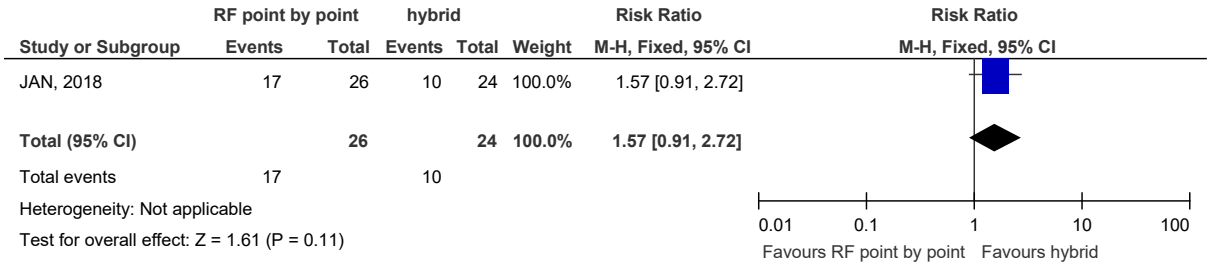
4

Figure 19: Mortality



5

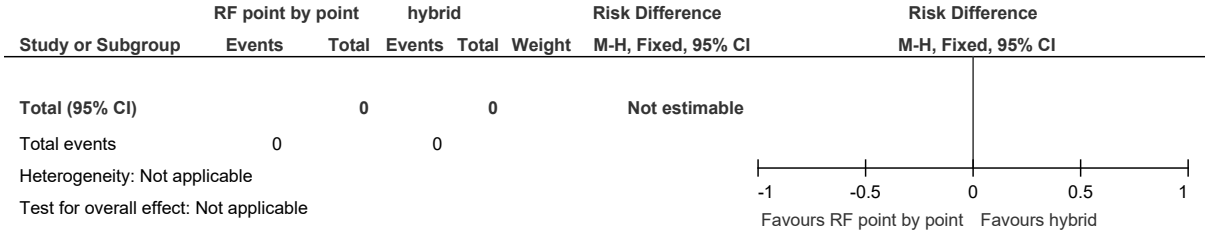
Figure 20: Recurrent symptomatic AF (post blanking period)



1

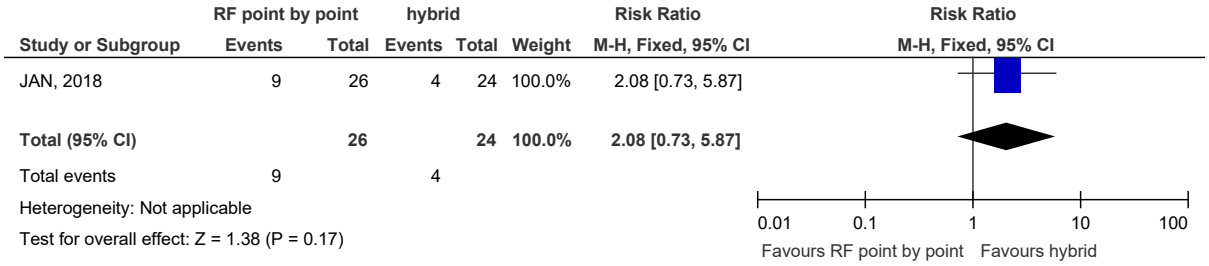
2

Figure 21: Hospitalisation with a primary diagnosis of AF



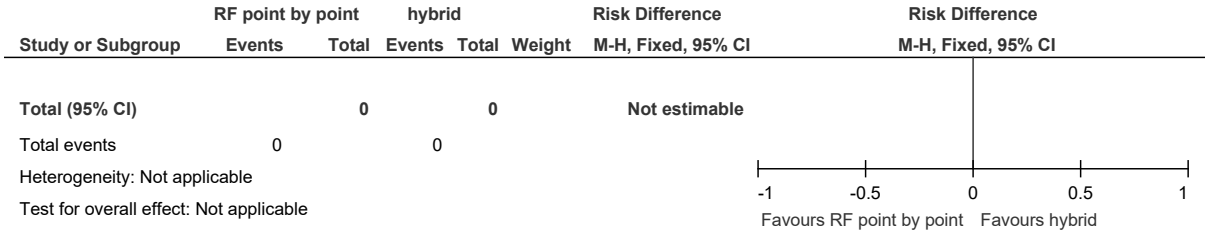
3

Figure 22: Redo of procedure



4

Figure 23: HF incidence or exacerbation



5

Figure 24: Serious AEs

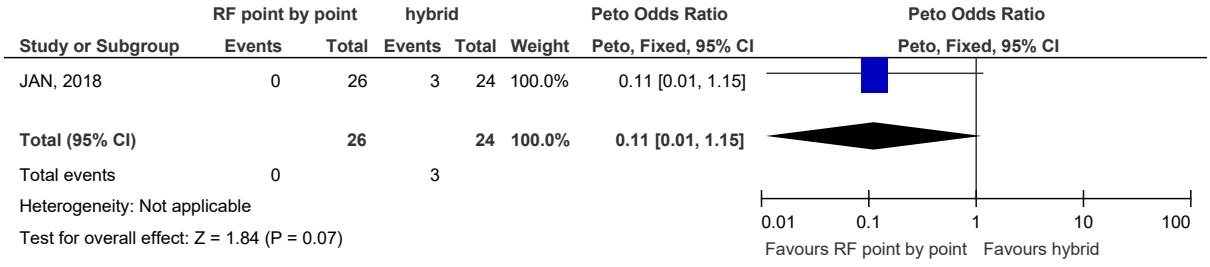
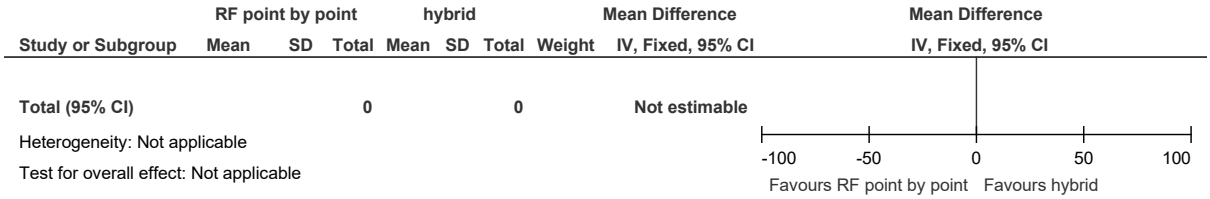


Figure 25: Hospital length of stay



RF point by point versus laser [PAROXYSMAL STRATUM]

Figure 26: Health-related quality of life

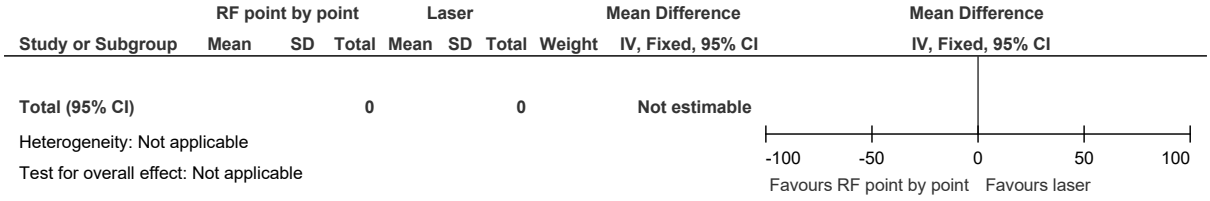


Figure 27: Stroke or thromboembolic complications

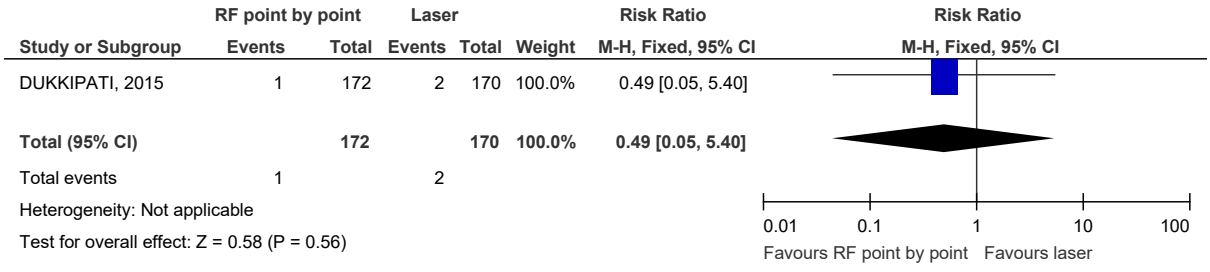


Figure 28: Asymptomatic cerebral lesions on MRI

Study or Subgroup	RF point by point Events	Total	Laser Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
SCHMIDT, 2013	8	33	8	33	100.0%	1.00 [0.43, 2.35]
Total (95% CI)		**33**		**33**	**100.0%**	**1.00 [0.43, 2.35]**
Total events	8		8			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)

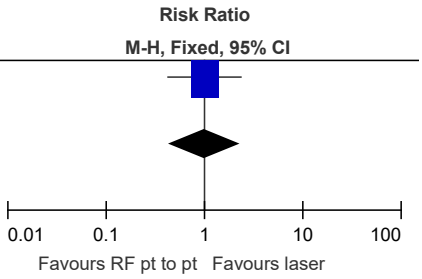


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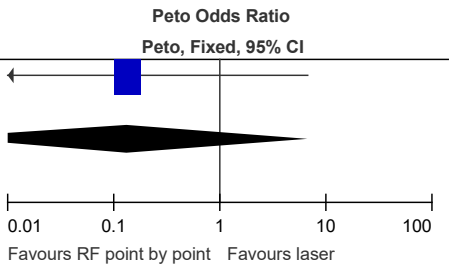
Figure 29: Mortality

Study or Subgroup	RF point by point Events	Total	Laser Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
DUKKIPATI, 2015	0	172	1	170	100.0%	0.13 [0.00, 6.74]
Total (95% CI)		**172**		**170**	**100.0%**	**0.13 [0.00, 6.74]**
Total events	0		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.01 (P = 0.31)

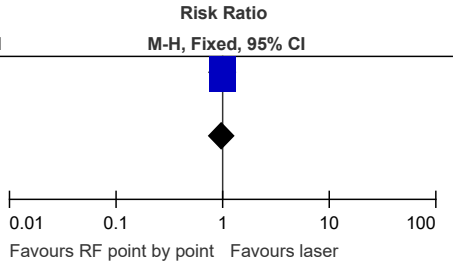


3

Figure 30: Recurrent symptomatic AF (post blanking period)

Study or Subgroup	RF point by point Events	Total	Laser Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
DUKKIPATI, 2015	60	166	61	167	100.0%	0.99 [0.74, 1.31]
Total (95% CI)		**166**		**167**	**100.0%**	**0.99 [0.74, 1.31]**
Total events	60		61			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.07 (P = 0.94)



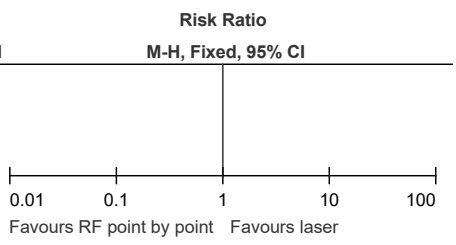
4

5

Figure 31: Hospitalisation with a primary diagnosis of AF

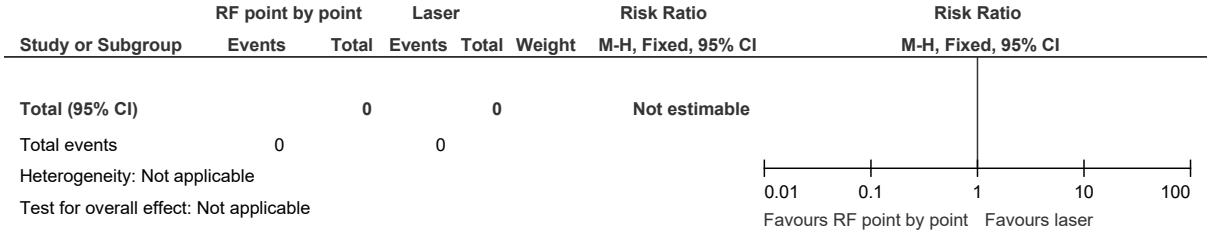
Study or Subgroup	RF point by point Events	Total	Laser Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Total (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable



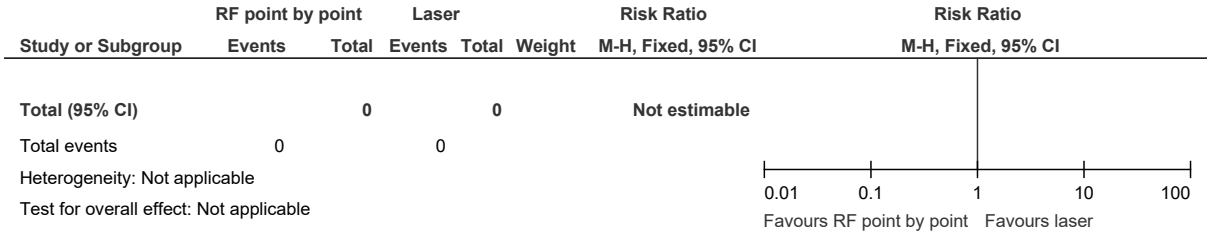
1

Figure 32: Redo of procedure



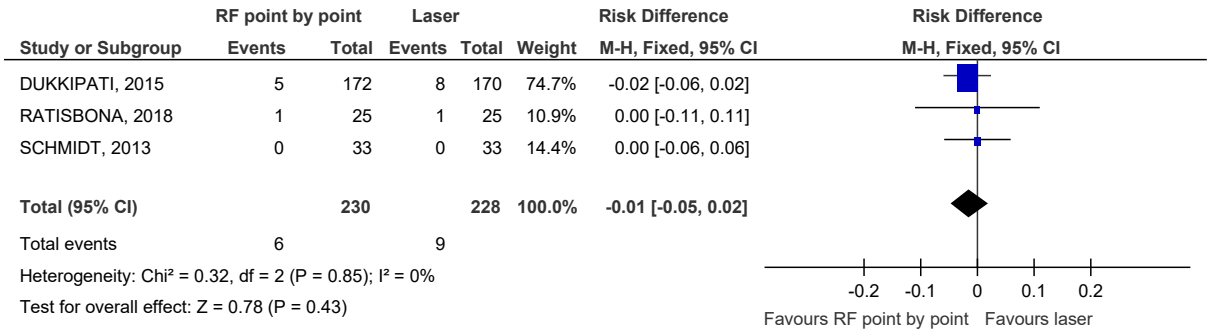
2

Figure 33: HF incidence or exacerbation



3

Figure 34: Serious AEs



4

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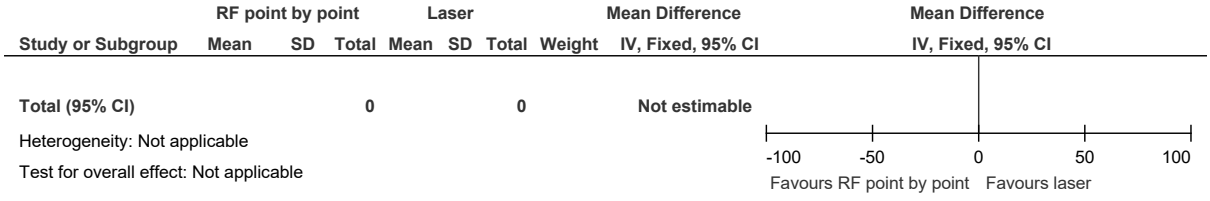
Figure 35: Hospital length of stay



RF point by point versus RF Multielectrode[PAROXYSMAL STRATUM]

Figure 36: Quality of life

Study or Subgroup	RF point by point Mean	SD	Total	RF multielectrode Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
BOERSMA, 2016	6.6	3.5	58	6.5	2.6	59	70.3%	0.03 [-0.33, 0.39]
PODD, 2015	6.6	13	25	10.6	15.1	25	29.7%	-0.28 [-0.84, 0.28]
Total (95% CI)			**83**			**84**	**100.0%**	**-0.06 [-0.36, 0.24]**

Heterogeneity: Chi² = 0.84, df = 1 (P = 0.36); I² = 0%
Test for overall effect: Z = 0.39 (P = 0.70)

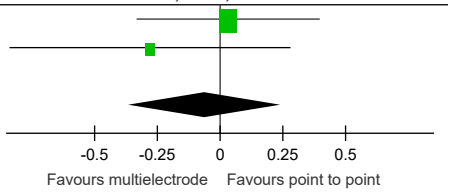


Figure 37: Stroke or thromboembolic complications

Study or Subgroup	RF point by point Events	Total	RF multielectrode Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
BOERSMA, 2016	0	58	0	59	14.4%	0.00 [-0.03, 0.03]
GAL, 2014	0	230	0	230	56.8%	0.00 [-0.01, 0.01]
McREADY, 2014	0	91	2	92	22.6%	-0.02 [-0.06, 0.01]
PODD, 2015	0	25	0	25	6.2%	0.00 [-0.07, 0.07]
Total (95% CI)		**404**		**406**	**100.0%**	**-0.00 [-0.02, 0.01]**
Total events	0		2			

Heterogeneity: Chi² = 2.23, df = 3 (P = 0.53); I² = 0%
Test for overall effect: Z = 0.82 (P = 0.41)

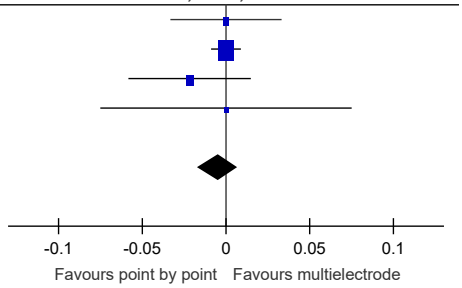


Figure 38: Asymptomatic cerebral lesions

Study or Subgroup	RF point by point Events	Total	RF multielectrode Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kece, 2019	2	35	8	35	100.0%	0.25 [0.06, 1.09]
Total (95% CI)		**35**		**35**	**100.0%**	**0.25 [0.06, 1.09]**
Total events	2		8			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.84 (P = 0.07)

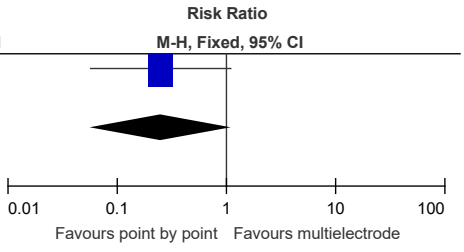
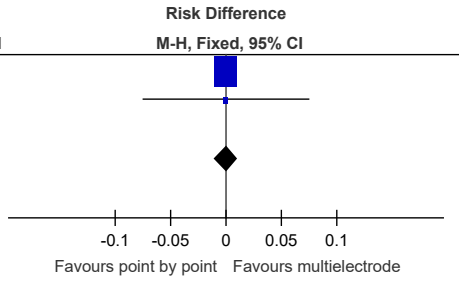


Figure 39: Mortality

Study or Subgroup	RF point by point Events	Total	RF multielectrode Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
GAL, 2014	0	230	0	230	90.2%	0.00 [-0.01, 0.01]
PODD, 2015	0	25	0	25	9.8%	0.00 [-0.07, 0.07]
Total (95% CI)		**255**		**255**	**100.0%**	**0.00 [-0.01, 0.01]**
Total events	0		0			

Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%

Test for overall effect: Z = 0.00 (P = 1.00)



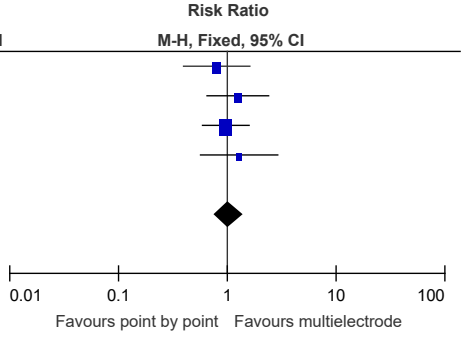
1

Figure 40: Recurrent symptomatic AF (post blanking period)

Study or Subgroup	RF point by point Events	Total	RF multielectrode Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
BOERSMA, 2016	11	58	14	59	24.5%	0.80 [0.40, 1.61]
BULAVA, 2010	15	51	12	51	21.1%	1.25 [0.65, 2.40]
McREADY, 2014	23	91	24	92	42.1%	0.97 [0.59, 1.59]
PODD, 2015	9	25	7	25	12.3%	1.29 [0.57, 2.91]
Total (95% CI)		**225**		**227**	**100.0%**	**1.03 [0.75, 1.41]**
Total events	58		57			

Heterogeneity: Chi² = 1.18, df = 3 (P = 0.76); I² = 0%

Test for overall effect: Z = 0.16 (P = 0.87)



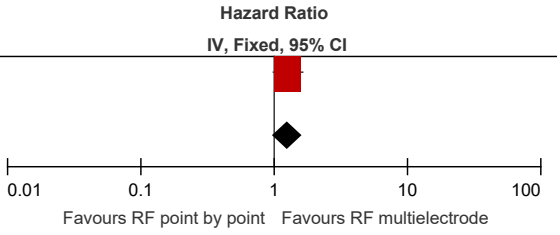
2

Figure 41: Recurrent AF – survival analysis

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
GAL, 2014	0.2398	0.129	100.0%	1.27 [0.99, 1.64]
Total (95% CI)			**100.0%**	**1.27 [0.99, 1.64]**

Heterogeneity: Not applicable

Test for overall effect: Z = 1.86 (P = 0.06)



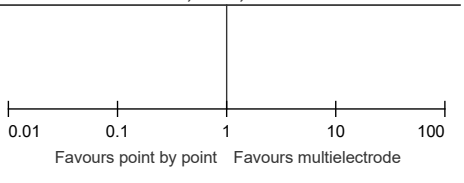
3

Figure 42: Hospitalisation with a primary diagnosis of AF

Study or Subgroup	RF point by point Events	Total	RF multielectrode Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Total (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			

Heterogeneity: Not applicable

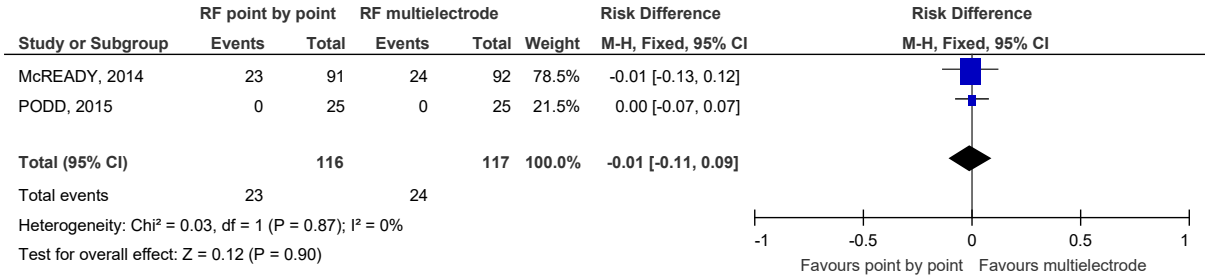
Test for overall effect: Not applicable



1

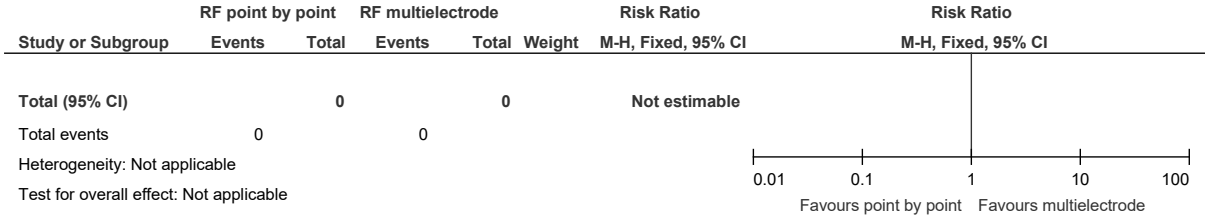
2

Figure 43: Redo of procedure



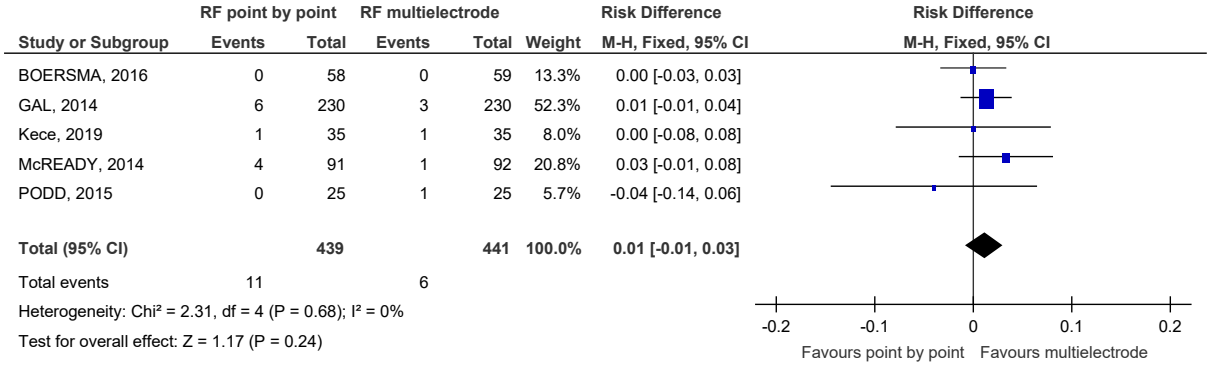
3

Figure 44: HF incidence or exacerbation



4

Figure 45: Serious AEs



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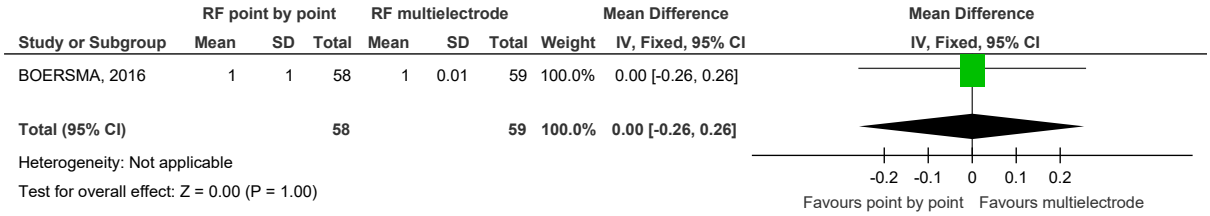
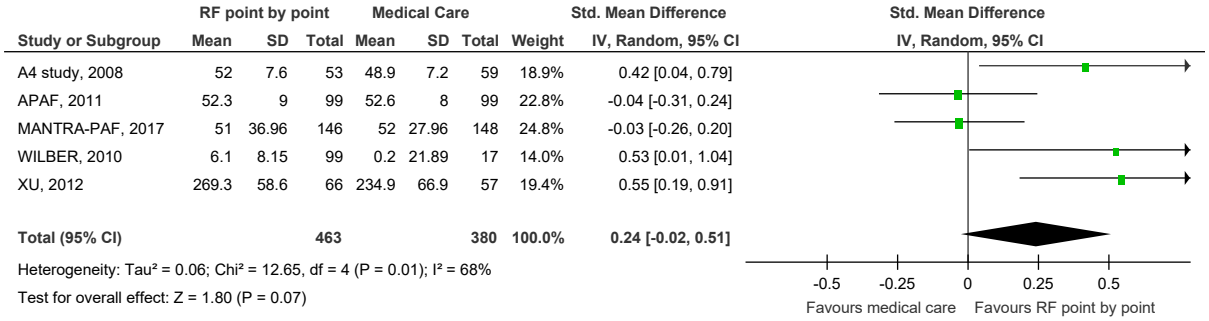
6

Figure 46: Hospital length of stay



1 RF point by point versus medical care [PAROXYSMAL 2 STRATUM]

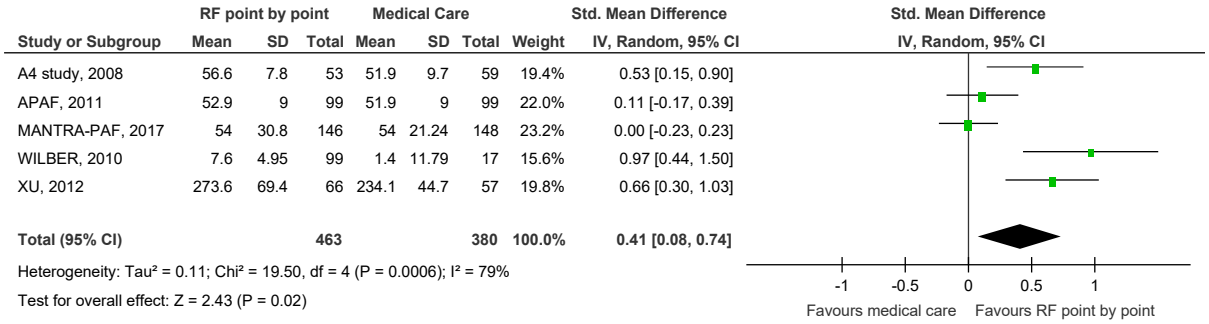
Figure 47: Health-related quality of life – SF36 Physical



3

4

Figure 48: Health-related quality of life – SF36 mental

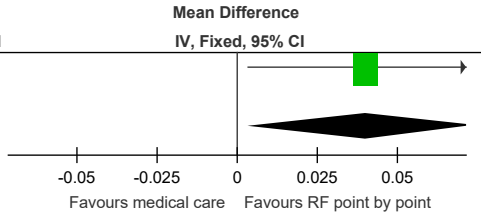


5

Figure 49: Health-related quality of life – EQ5D index

Study or Subgroup	RF point by point Mean	SD	Total	Medical Care Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
MANTRA-PAF, 2017	0.9	0.16	146	0.86	0.16	148	100.0%	0.04 [0.00, 0.08]
Total (95% CI)			**146**			**148**	**100.0%**	**0.04 [0.00, 0.08]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.14 (P = 0.03)



1

2

Figure 50: Health-related quality of life – EQ5D VAS

Study or Subgroup	RF point by point Mean	SD	Total	Medical Care Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
MANTRA-PAF, 2017	79.5	15.7	146	79.8	14.5	148	100.0%	-0.30 [-3.76, 3.16]
Total (95% CI)			**146**			**148**	**100.0%**	**-0.30 [-3.76, 3.16]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.17 (P = 0.86)

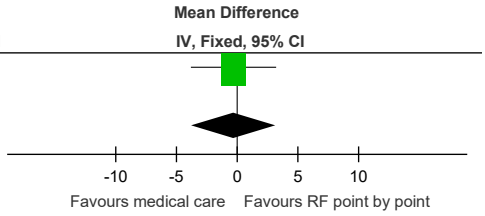


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Figure 51: Stroke or thromboembolic complications

Study or Subgroup	RF point by point Events	Total	Medical Care Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
APAF, 2011	1	99	0	99	28.9%	0.01 [-0.02, 0.04]
MANTRA-PAF, 2017	2	146	1	148	42.9%	0.01 [-0.02, 0.03]
RAAFT2, 2014	0	66	0	61	18.5%	0.00 [-0.03, 0.03]
WAZNI, 2005	0	32	0	35	9.8%	0.00 [-0.06, 0.06]
Total (95% CI)		**343**		**343**	**100.0%**	**0.01 [-0.01, 0.02]**
Total events	3		1			

Heterogeneity: Chi² = 0.28, df = 3 (P = 0.96); I² = 0%
Test for overall effect: Z = 0.77 (P = 0.44)

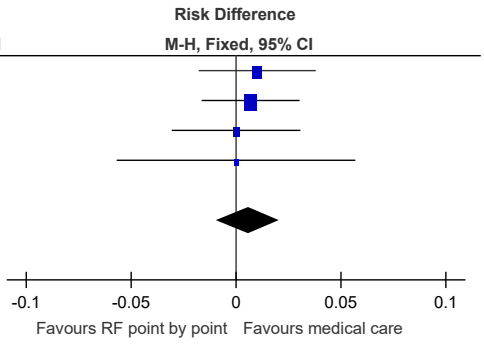

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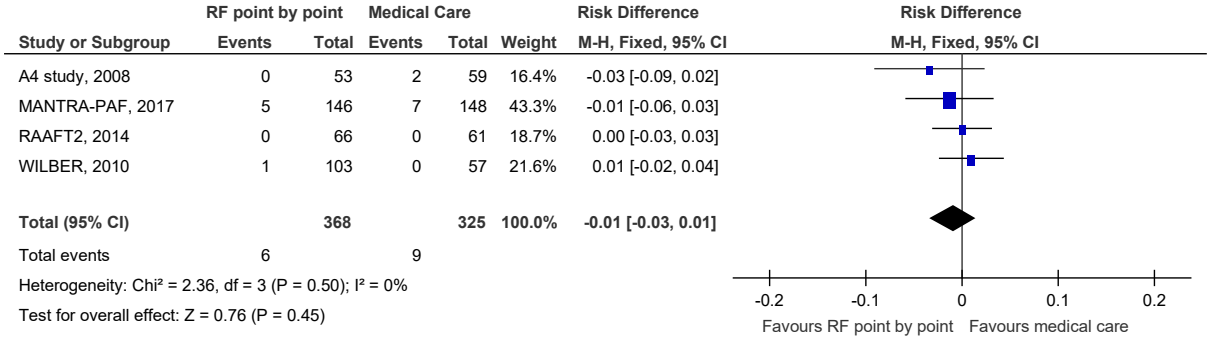
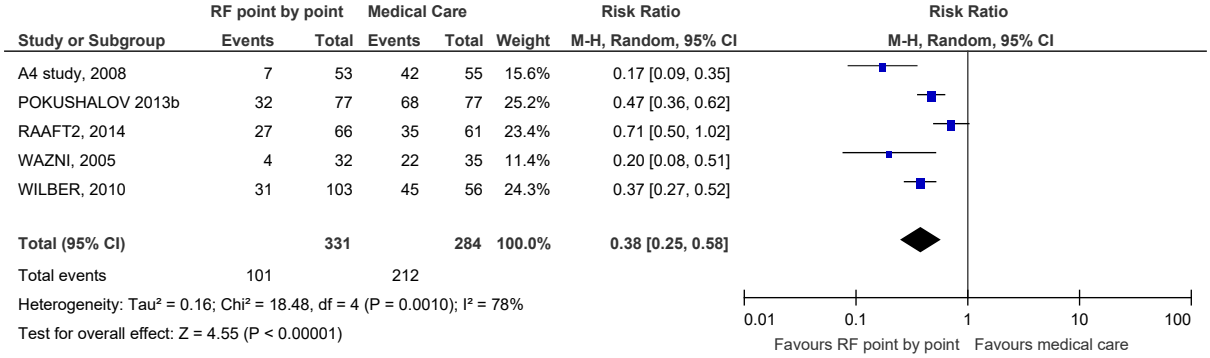
Figure 52: Mortality



1

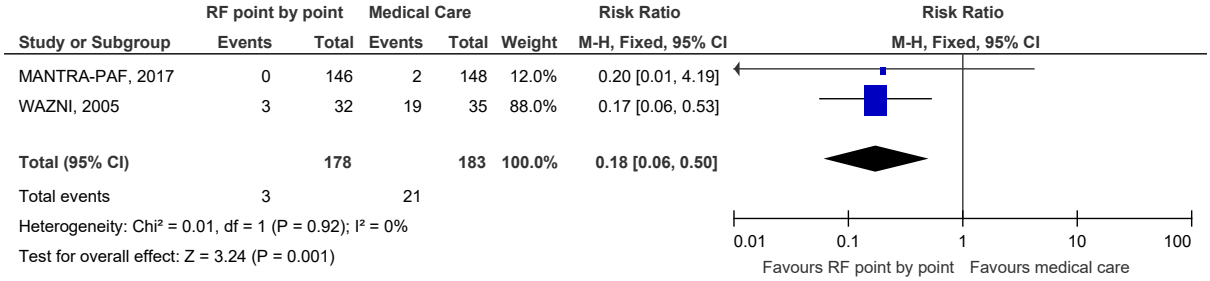
Figure 53: Recurrent symptomatic AF (post blanking period)



2

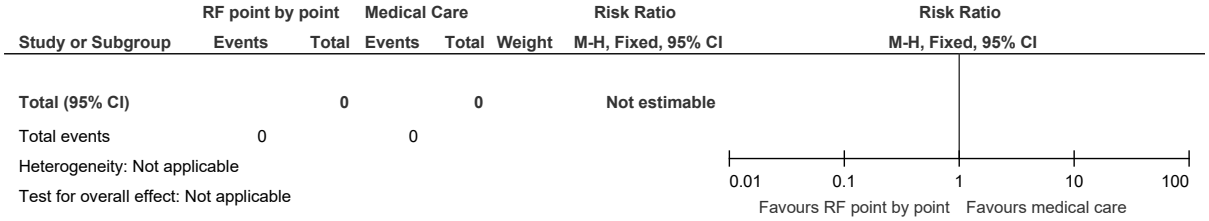
3

Figure 54: Hospitalisation with a primary diagnosis of AF



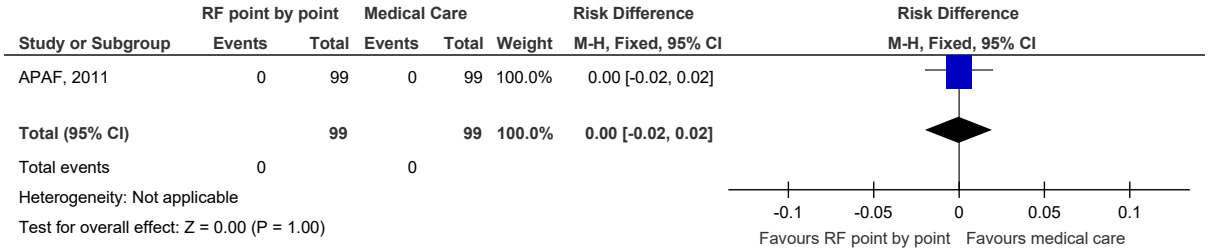
4

Figure 55: Redo of procedure



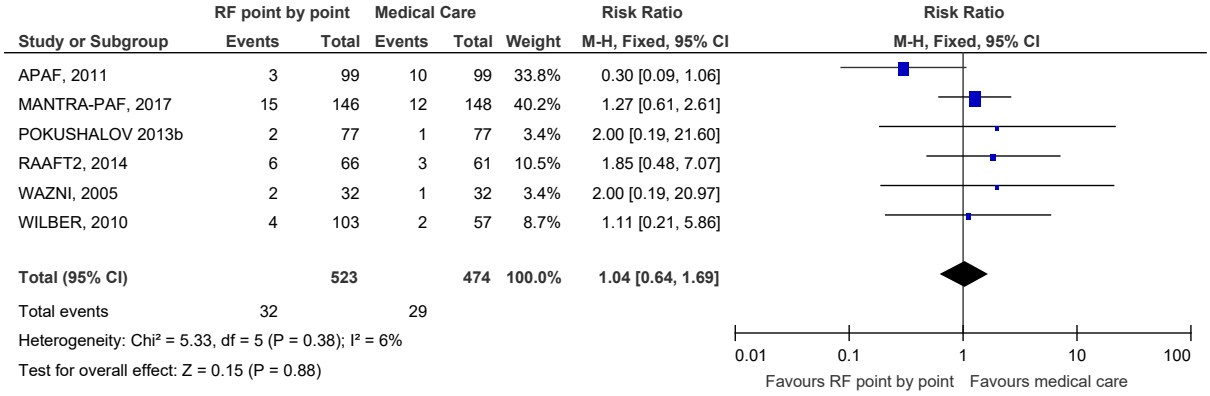
1

Figure 56: HF incidence or exacerbation



2

Figure 57: Serious AEs



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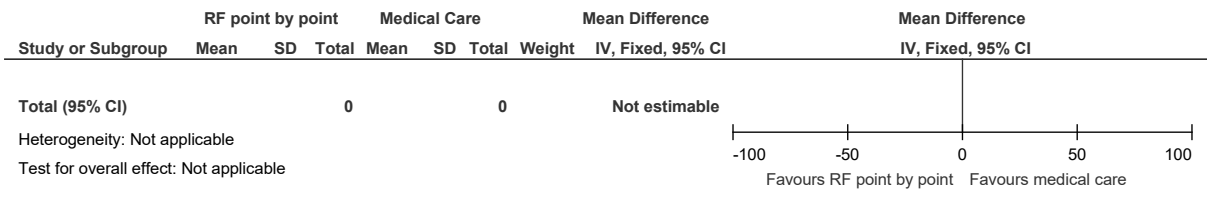
4

Figure 58: Hospital length of stay



RF multielectrode versus cryoballoon [PAROXYSMAL STRATUM]

Figure 59: Health-related quality of life

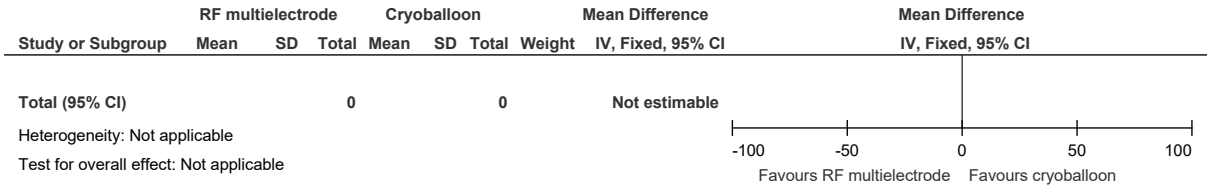


Figure 60: Stroke or thromboembolic complications

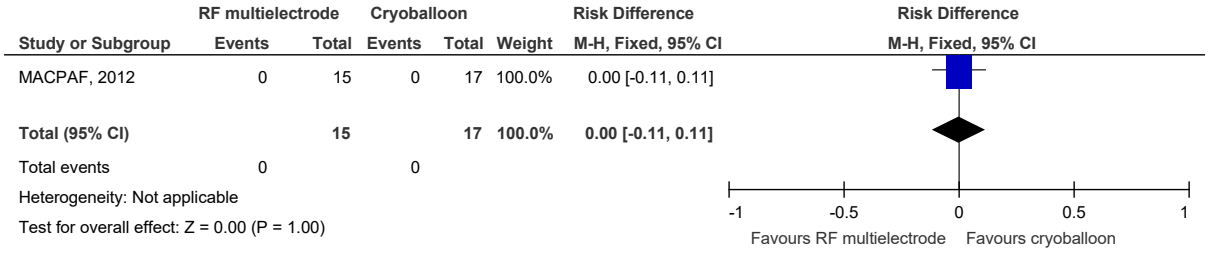


Figure 61: Mortality

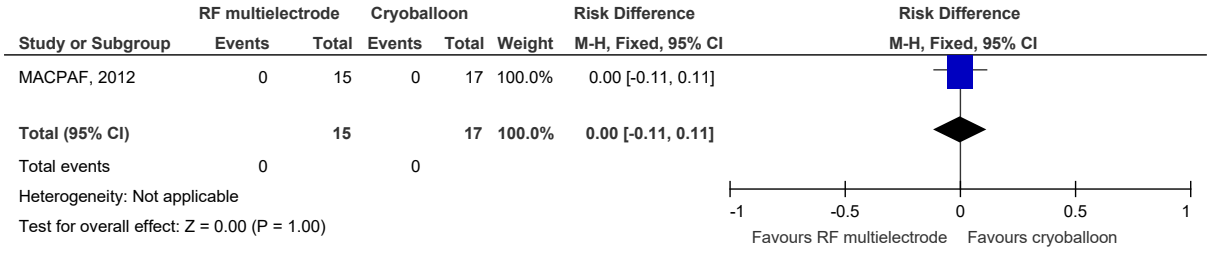


Figure 62: Recurrent symptomatic AF (post blanking period)

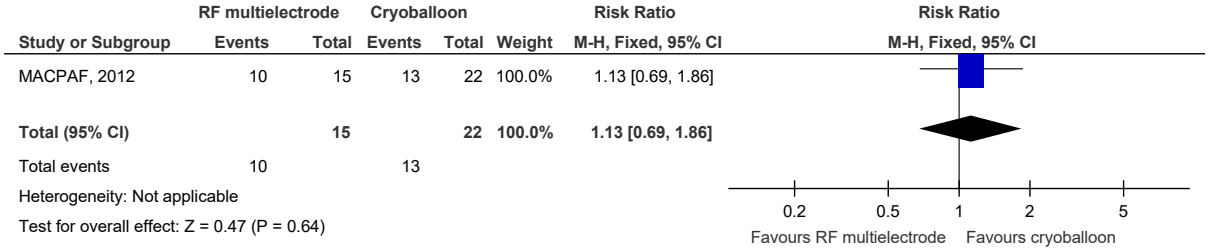


Figure 63: Hospitalisation with a primary diagnosis of AF

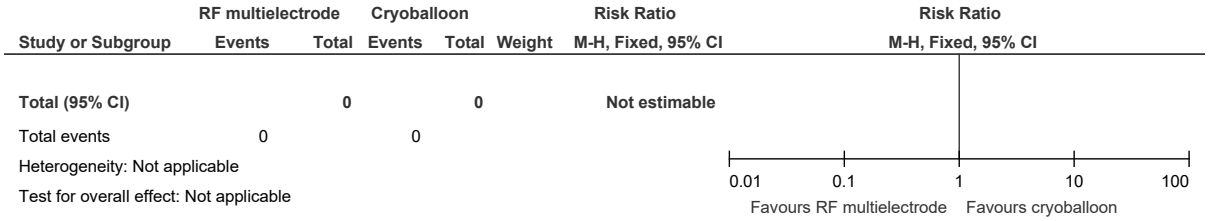


Figure 64: Redo of procedure

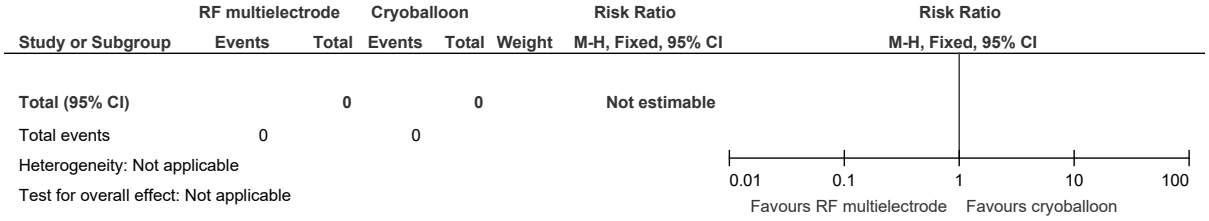


Figure 65: HF incidence or exacerbation

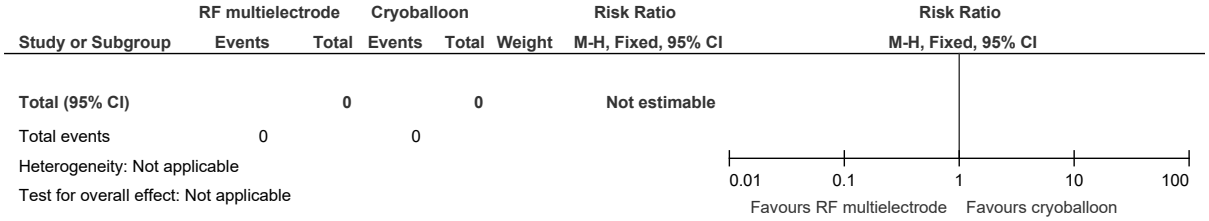


Figure 66: Serious AEs

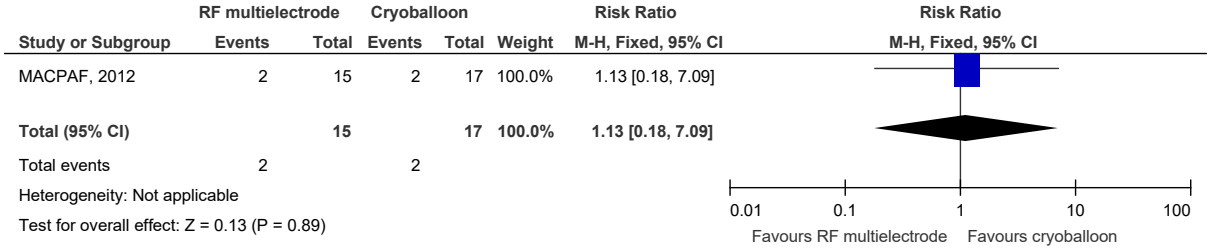


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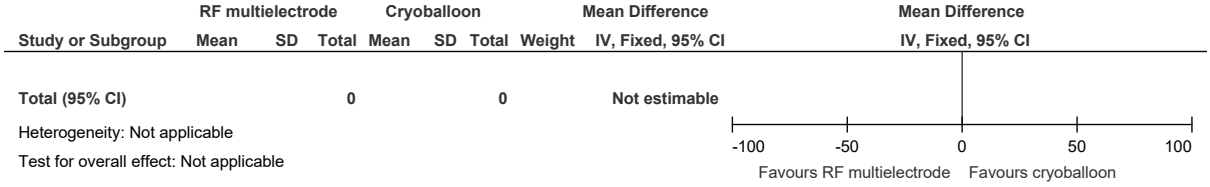
Figure 67: Hospital length of stay



3 RF multielectrode versus thoracoscopy [PAROXYSMAL 4 STRATUM]

Figure 68: Health-related quality of life

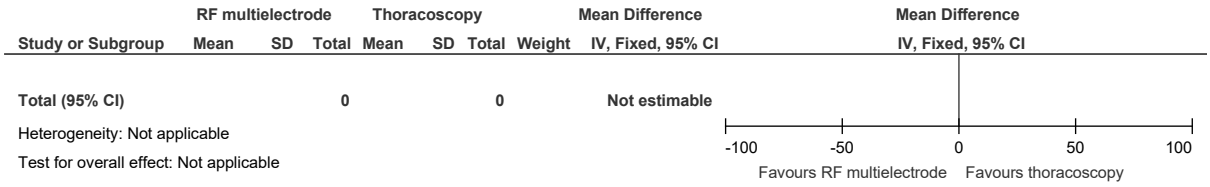


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Figure 69: Stroke or thromboembolic complications

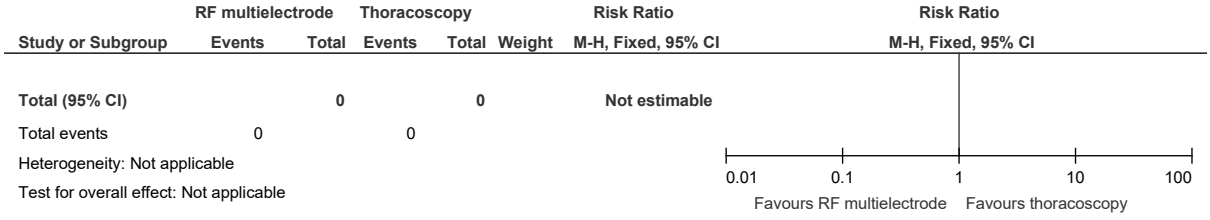

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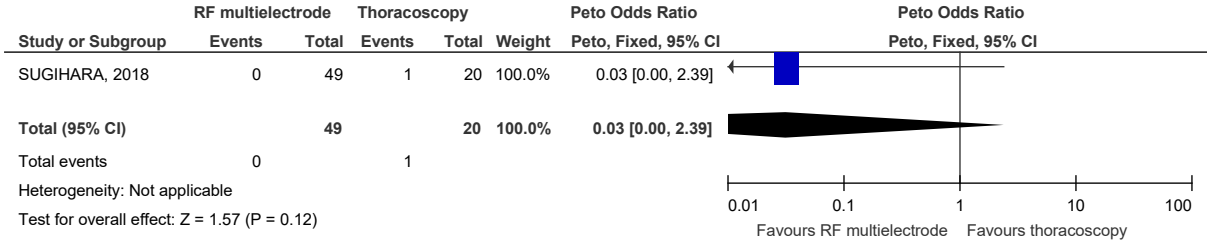
Figure 70: Mortality



1

Figure 71: Recurrent symptomatic AF (post blanking period)

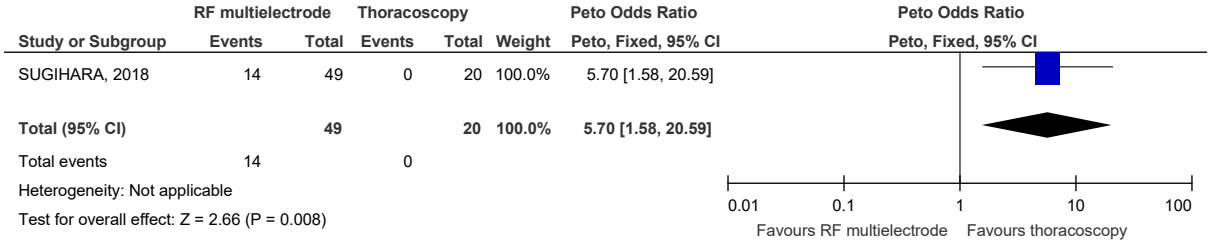


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Figure 72: Hospitalisation with a primary diagnosis of AF

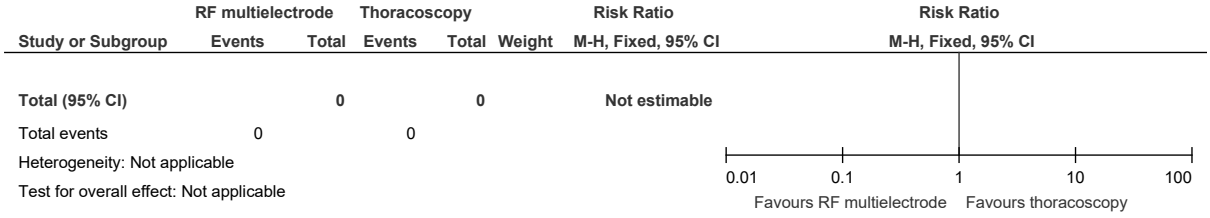

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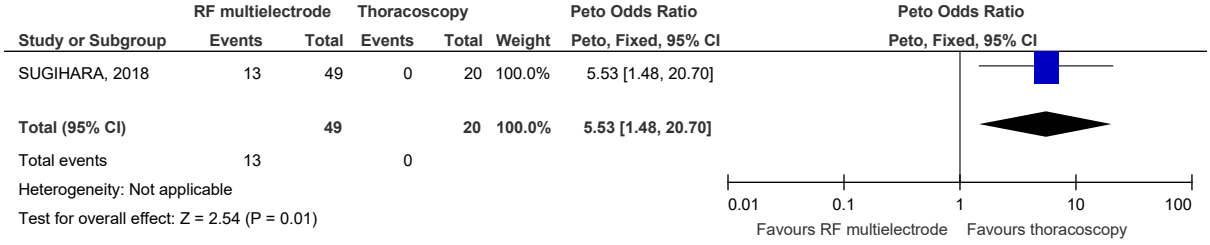
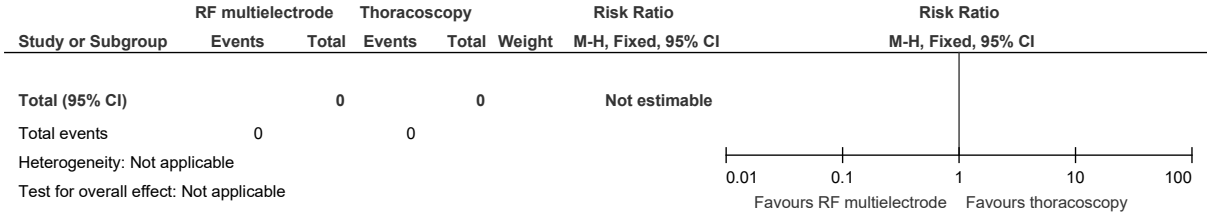
Figure 73: Redo of procedure



5

Figure 74: HF incidence or exacerbation



1

Figure 75: Serious AEs

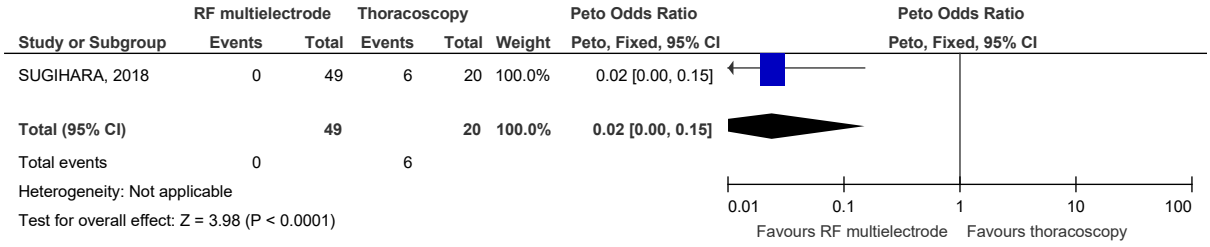


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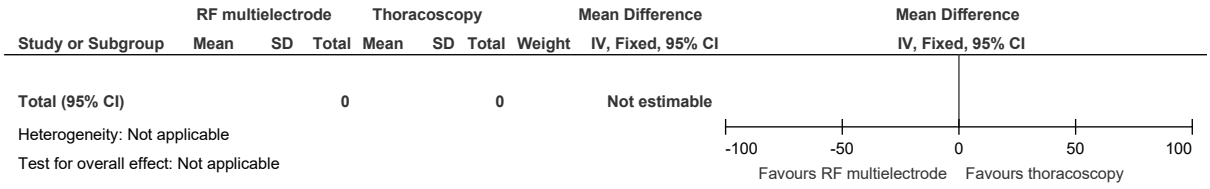
Figure 76: Hospital length of stay



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6 Laser versus cryoballoon [PAROXYSMAL STRATUM]

7

Figure 77: Health-related quality of life

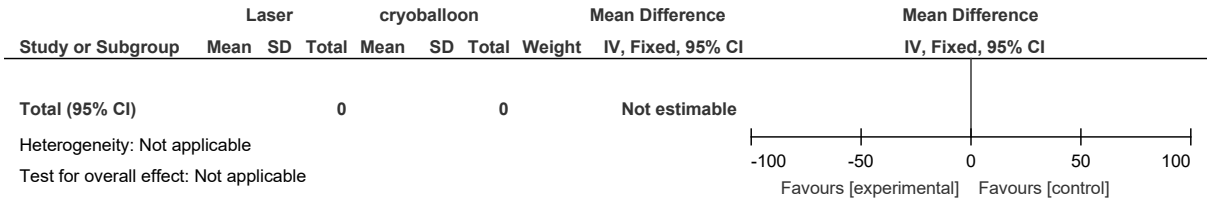
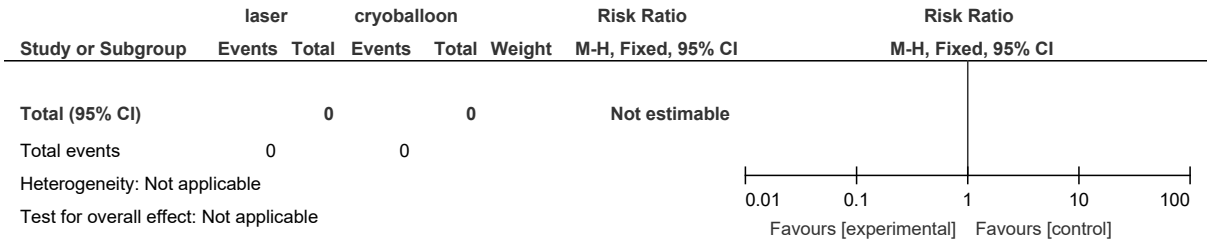


Figure 78: Stroke or thromboembolic complications



1

Figure 79: Asymptomatic cerebral lesions on MRI

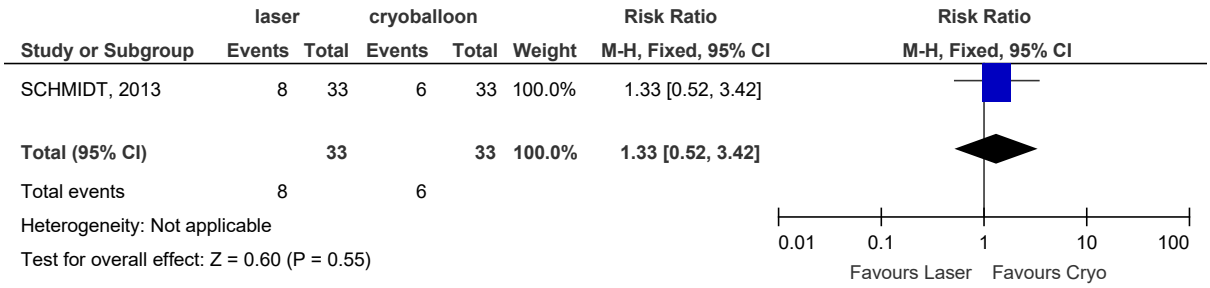


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Figure 80: Mortality

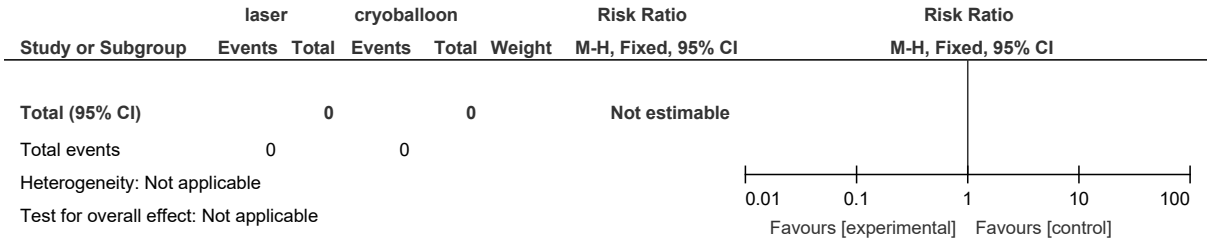

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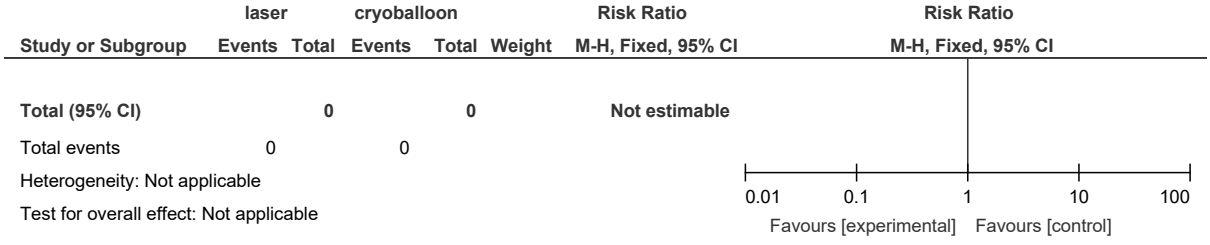
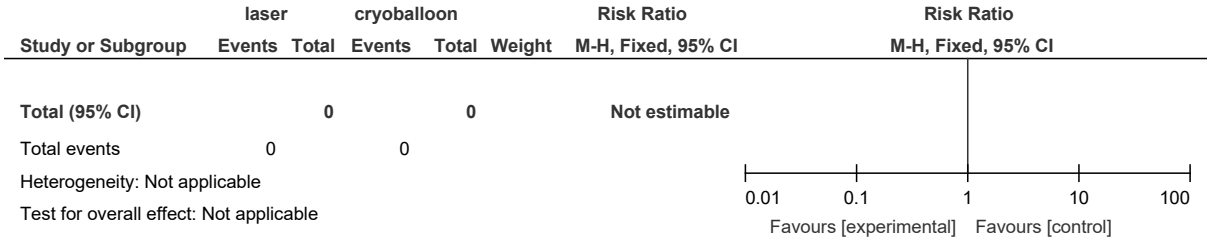
Figure 81: Recurrent symptomatic AF (post blanking period)



1

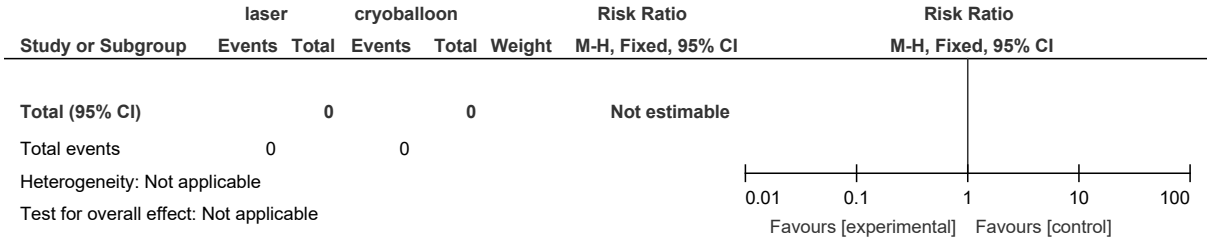
2

Figure 82: Hospitalisation with a primary diagnosis of AF



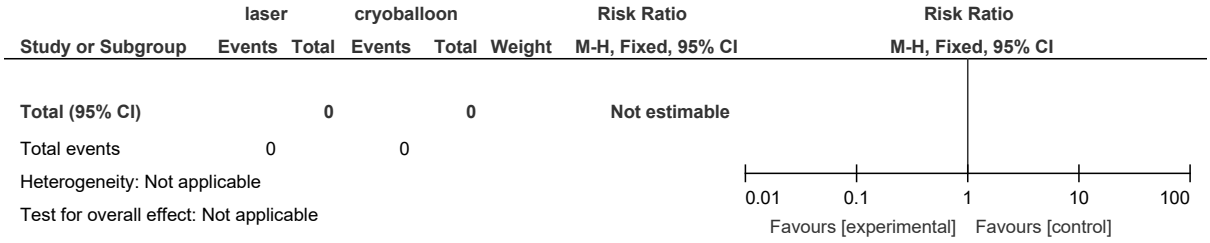
3

Figure 83: Redo of procedure



4

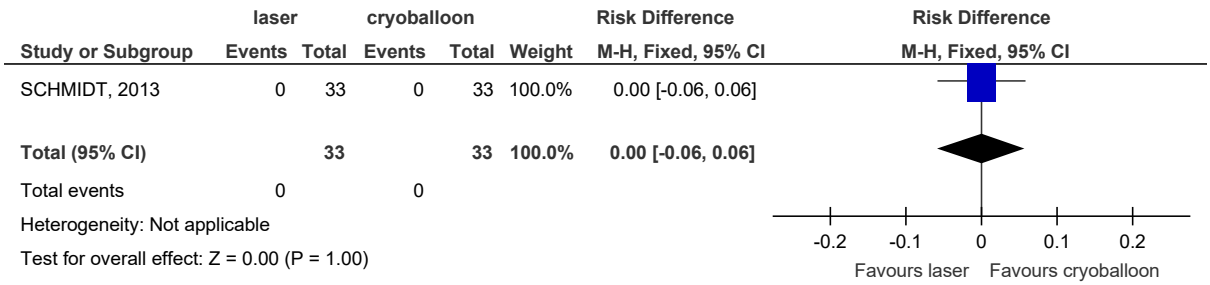
Figure 84: HF incidence or exacerbation



Source: <Insert Source text here>

5

Figure 85: Serious AEs



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1

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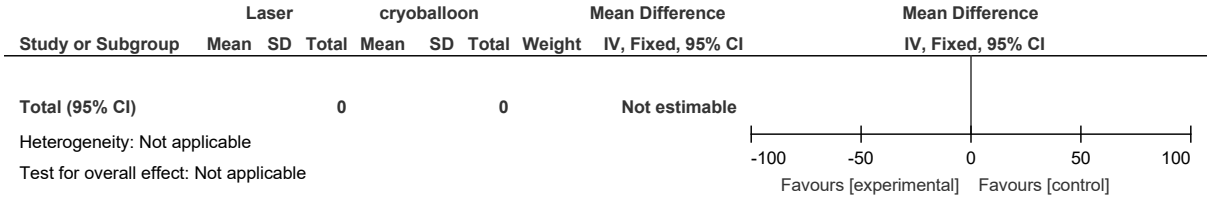
Figure 86: Hospital length of stay



3 Cryoballoon versus medical care[PAROXYSMAL 4 STRATUM]

Figure 87: Quality of life

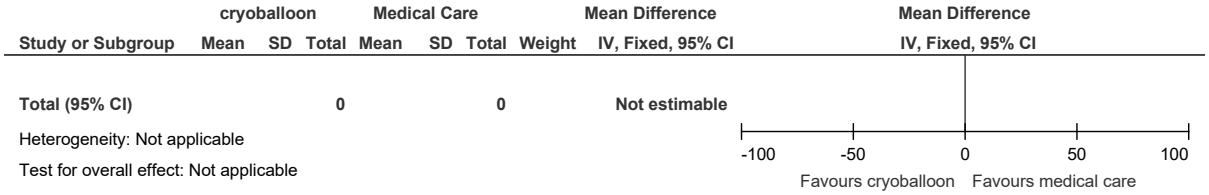


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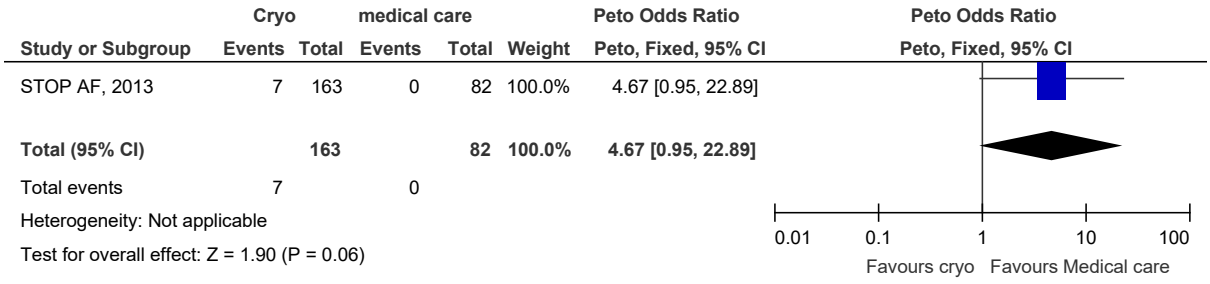
Figure 88: Stroke or thromboembolic complications



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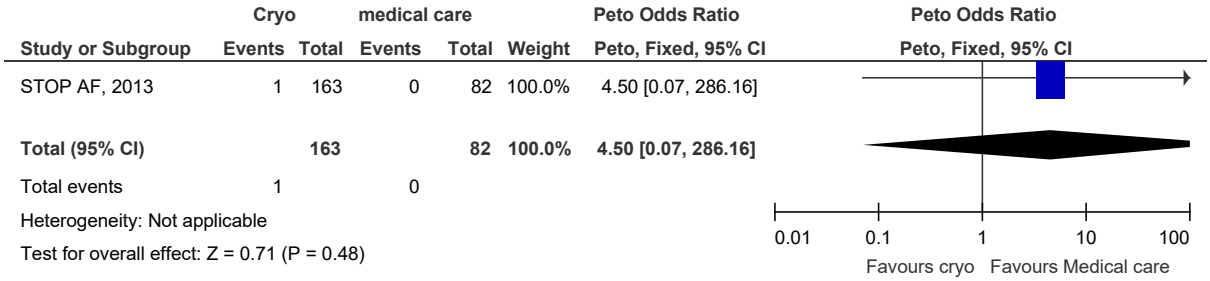
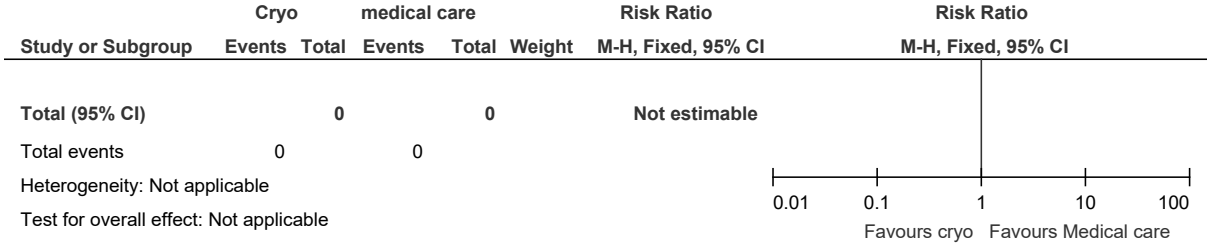
8

Figure 89: Mortality



1

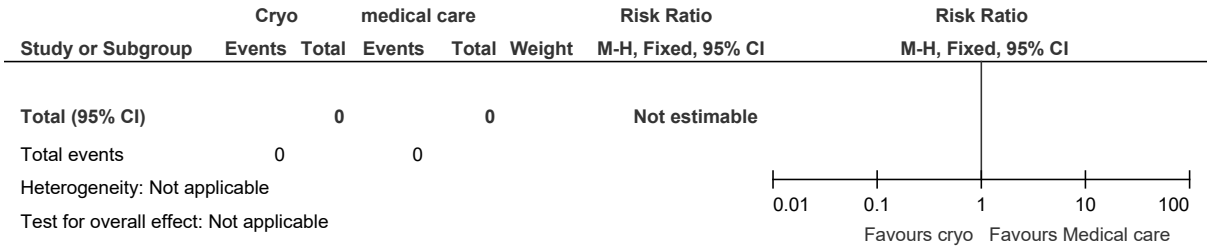
Figure 90: Recurrent symptomatic AF (post blanking period)



2

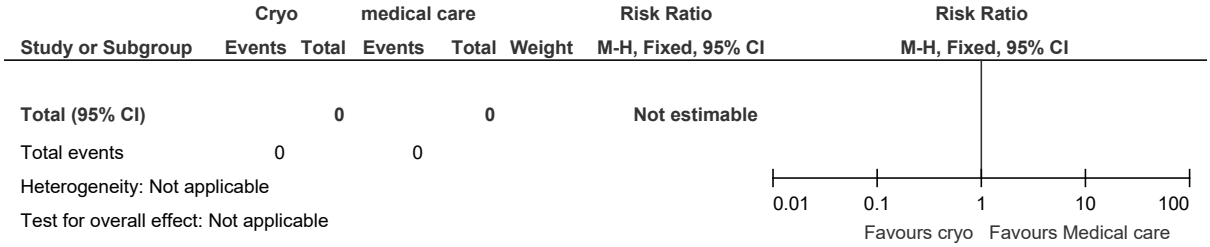
3

Figure 91: Hospitalisation with a primary diagnosis of AF



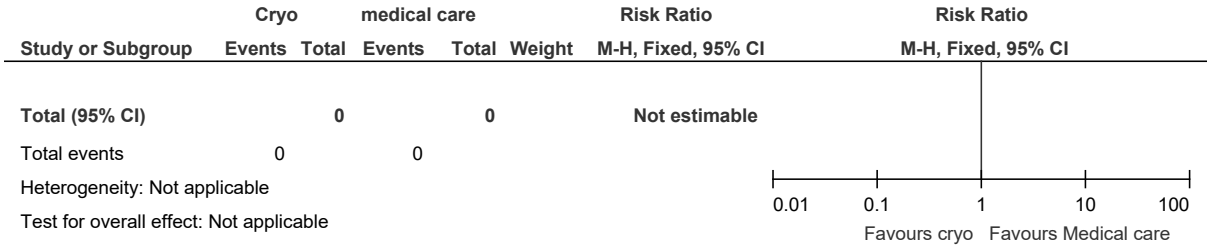
4

Figure 92: Redo of procedure



5

Figure 93: HF incidence or exacerbation



1

Figure 94: Serious AEs

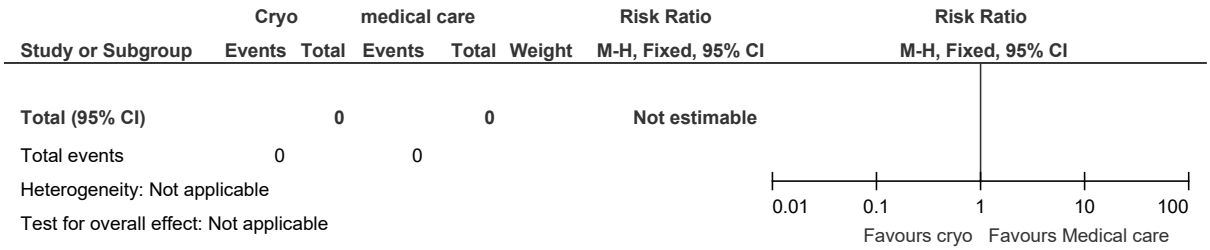


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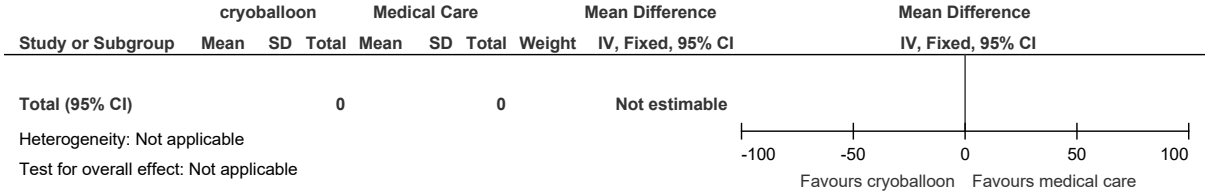
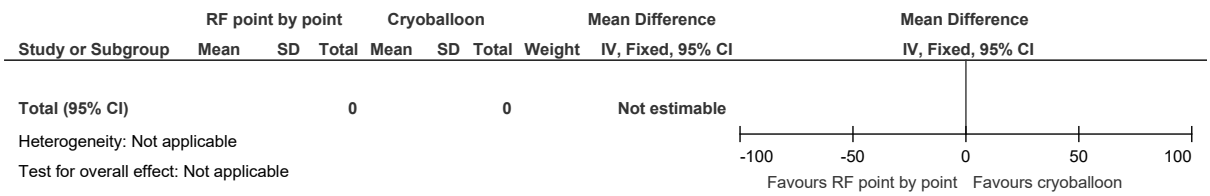
Figure 95: Hospital length of stay



4 **MIXED STRATUM**

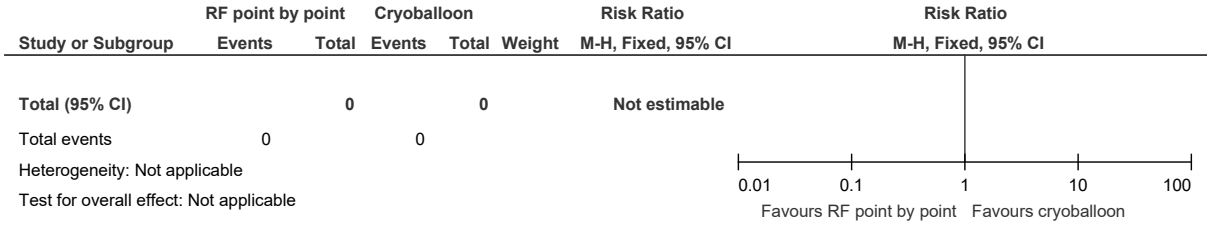
5 **RF point by point versus cryoballoon [MIXED STRATUM]**

Figure 96: Quality of life



6

Figure 97: Stroke or thromboembolic complications



1

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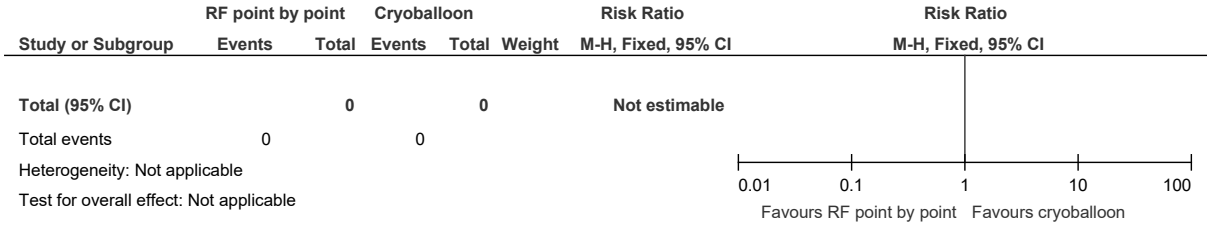
Figure 98: Mortality



3

Figure 99: Recurrent symptomatic AF (post blanking period)

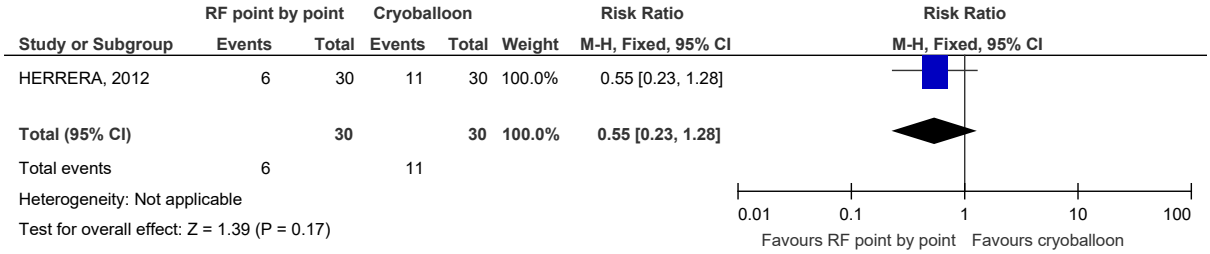


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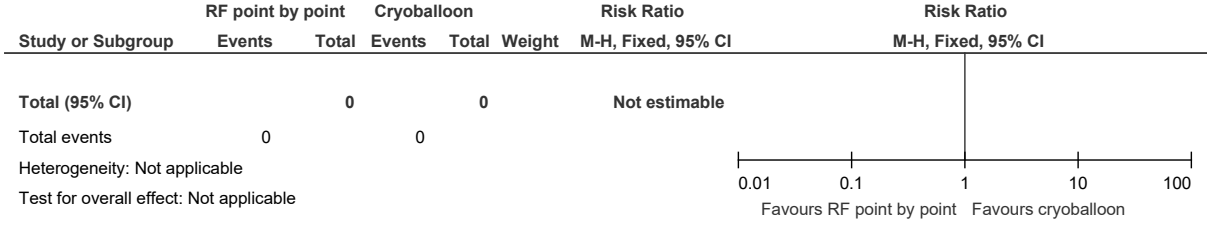
Figure 100: Hospitalisation with a primary diagnosis of AF

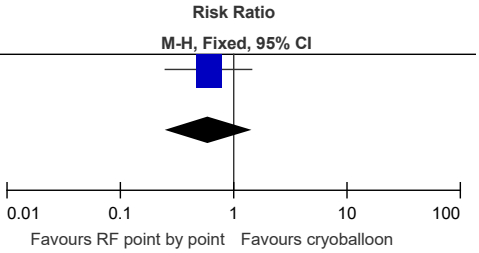


6

Figure 101: Redo of procedure

Study or Subgroup	RF point by point Events	Total	Cryoballoon Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
HERRERA, 2012	6	30	10	30	100.0%	0.60 [0.25, 1.44]
Total (95% CI)		**30**		**30**	**100.0%**	**0.60 [0.25, 1.44]**
Total events	6		10			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.14 (P = 0.25)



1

Figure 102: HF incidence or exacerbation

Study or Subgroup	RF point by point Events	Total	Cryoballoon Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Total (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable

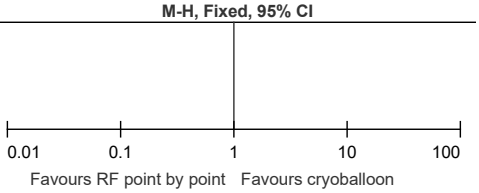
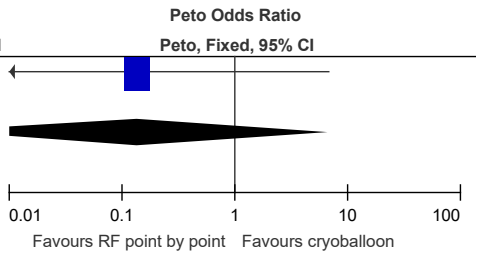


Figure 103: Serious AEs

Study or Subgroup	RF point by point Events	Total	Cryoballoon Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
HERRERA, 2012	0	30	1	30	100.0%	0.14 [0.00, 6.82]
Total (95% CI)		**30**		**30**	**100.0%**	**0.14 [0.00, 6.82]**
Total events	0		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.00 (P = 0.32)



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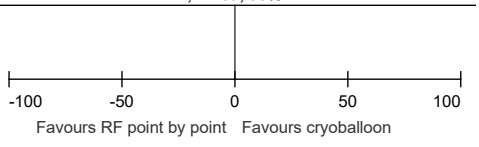
3

Figure 104: Hospital length of stay

Study or Subgroup	RF point by point Mean	SD	Total	Cryoballoon Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Total (95% CI)			**0**			**0**		**Not estimable**

Heterogeneity: Not applicable
Test for overall effect: Not applicable



4

RF point by point versus RF multielectrode [MIXED STRATUM]

Figure 105: Health-related quality of life

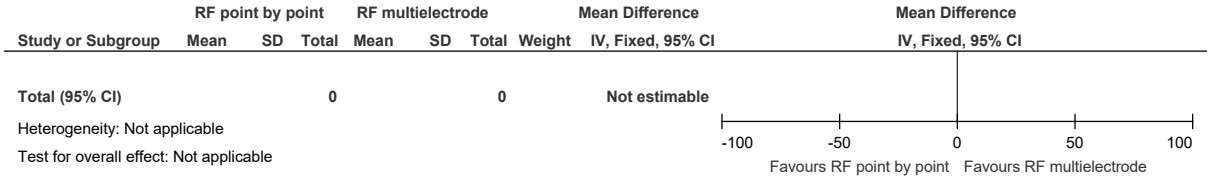


Figure 106: Stroke or thromboembolic complications

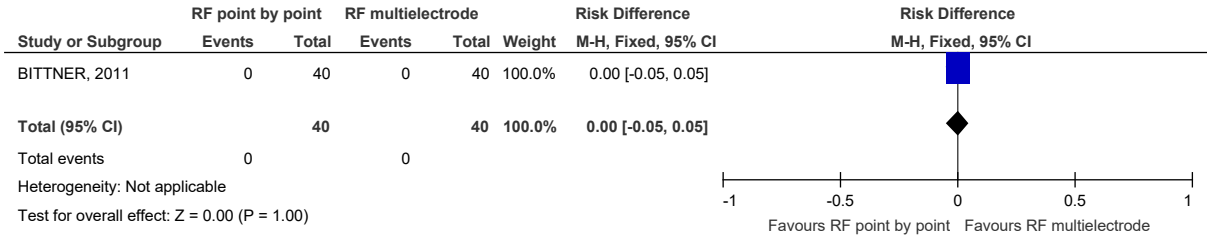


Figure 107: Mortality

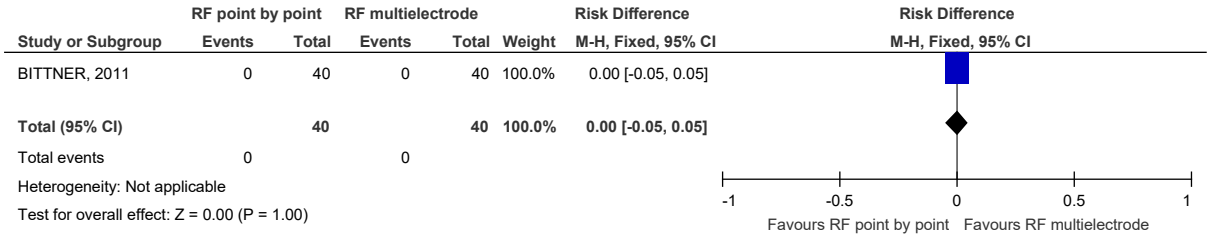
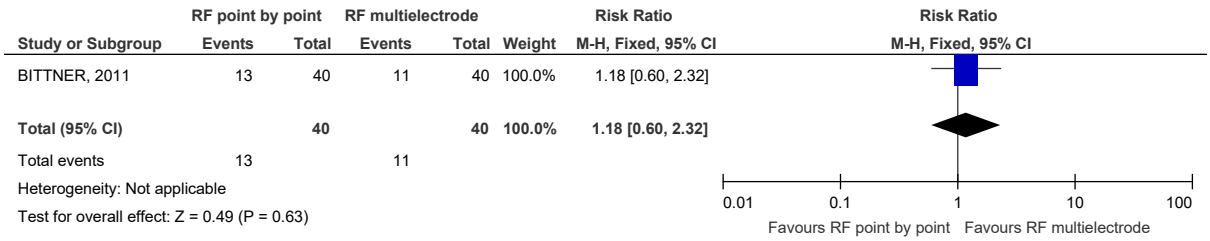


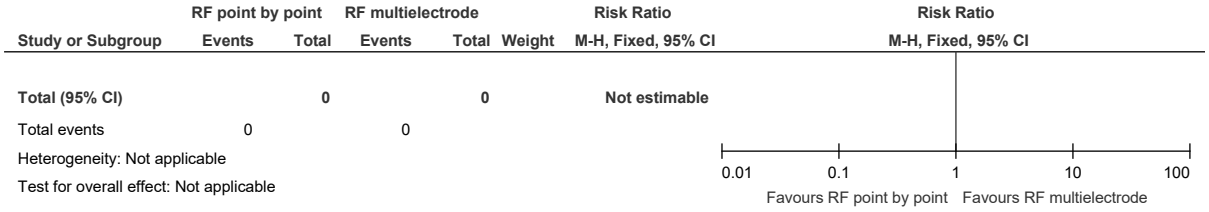
Figure 108: Recurrent symptomatic AF (post blanking period)



1

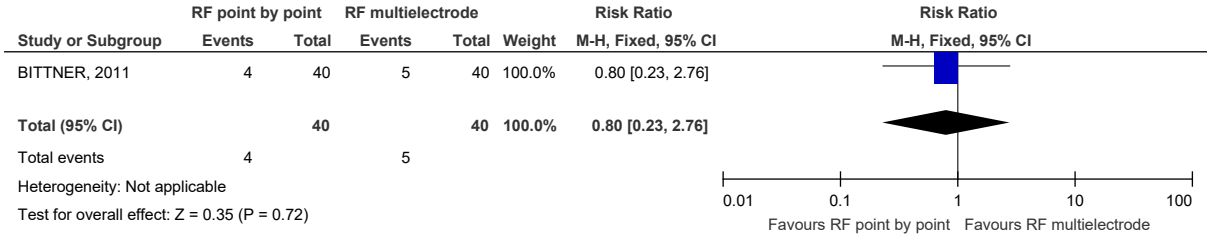
2

Figure 109: Hospitalisation with a primary diagnosis of AF



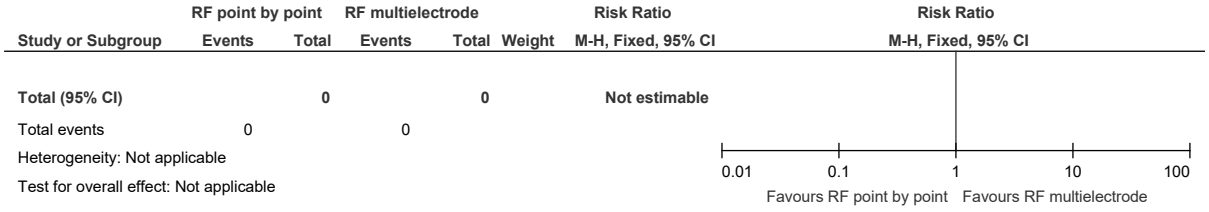
3

Figure 110: Redo of procedure



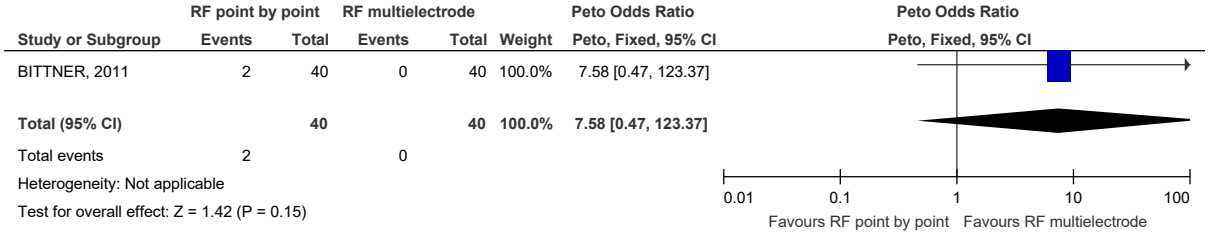
4

Figure 111: HF incidence or exacerbation



5

Figure 112: Serious AEs

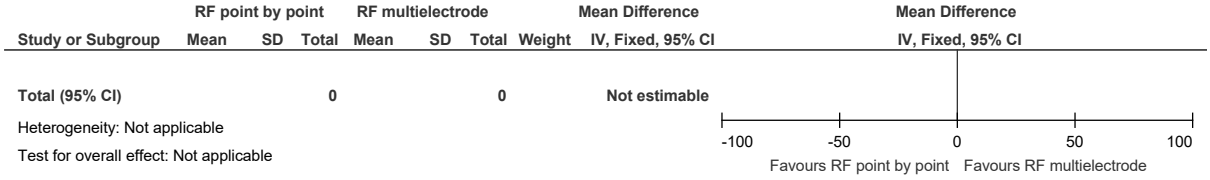


Source: <Insert Source text here>

6

1

Figure 113: Hospital length of stay



2 # RF point by point versus medical care [MIXED STRATUM]

Figure 114: Quality of life

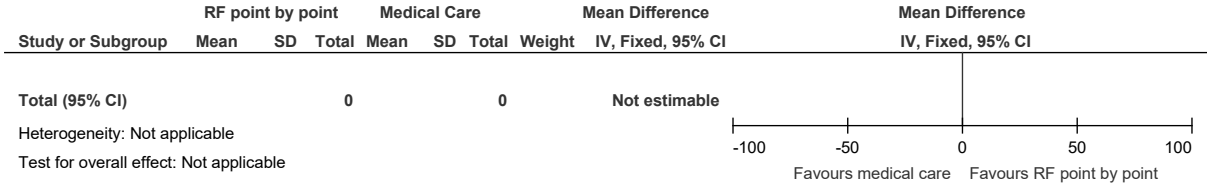


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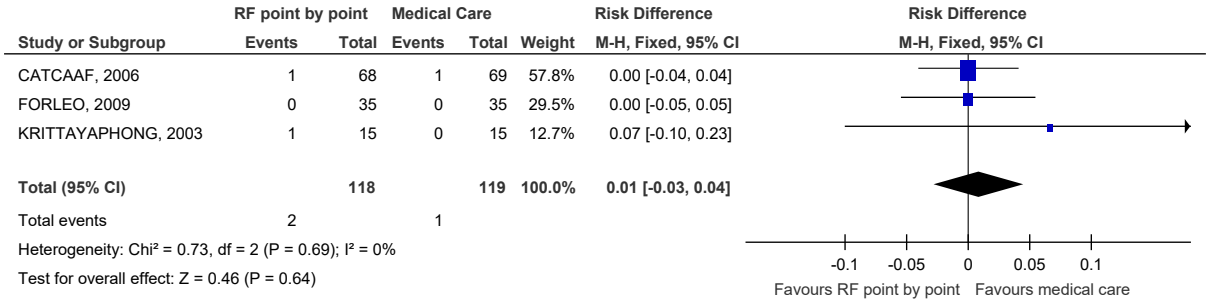
Figure 115: Stroke or thromboembolic complications



4

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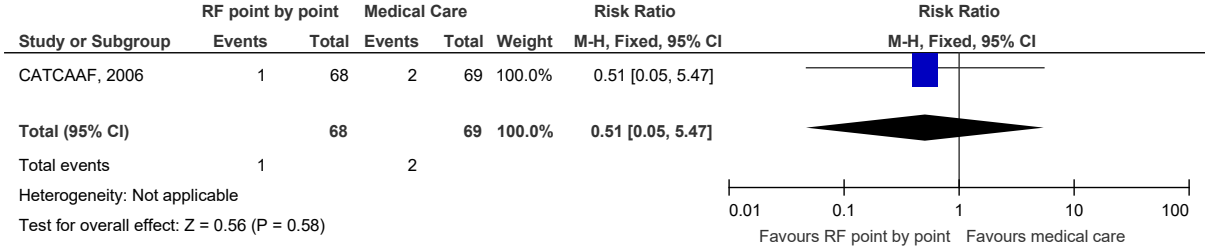
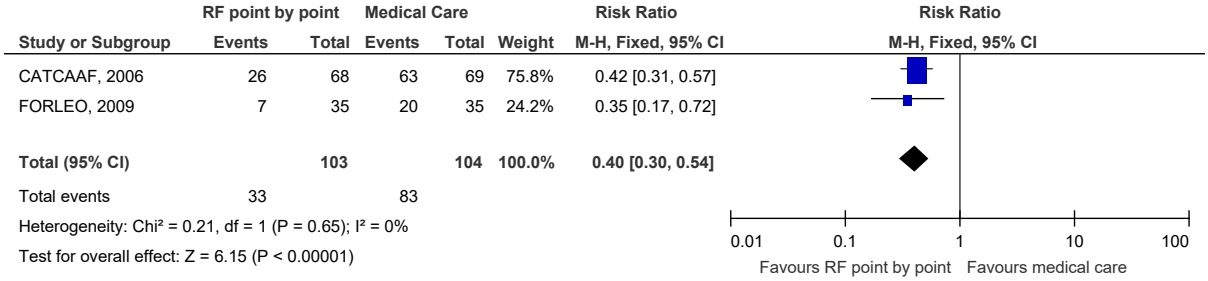
Figure 116: Mortality



6

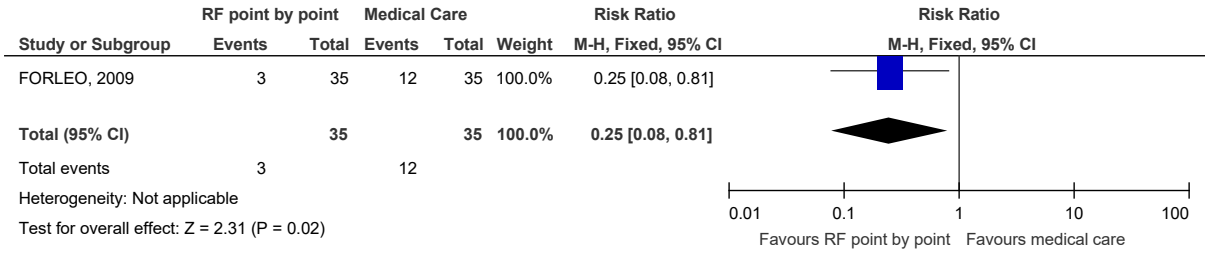
Figure 117: Recurrent symptomatic AF (post blanking period)



1

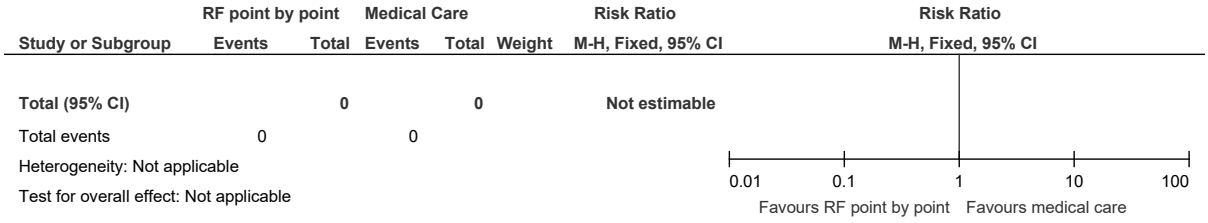
2

Figure 118: Hospitalisation with a primary diagnosis of AF



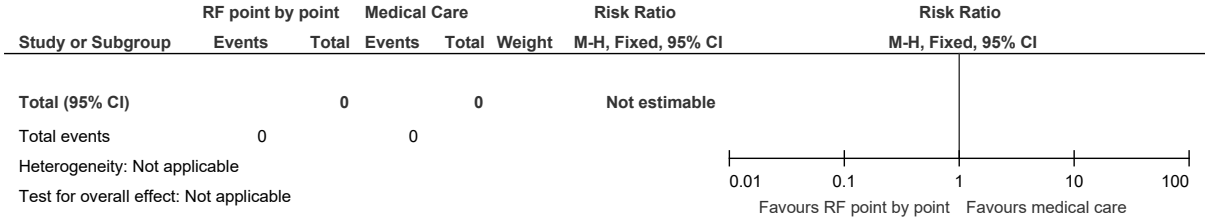
3

Figure 119: Redo of procedure



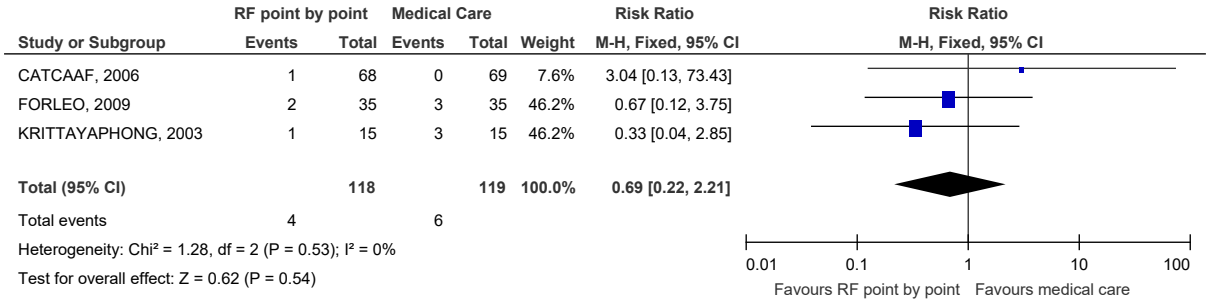
4

Figure 120: HF incidence or exacerbation



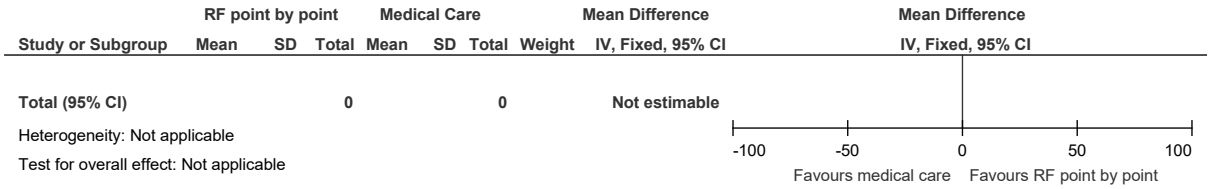
5

Figure 121: Serious AEs



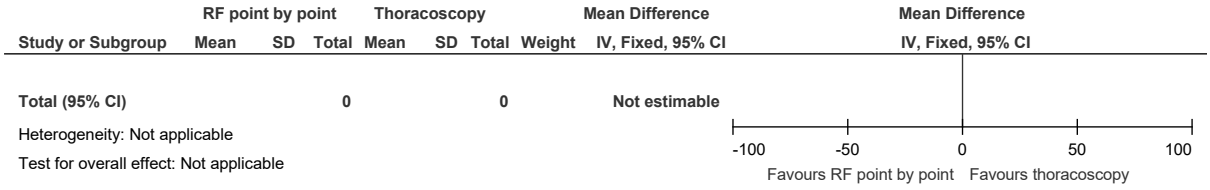
1

Figure 122: Hospital length of stay



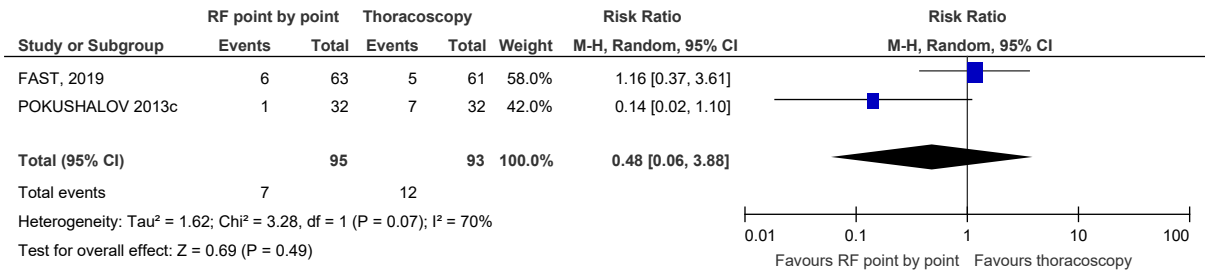
2 # RF point by point versus thoracoscopy [MIXED STRATUM]

Figure 123: Quality of life



3

Figure 124: Stroke or thromboembolic complications



4

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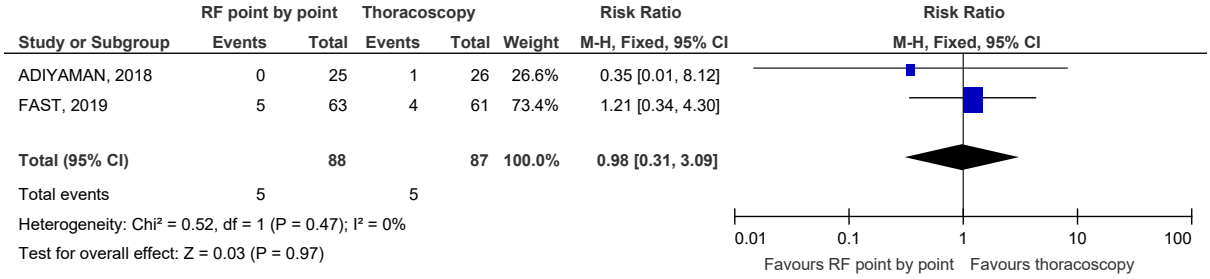
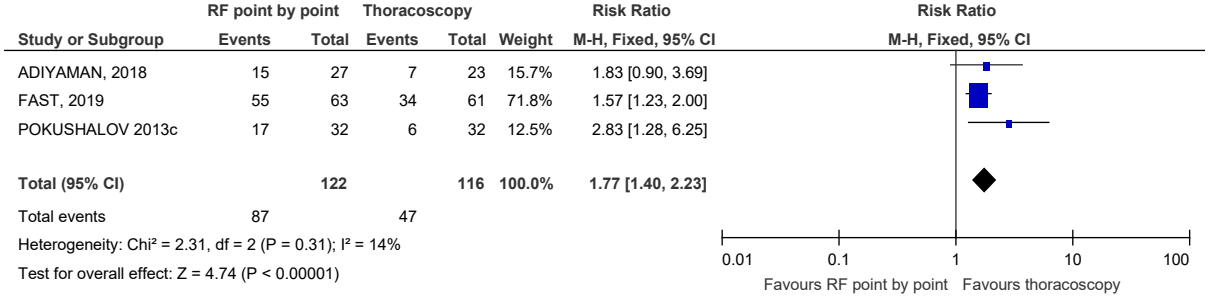
Figure 125: Mortality



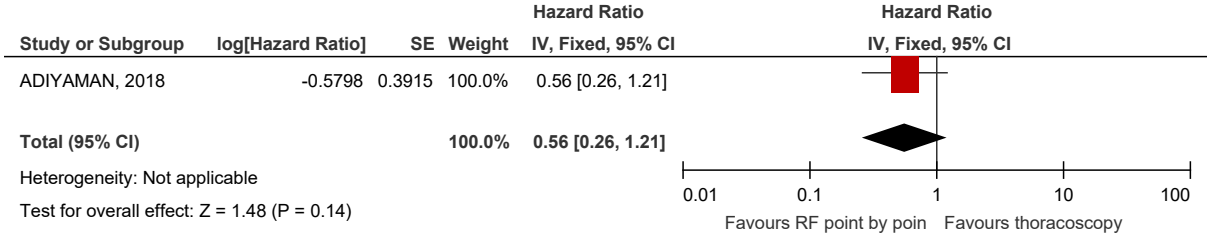
1

Figure 126: Recurrent symptomatic AF (post blanking period)



2

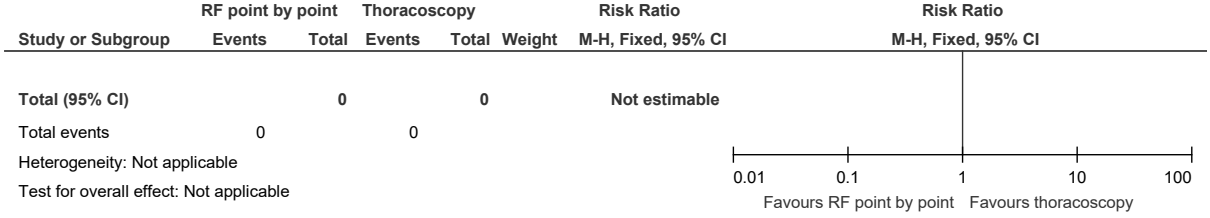
Figure 127: Recurrent AF – survival analysis



3

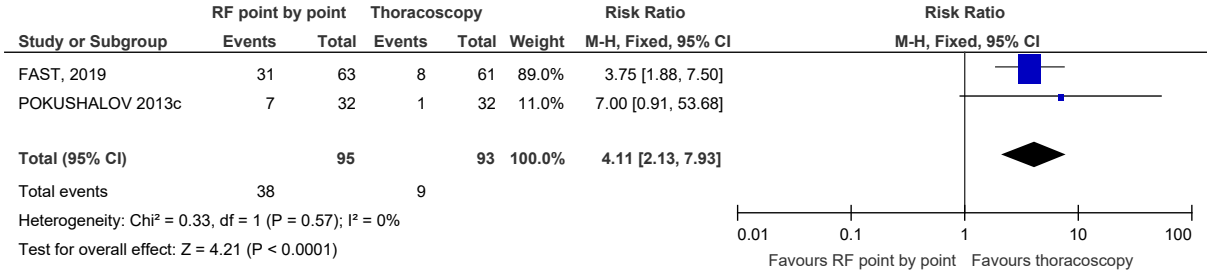
4

Figure 128: Hospitalisation with a primary diagnosis of AF



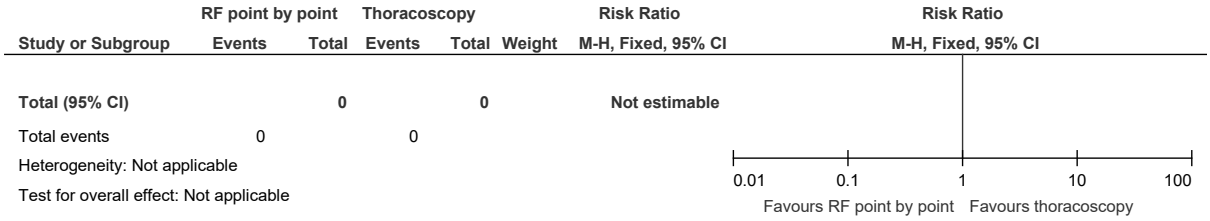
5

Figure 129: Redo of procedure



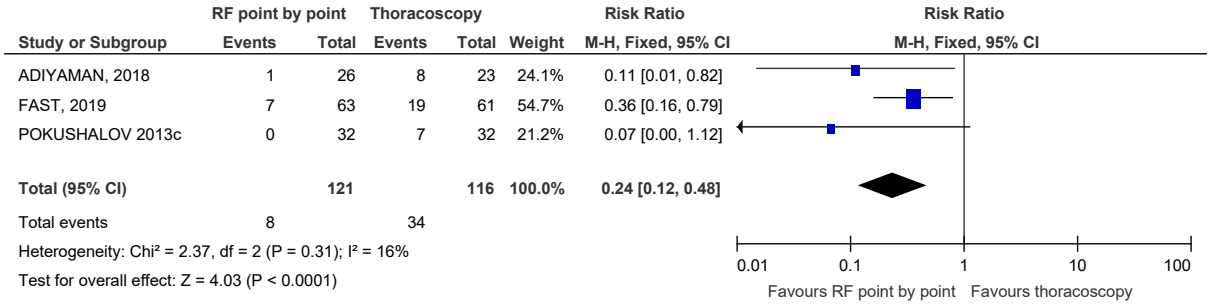
1

Figure 130: HF incidence or exacerbation



2

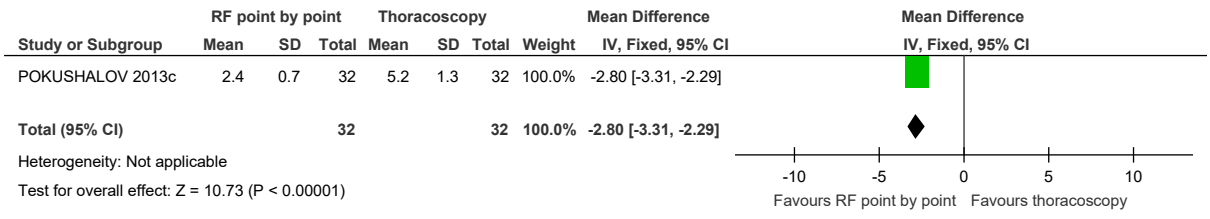
Figure 131: Serious AEs



3

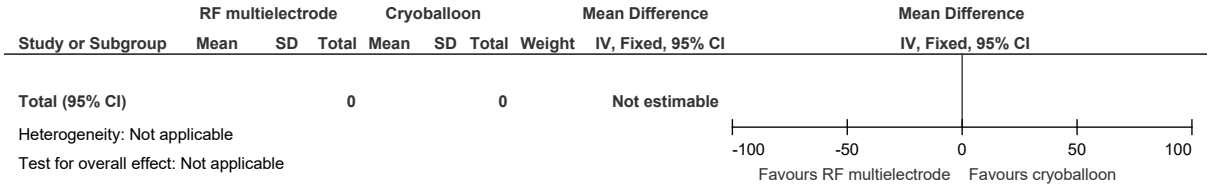
4

Figure 132: Hospital length of stay



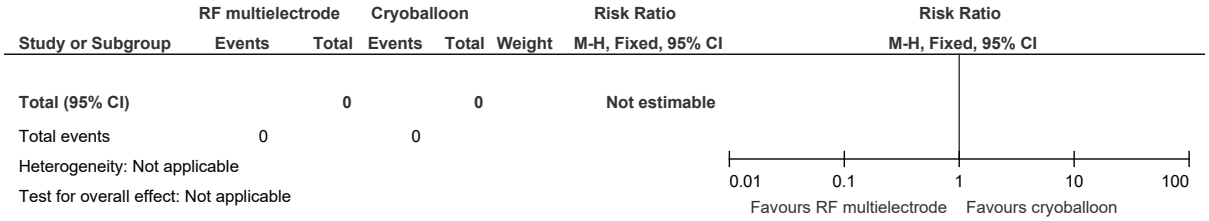
1 RF multielectrode versus cryoballoon [MIXED STRATUM]

Figure 133: Health-related quality of life



2

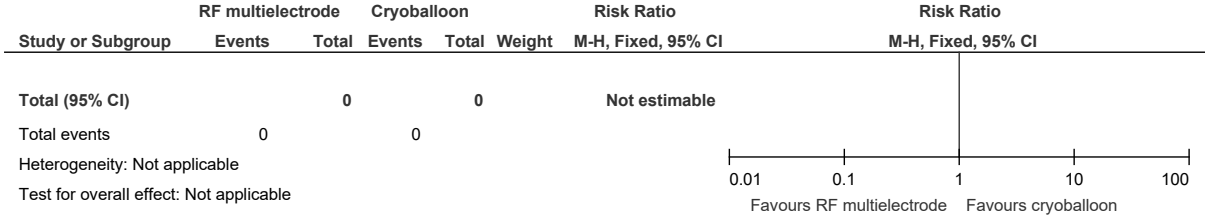
Figure 134: Stroke or thromboembolic complications



3

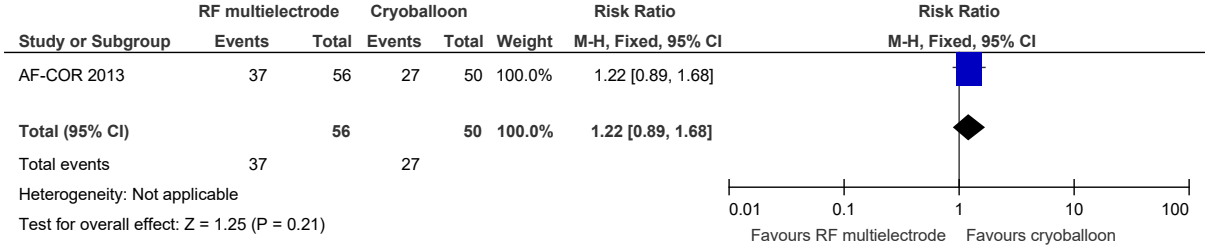
4

Figure 135: Mortality



5

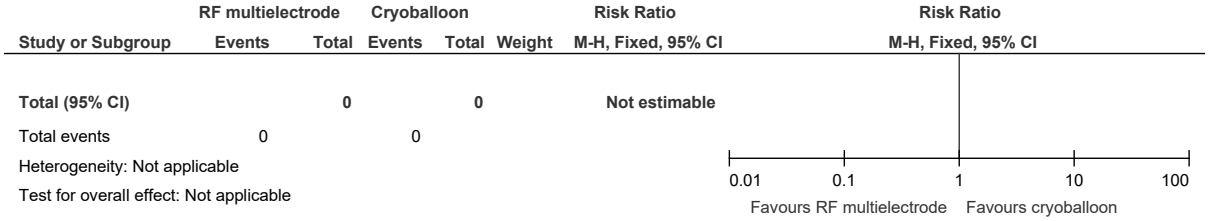
Figure 136: Recurrent symptomatic AF (post blanking period)



6

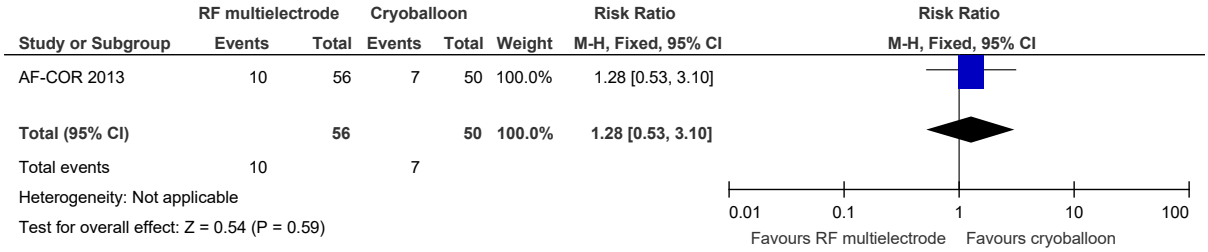
1

Figure 137: Hospitalisation with a primary diagnosis of AF



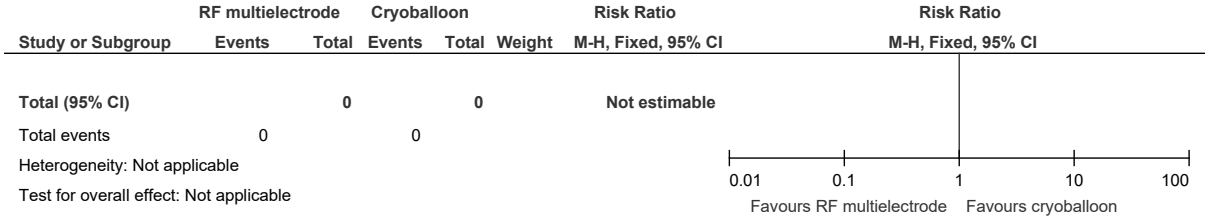
2

Figure 138: Redo of procedure



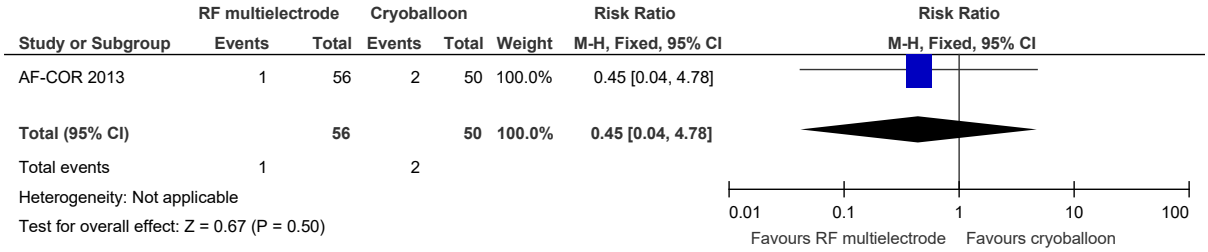
3

Figure 139: HF incidence or exacerbation



4

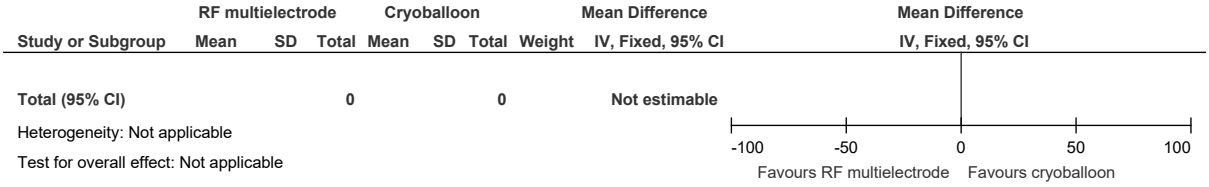
Figure 140: Serious AEs



5

6

Figure 141: Hospital length of stay

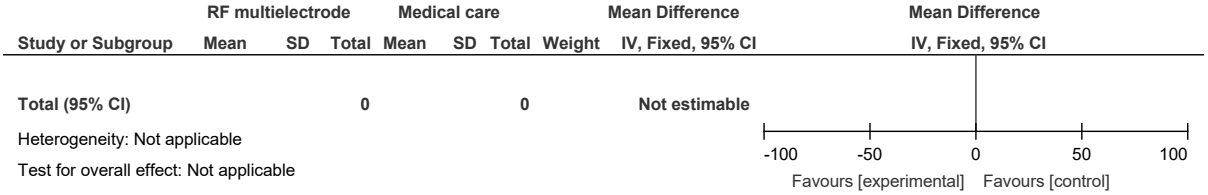


1

2

3 RF multielectrode versus medical care [MIXED STRATUM]

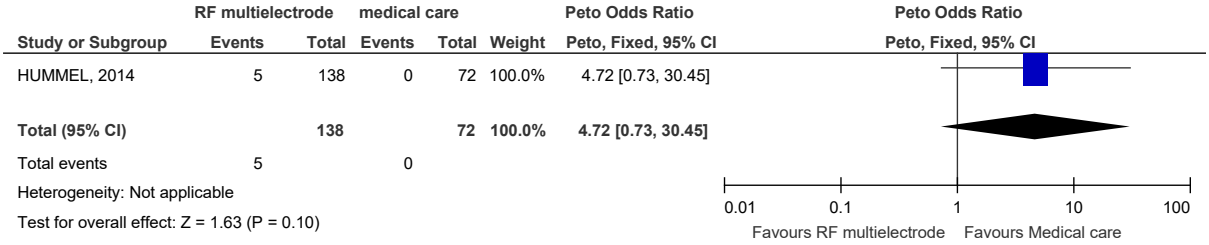
Figure 142: Health related quality of life



4

5

Figure 143: Stroke or thromboembolic complications

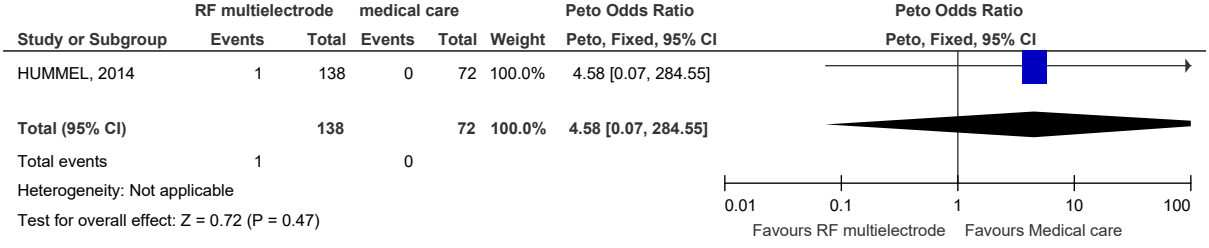


6

7

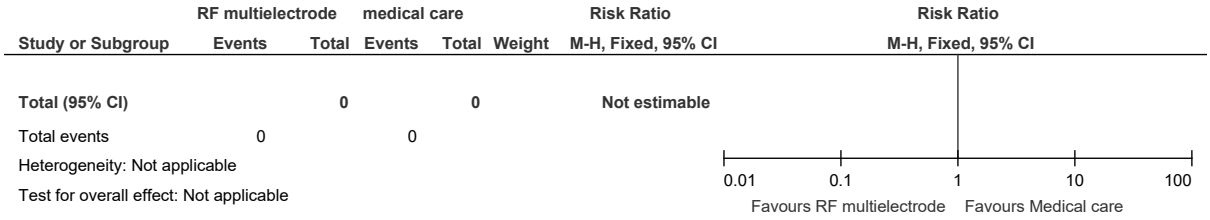
8

Figure 144: Mortality



1

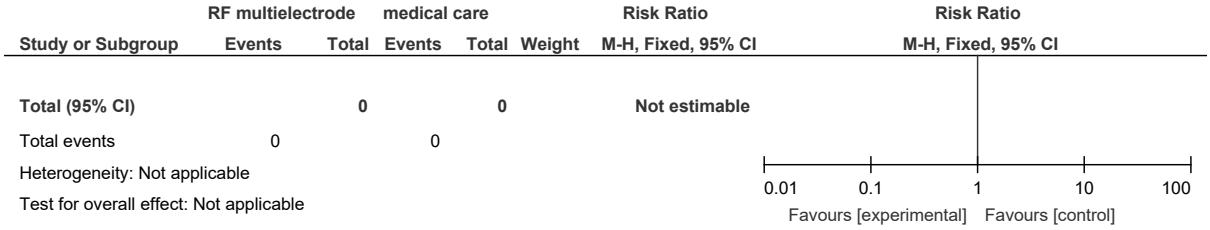
Figure 145: Recurrent symptomatic AF (post blanking period)



2

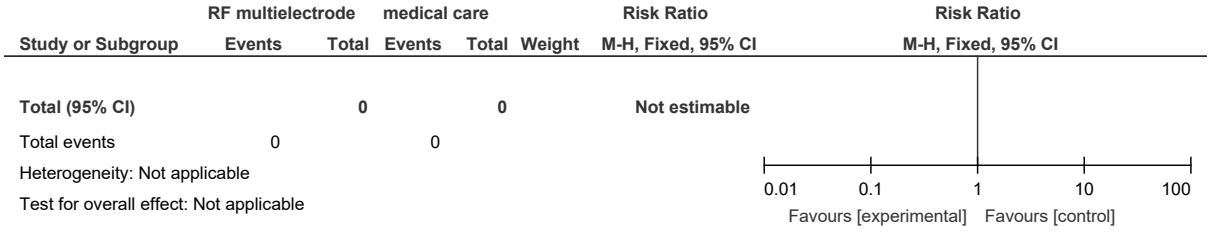
3

Figure 146: Hospitalisation with a primary diagnosis of AF



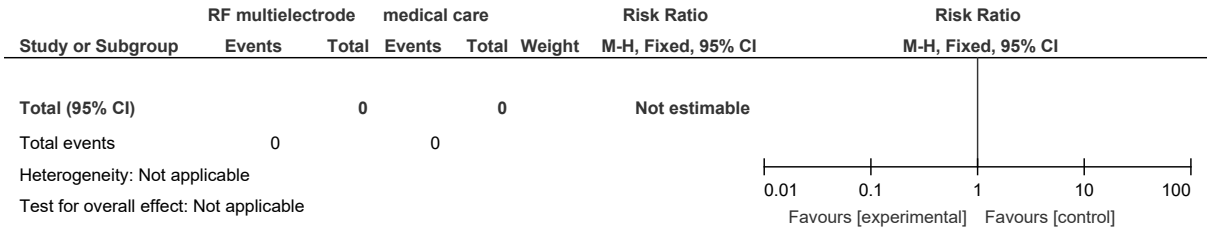
4

Figure 147: Redo of procedure



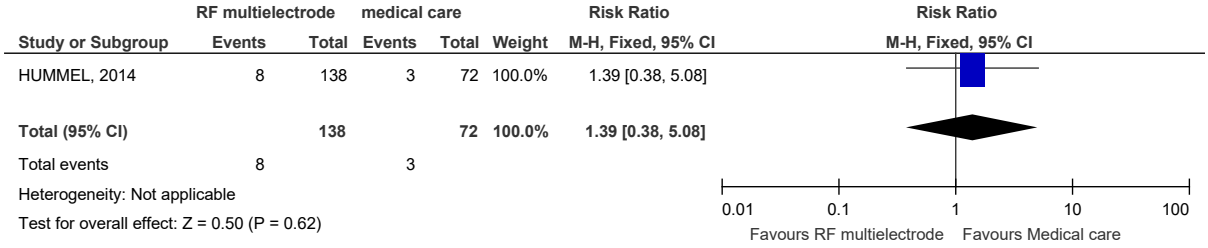
5

Figure 148: HF incidence or exacerbation



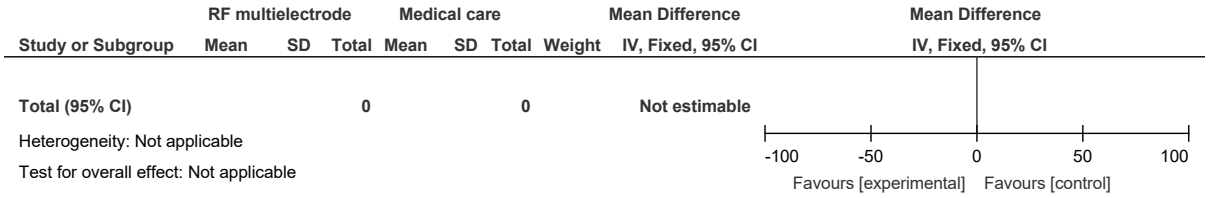
6

Figure 149: Serious AEs (chronic)



1

Figure 150: Hospital length of stay

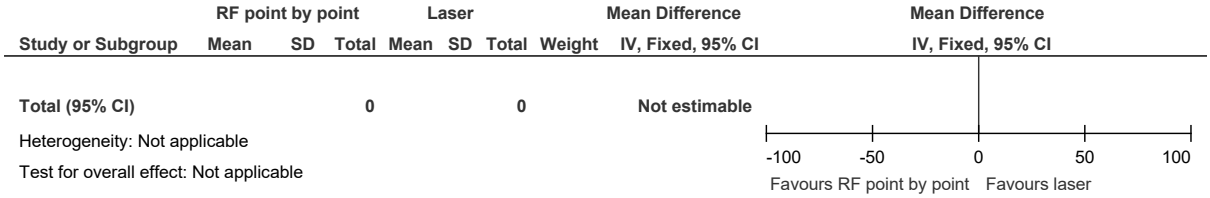


2 **PERSISTENT <1 YEAR STRATUM**

3

4 RF point by point versus laser [Persistent <1 yr STRATUM]

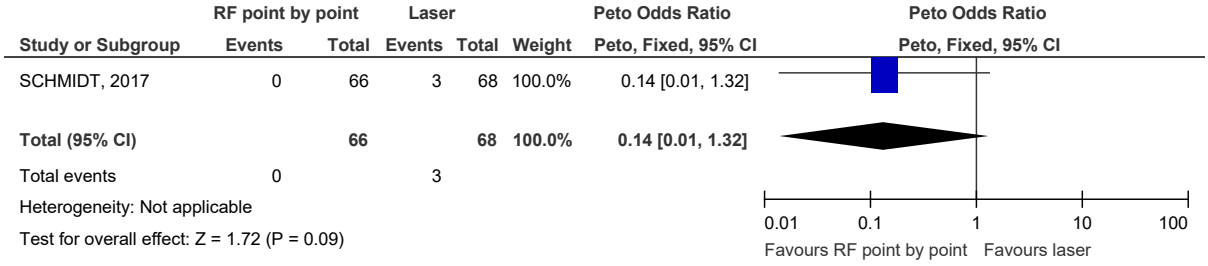
Figure 151: Health related quality of life



5

6

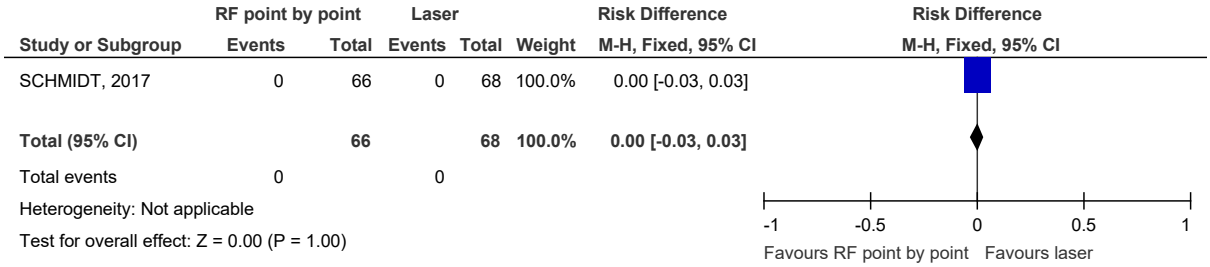
Figure 152: Stroke or thromboembolic complications



7

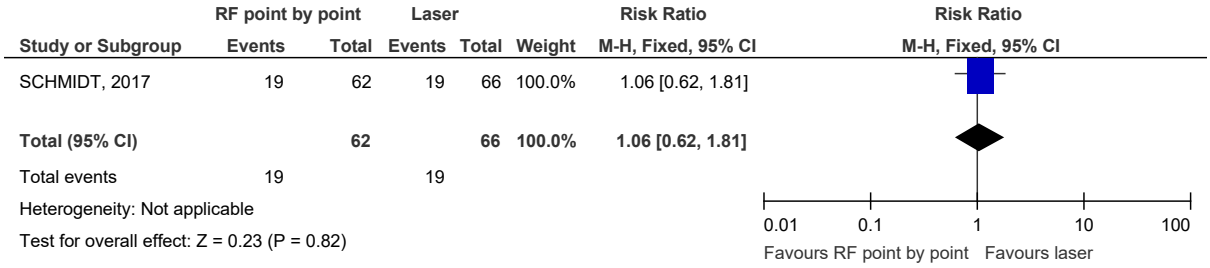
1

Figure 153: Mortality



2

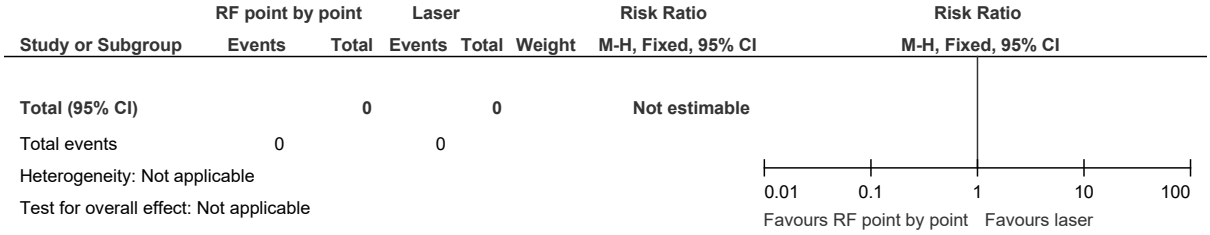
Figure 154: Recurrent symptomatic AF (post blanking period)



3

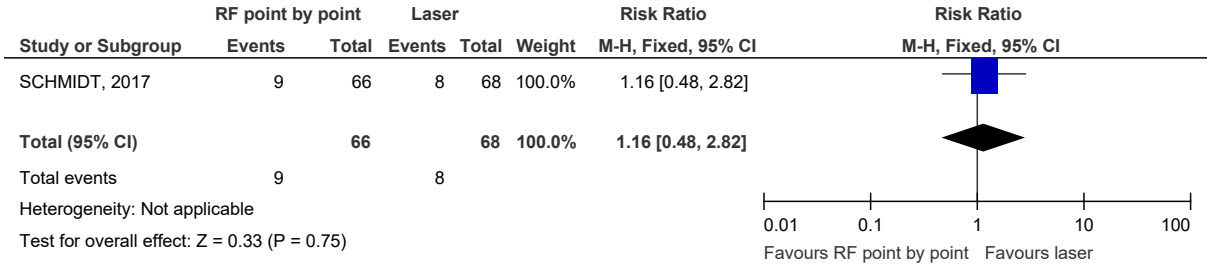
4

Figure 155: Hospitalisation with a primary diagnosis of AF



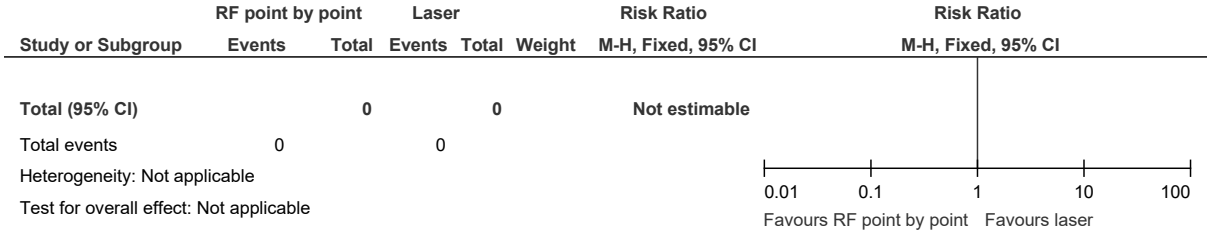
5

Figure 156: Redo of procedure



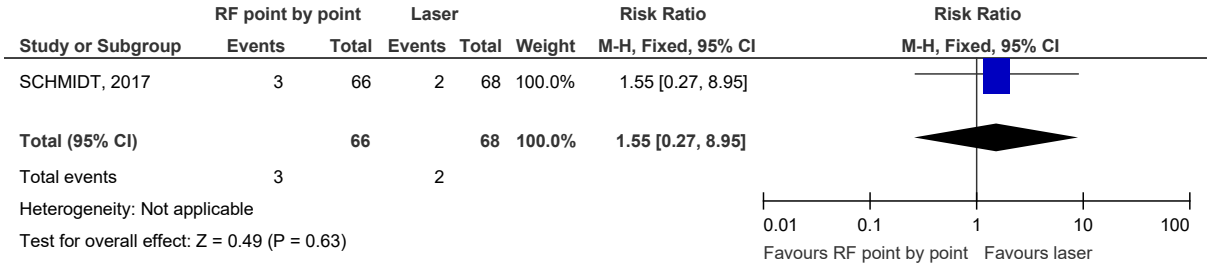
1

Figure 157: HF incidence or exacerbation



2

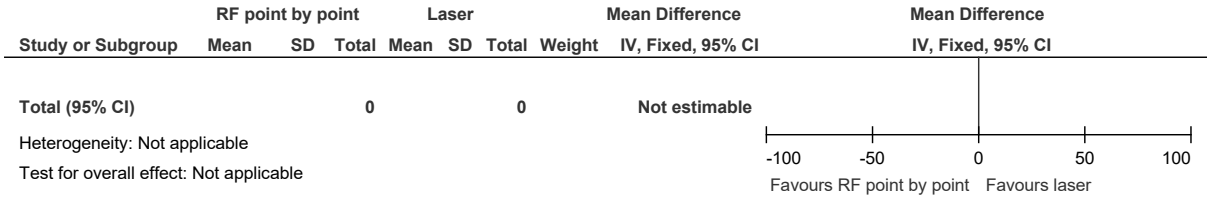
Figure 158: Serious AEs



3

4

Figure 159: Hospital length of stay



5

6

7

RF point by point versus medical care [persistent <1 year stratum]

Figure 160: Health-related quality of life AF QoL

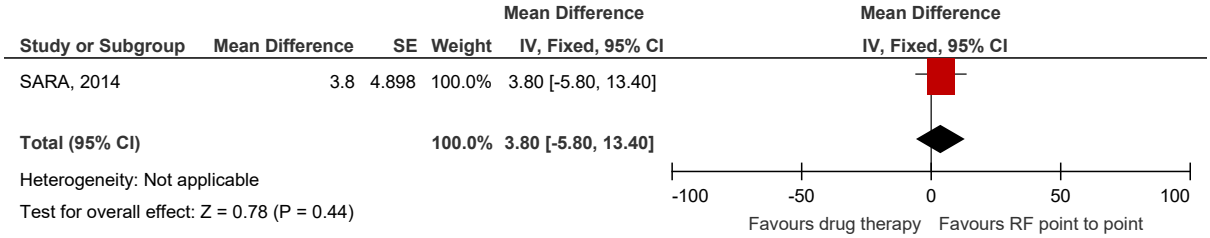


Figure 161: Health related quality of life - MLHFQ

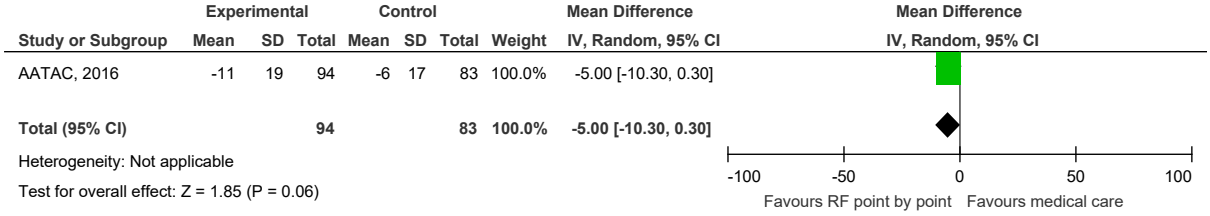


Figure 162: Stroke or thromboembolic complications

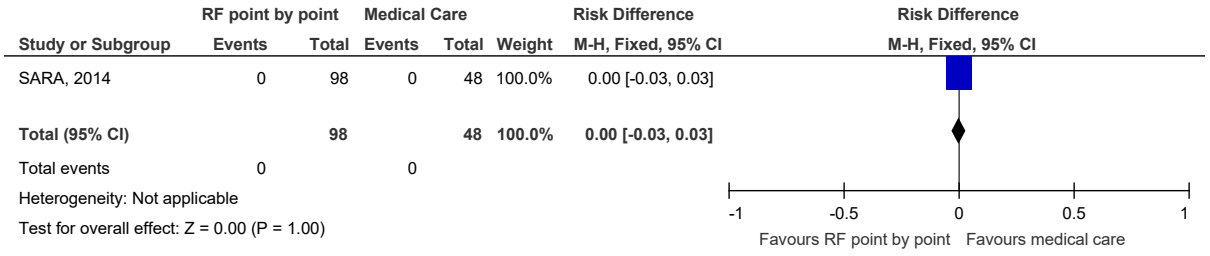
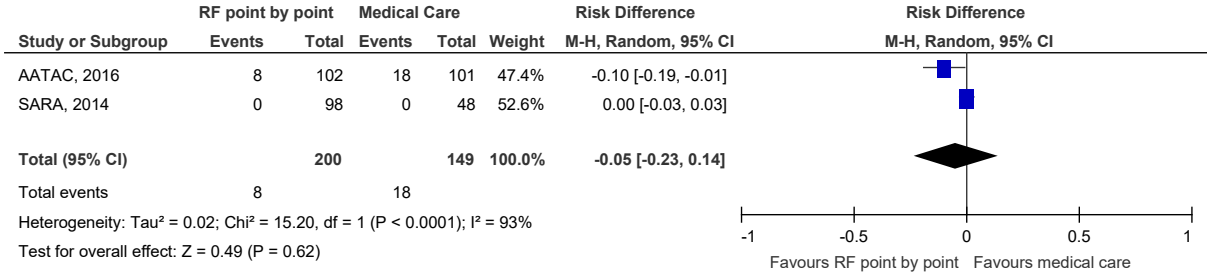
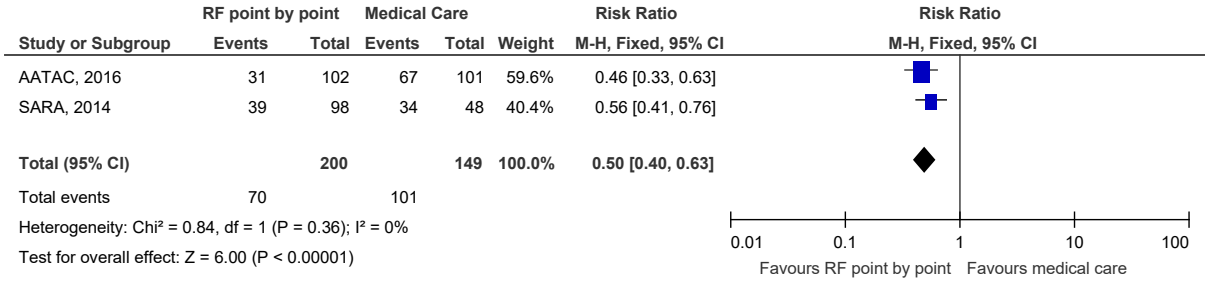


Figure 163: Mortality



1

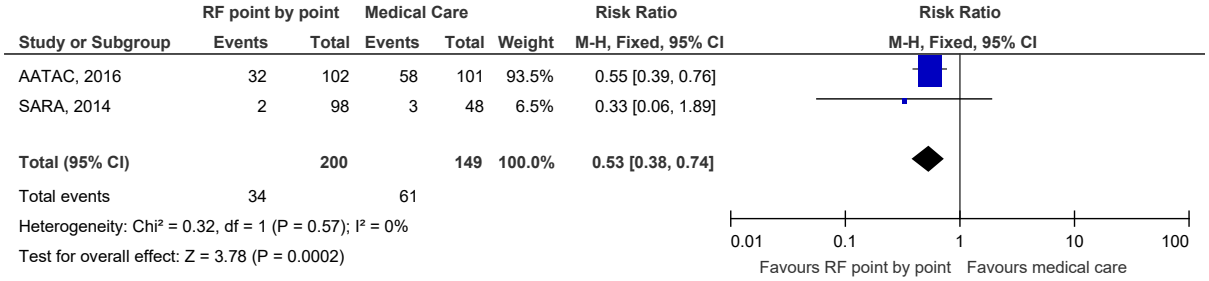
Figure 164: Recurrent symptomatic AF (post blanking period)



2

3

Figure 165: Hospitalisation with a primary diagnosis of AF



4

Figure 166: Redo of procedure

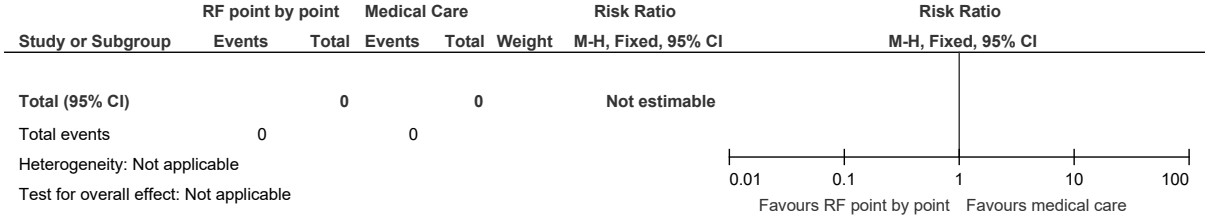


Figure 167: HF incidence or exacerbation

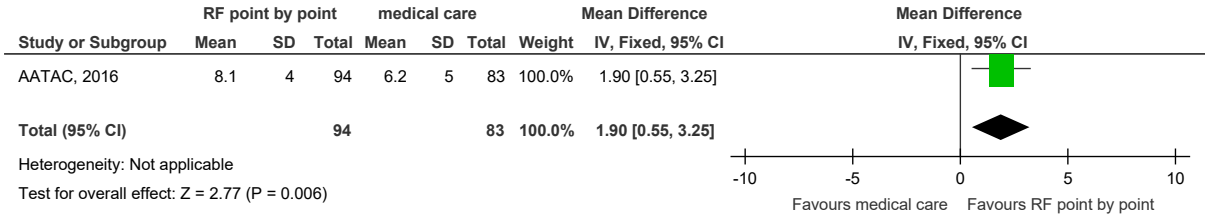


Figure 168: Serious AEs

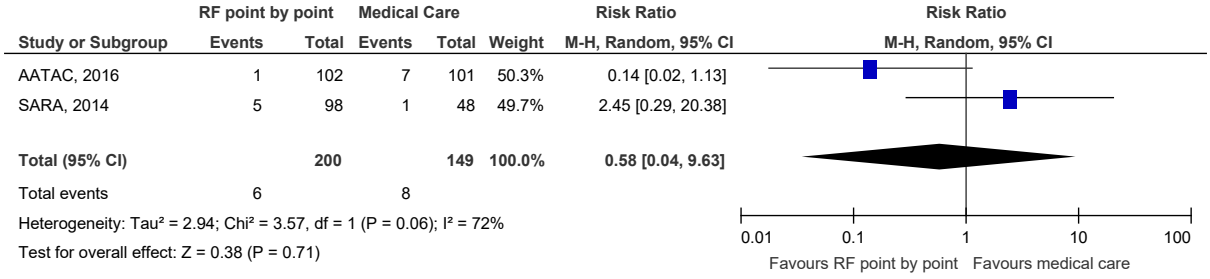
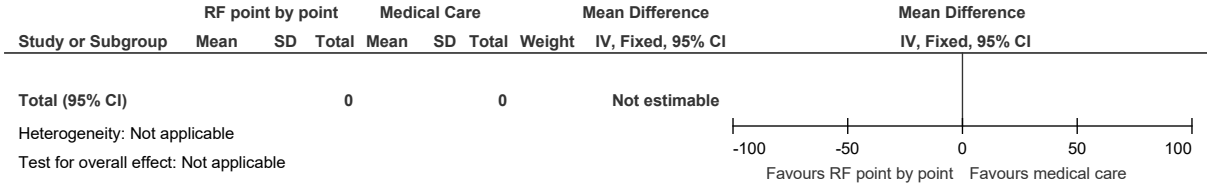


Figure 169: Hospital length of stay



PERSISTENT >1 YEAR STRATUM

RF point by point versus medical care [PERSISTENT >1 YEAR STRATUM]

Figure 170: Health related quality of life – SF36 physical

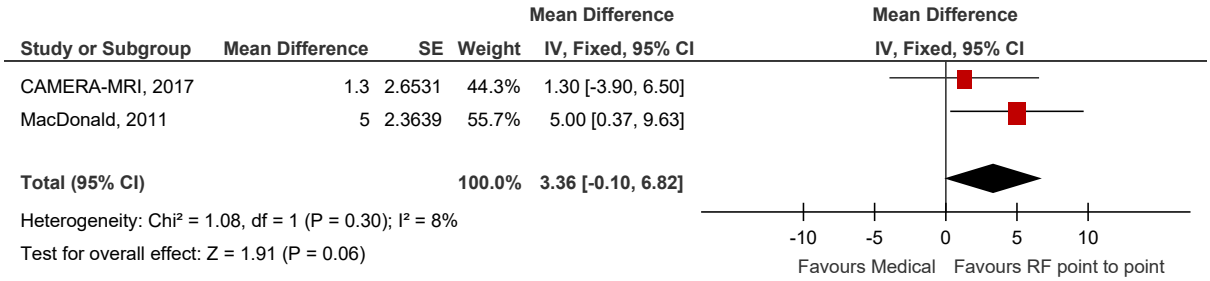


Figure 171: Quality of life – SF36 mental

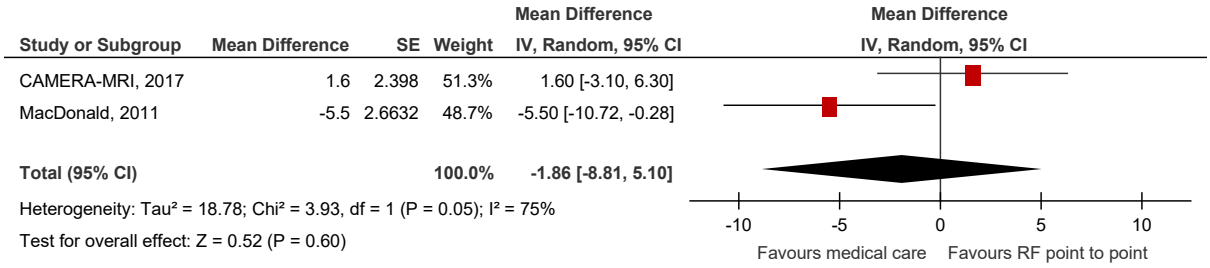


Figure 172: Stroke or thromboembolic complications

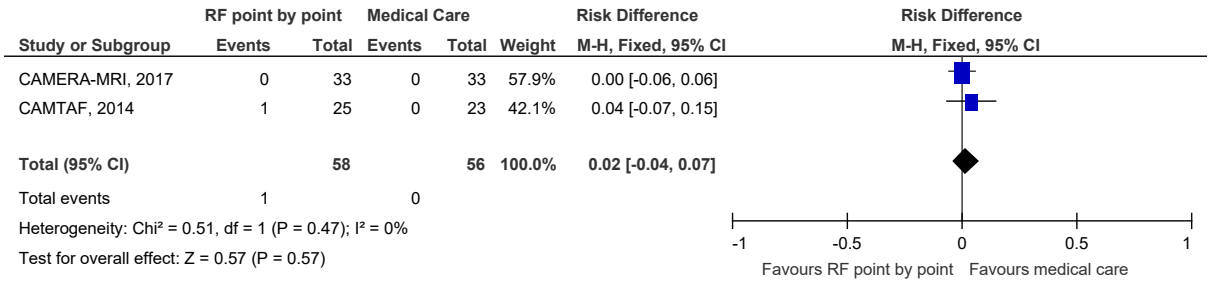


Figure 173: Mortality

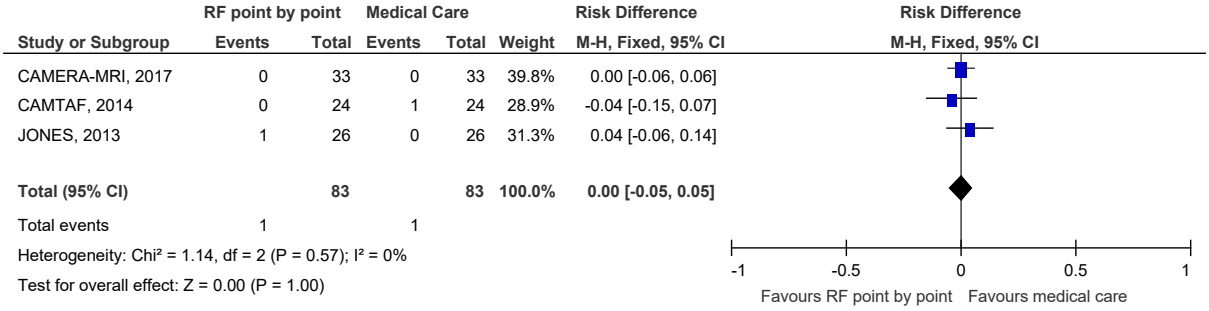


Figure 174: Recurrent symptomatic AF (post blanking period)

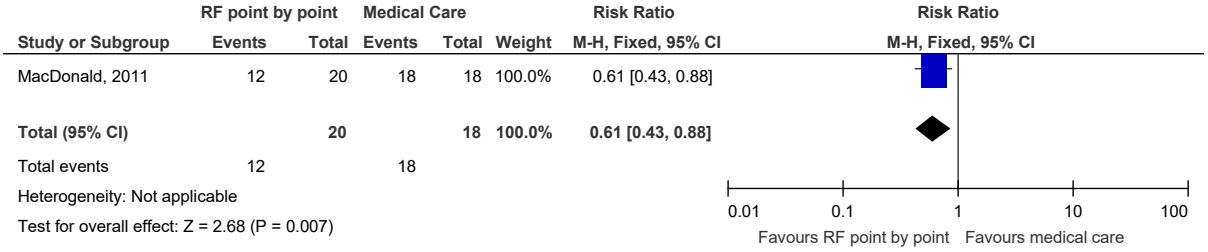


Figure 175: Hospitalisation with a primary diagnosis of AF

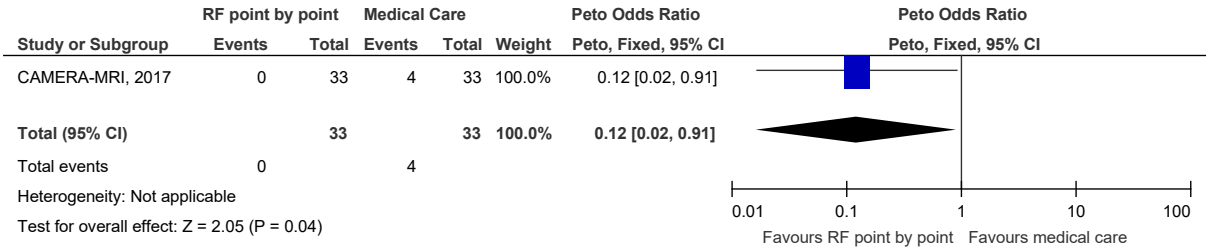
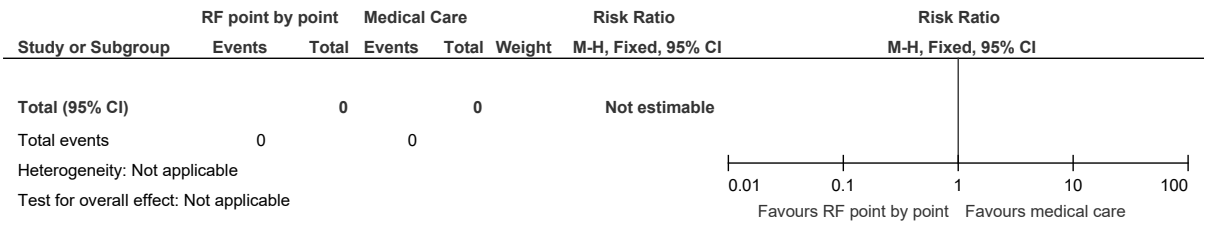
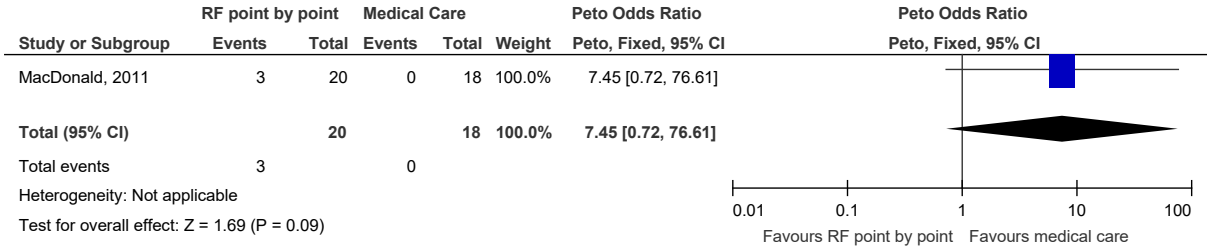


Figure 176: Redo of procedure



1

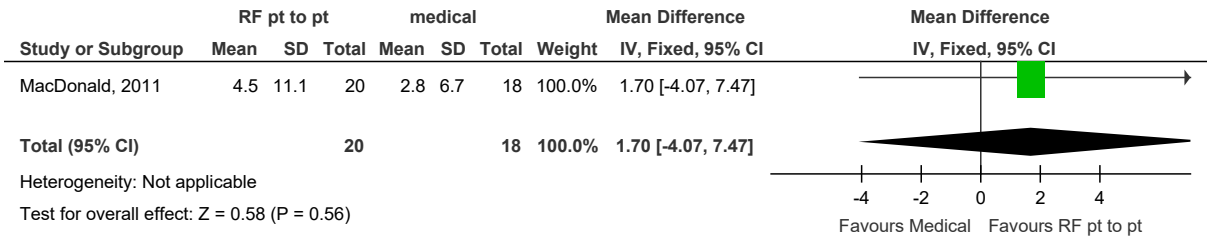
Figure 177: HF incidence or exacerbation



2

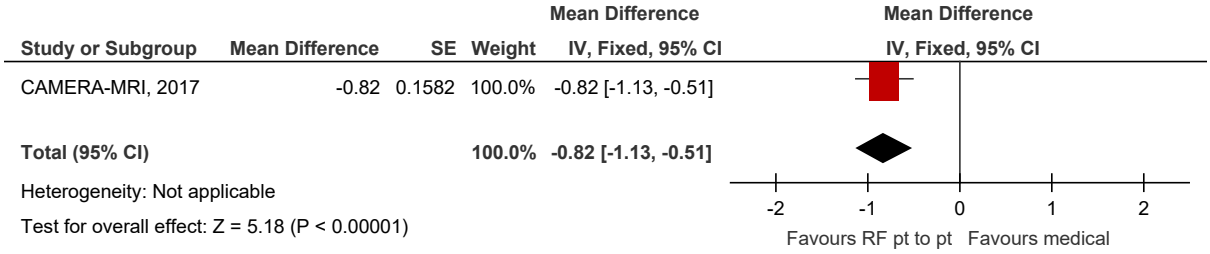
3

Figure 178: Change in LVEF



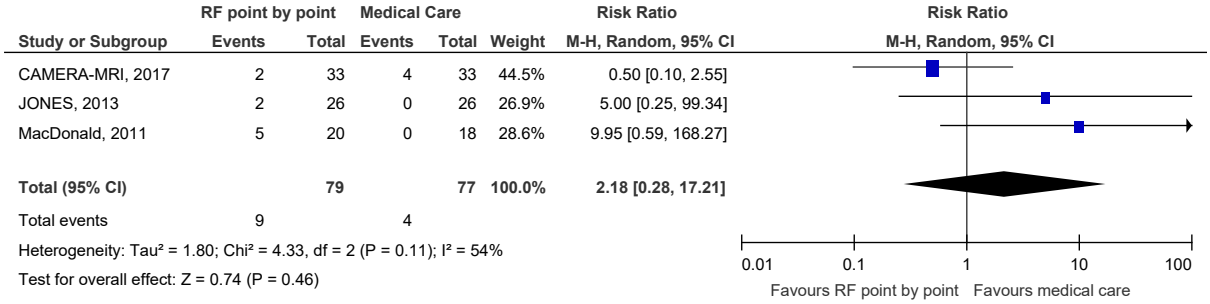
4

Figure 179: Change in NYHA grade



5

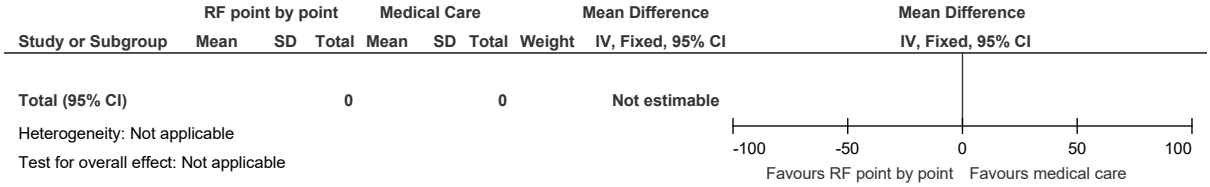
Figure 180: Serious AEs



1

2

Figure 181: Hospital length of stay



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Appendix F: GRADE tables

Table 34: Clinical evidence profile: RF point by point vs Cryoballoon [PAROXYSMAL] for AF

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RF point by point	Cryoballoon [PAROXYSMAL]	Relative (95% CI)	Absolute		
Health related quality of life SF12 mental (Better indicated by higher values)												
1	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	No serious risk of imprecision	none	50.7(9.2) [230]	51.2(9.4)[236]	-	MD 0.5 lower (2.19 lower to 1.19 higher)	LOW	CRITICAL
Health related quality of life SF12 physical (Better indicated by higher values)												
1	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	No serious risk of imprecision	none	47.8(8.4) [230]	47.0(9.2) [236]	-	MD 0.8 higher (0.8 lower to 2.4 higher)	LOW	CRITICAL
Health related quality of life EQ-5D-3L (Better indicated by higher values)												
1	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	No serious risk of imprecision	none	0.88(0.13) [254]	0.88(0.13) [257]	-	MD 0 higher (0.02 lower to 0.02 higher)	LOW	CRITICAL
Stroke or thromboembolic complications												
6	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Very serious risk of imprecision[2]	none	2/749 (0.3%)	4/861 (0.5%)	RD 0.00 (-0.01 to 0.01)	2 fewer per 1000 (from 10 fewer to 10 more)	VERY LOW	CRITICAL

asymptomatic cerebral lesions on MRI												
1	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	Serious risk of indirectness[3]	Very serious risk of imprecision[2]	none	8/33 (24.2%)	18.2%	RR 1.33 (0.52 to 3.42)	60 more per 1000 (from 87 fewer to 440 more)	VERY LOW	CRITICAL
Mortality												
6	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Very serious risk of imprecision[2]	none	1/672 (0.2%)	0.2%	RD -0.01 (-0.01 to 0.00)	2 fewer per 1000 (from 3 fewer to 0 more)	VERY LOW	CRITICAL
Recurrent symptomatic AF (post blanking period)												
7	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	Serious risk of indirectness[4]	No serious risk of imprecision	none	239/692 (34.5%)	33.3%	RR 1.00 (0.87 to 1.15)	0 fewer per 1000 (from 43 fewer to 50 more)	VERY LOW	CRITICAL
hospitalisation with a primary diagnosis of AF												
1	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	Serious risk of indirectness[5]	Serious risk of imprecision[2]	none	135/376 (35.9%)	23.8%	RR 1.51 (1.2 to 1.89)	121 more per 1000 (from 48 more to 212 more)	VERY LOW	IMPORTANT
Redo of procedure												
8	RCT	Very serious risk of bias[1]	Serious risk of inconsistency[6]	No serious risk of indirectness	Very serious risk of imprecision[2]	none	185/844 (21.9%)	26.4%	Random effects RR 0.95 (0.71 to 1.27)	13 fewer per 1000 (from 77 fewer to 71 more)	VERY LOW	CRITICAL
HF incidence or exacerbation												
0	No evidence available					none	-	0%	not pooled	not pooled		
Serious AEs												
11	RCT	Very	No serious risk of	No serious risk	Very serious risk	none	42/994	2.1%	RD -0.01 (-	3 fewer per 1000	VERY	CRITICAL

		serious risk of bias[1]	inconsistency	of indirectness	of imprecision[2]		(4.2%)		0.03 to 0.01)	(from 13 fewer to 4 more)	LOW	
Hospital length of stay (Better indicated by lower values)												
0	No evidence available					none	0	-	-	not pooled		

[1] Risk of bias was graded as very serious because the majority of studies did not report allocation concealment and blinding of patients, carers and assessors was not possible / not carried out
[2] Imprecision was graded as very serious if the confidence intervals crossed both default 'minimum important differences' (MIDs), and as serious imprecision if the confidence intervals crossed one of the MIDs. If risk differences were used because of zero events in both arms, then imprecision was decided on the basis of the optimum information size (power<0.8=very serious, power 0.8-0.89=serious)
[3] Indirectness was graded as serious because the thromboembolic complications were asymptomatic
[4] Indirectness was graded as serious because the majority of studies did not evaluate recurrence of symptomatic AF as specified in the protocol – instead most studies evaluated any AF (symptomatic or asymptomatic).
[5]Indirectness was graded as serious because hospitalisation was not specifically for AF
[6] Inconsistency was graded as serious if I^2 was between 50% and 74% and very serious if I^2 was 75% or higher

Table 35: Clinical evidence profile: RF point by point vs hybrid [PAROXYSMAL] for AF

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**RF point by point**	**Thoracoscopy [PAROXYSMAL]**	**Relative (95% CI)**	**Absolute**		
Health related quality of life												
0	No evidence available					none	0	-	-	not pooled		
Stroke or thromboembolic complications												
1	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Very serious risk of imprecision[3]	none	0/26 (0%)	0%	RD 0.00 (-0.07 to 0.07)	0 more per 1000 (from 70 fewer to 70 more)	VERY LOW	CRITICAL
Mortality												

1	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Very serious risk of imprecision[3]	none	0/26 (0%)	0%	RD 0.00 (-0.07 to 0.07)	0 more per 1000 (from 70 fewer to 70 more)	VERY LOW	CRITICAL
Recurrent symptomatic AF (post blanking period)												
1	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	Serious risk of indirectness[2]	Serious risk of imprecision[3]	none	17/26 (65.4%)	41.7%	RR 1.57 (0.91 to 2.72)	238 more per 1000 (from 38 fewer to 717 more)	VERY LOW	CRITICAL
hospitalisation with a primary diagnosis of AF												
0	No evidence available					none	-	0%	not pooled	not pooled		
Redo of procedure												
1	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Very serious risk of imprecision[3]	none	9/26 (34.6%)	16.7%	RR 2.08 (0.73 to 5.87)	180 more per 1000 (from 45 fewer to 813 more)	VERY LOW	CRITICAL
HF incidence or exacerbation												
0	No evidence available					none	-	0%	not pooled	not pooled		
Serious AEs												
1	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Serious risk of imprecision[3]	none	0/26 (0%)	12.5%	OR 0.11 (0.01 to 1.15)	110 fewer per 1000 (from 124 fewer to 16 more)	VERY LOW	CRITICAL
Hospital length of stay (Better indicated by lower values)												
0	No evidence available					none	0	-	-	not pooled		

[1] Risk of bias was graded as very serious because the majority of studies did not report allocation concealment and blinding of patients, carers and assessors was not possible / not carried out
[2] Indirectness was graded as serious because the majority of studies did not evaluate recurrence of symptomatic AF as specified in the protocol – instead most studies evaluated any AF (symptomatic or asymptomatic).

[3]Imprecision was graded as very serious if the confidence intervals crossed both default 'minimum important differences' (MIDs), and as serious imprecision if the confidence intervals crossed one of the MIDs. If risk differences were used because of zero events in both arms, then imprecision was decided on the basis of the optimum information size (power<0.8=very serious, power 0.8-0.89=serious)

Table 36: Clinical evidence profile: RF point by point vs Laser [PAROXYSMAL] for AF

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RF point by point	Laser [PAROXYSMAL]	Relative (95% CI)	Absolute		
Health related quality of life (												
0	No evidence available					none	0	-	-	not pooled		
Stroke or thromboembolic complications												
1	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Very serious risk of imprecision[2]	none	1/172 (0.58%)	1.2%	RR 0.49 (0.05 to 5.4)	6 fewer per 1000 (from 11 fewer to 53 more)	VERY LOW	CRITICAL
asymptomatic cerebral lesions on MRI												
1	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	Serious risk of indirectness[3]	Very serious risk of imprecision[2]	none	8/33 (24.2%)	24.2%	RR 1 (0.43 to 2.35)	0 fewer per 1000 (from 138 fewer to 327 more)	VERY LOW	CRITICAL
Mortality												
1	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Very serious risk of imprecision[2]	none	0/172 (0%)	0.6%	OR 0.13 (0 to 6.74)	5 fewer per 1000 (from 6 fewer to 33 more)	VERY LOW	CRITICAL
Recurrent symptomatic AF (post blanking period)												
1	RCT	Very serious risk	No serious risk of inconsistency	No serious risk of indirectness	Very serious risk of imprecision[2]	none	60/166 (36.1%)	36.5%	RR 0.99 (0.74 to	4 fewer per 1000 (from 95 fewer to	VERY LOW	CRITICAL

		of bias[1]							1.31)	113 more)		
hospitalisation with a primary diagnosis of AF												
0	No evidence available					none	-	0%	not pooled	not pooled		
Redo of procedure												
0	No evidence available					none	-	0%	not pooled	not pooled		
HF incidence or exacerbation												
0	No evidence available					none	-	0%	not pooled	not pooled		
Serious AEs												
3	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Very serious risk of imprecision[2]	none	6/230 (11.7%)	(9/228) 3.9%	RD -0.01 (-0.05 to 0.02)	13 fewer per 1000 (from 50 fewer to 20 more)	VERY LOW	CRITICAL
Hospital length of stay (Better indicated by lower values)												
0	No evidence available					none	0	-	-	not pooled		

[1] Risk of bias was graded as very serious because the majority of studies did not report allocation concealment and blinding of patients, carers and assessors was not possible / not carried out

[2] Imprecision was graded as very serious if the confidence intervals crossed both default 'minimum important differences' (MIDs), and as serious imprecision if the confidence intervals crossed one of the MIDs. If risk differences were used because of zero events in both arms, then imprecision was decided on the basis of the optimum information size (power<0.8=very serious, power 0.8-0.89=serious)

[3] Indirectness was graded as serious because the outcome was not exactly as specified in the protocol. The protocol outcome is stroke/systemic thromboembolism, and whilst asymptomatic cerebral lesions fit into the category they are not the clinical outcome that would normally be regarded as clinically important.

Table 37: Clinical evidence profile: RF point by point vs RF multielectrode [PAROXYSMAL] for AF

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RF point by point	RF multielectrode [PAROXYSMAL]	Relative (95% CI)	Absolute		
Quality of life (Better indicated by higher values)												
2	RCT	Serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	No serious risk of imprecision	none	83	84	-	SMD 0.06 lower (0.36 lower to 0.24 higher)	MODERATE	CRITICAL
Stroke or thromboembolic complications												
4	RCT	No serious risk of bias	No serious risk of inconsistency	No serious risk of indirectness	Very serious risk of imprecision[2]	none	0/404 (0%)	2/406 (0.5%)	RD 0.00 (-0.02 to 0.01)	5 fewer per 1000 (from 20 fewer to 10 more)	LOW	CRITICAL
Asymptomatic cerebral lesions												
1	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	serious risk of imprecision[2]	none	2/35 (5.7%)	22.9%	RR 0.25 (0.06 to 1.09)	172 fewer per 1000 (from 215 fewer to 21 more)	VERY LOW	CRITICAL
Mortality												
2	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Very serious risk of imprecision[2]	none	0/255 (0%)	0/255 (0%)	RD 0.00 (-0.01 to 0.01)	0 more per 1000 (from 10 fewer to 10 more)	VERY LOW	CRITICAL
Recurrent symptomatic AF (post blanking period)												
4	RCT	Serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Very serious risk of imprecision[2]	none	58/260 (25.8%)	24.9%	RR 1.03 (0.75 to 1.41)	7 more per 1000 (from 62fewer to 102 more)	VERY LOW	CRITICAL
Survival from recurrent symptomatic AF (post blanking period)												
1	RCT	Very	No serious risk of	No serious risk	Serious risk of	none	-	-	HR 1.27	-	VERY LOW	CRITICAL

		serious risk of bias[1]	inconsistency	of indirectness	imprecision[2]				(0.99 to 1.64)			
hospitalisation with a primary diagnosis of AF												
0	No evidence available					none	-	0%	not pooled	not pooled		
Redo of procedure												
2	RCT	No serious risk of bias	No serious risk of inconsistency	No serious risk of indirectness	Very serious risk of imprecision[2]	none	23/116 (19.8%)	24/117 (20.5%)	RD -0.01 (-0.11 to 0.09)	10 fewer per 1000 (from 110 fewer to 90 more)	LOW	CRITICAL
HF incidence or exacerbation												
0	No evidence available					none	-	0%	not pooled	not pooled		
Serious AEs												
5	RCT	Serious risk of bias[1]	Serious risk of inconsistency[3]	No serious risk of indirectness	Very serious risk of imprecision[2]	none	11/439 (2.5%)	6/441 (1.4%)	RD 0.01 (-0.01 to 0.03)	11 more per 1000 (from 9 fewer to 29 more)	VERY LOW	CRITICAL
Hospital length of stay (Better indicated by lower values)												
1	RCT	Serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Very serious risk of imprecision[2]	none	0	-		MD: 0 higher (0.26 lower to 0.26 higher)	VERY LOW	IMPORTANT

[1] Risk of bias was graded as very serious because the majority of studies did not report allocation concealment and blinding of patients, carers and assessors was not possible / not carried out
[2] Imprecision was graded as very serious if the confidence intervals crossed both default 'minimum important differences' (MIDs), and as serious imprecision if the confidence intervals crossed one of the MIDs. If risk differences were used because of zero events in both arms, then imprecision was decided on the basis of the optimum information size (power<0.8=very serious, power 0.8-0.89=serious). For the continuous outcome of Hospital length of stay, imprecision was very serious because the 95% Cis crossed both MIDs, which were set at 0 (sd in comparator group was 0 presumably because all had the same value for the outcome).
[3] Inconsistency was graded as serious if I^2 was between 50% and 74% and very serious if I^2 was 75% or higher

1

2 **Table 38: Clinical evidence profile: RF point by point versus medical care [PAROXYSMAL] for AF**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RF point by point	Medical care [PAROXYSMAL]	Relative (95% CI)	Absolute		
Health related quality of life SF36 Phys (Better indicated by lower values)												
5	RCT	Very serious risk of bias[1]	Serious inconsistency[2]	No serious indirectness	Serious imprecision[3]	none	463	380	-	SMD (random effects) 0.24 higher (0.02 lower to 0.51 higher)	VERY LOW	CRITICAL
Health related quality of life SF36 mental (Better indicated by lower values)												
5	RCT	Very serious risk of bias[1]	Very serious inconsistency[2]	No serious indirectness	Serious imprecision[3]	none	463	380	-	SMD (random effects) 0.41 higher (0.08 to 0.74 higher)	VERY LOW	CRITICAL
Health related quality of life EQ5D index (Better indicated by lower values)												
1	RCT	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Serious imprecision[3]	none	146	148	-	MD 0.04 higher (0 to 0.08 higher)	LOW	CRITICAL
Health related quality of life EQ5D VAS (Better indicated by lower values)												
1	RCT	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	No serious imprecision	none	146	148	-	MD 0.3 lower (3.76 lower to 3.16 higher)	MODERATE	CRITICAL
Stroke or thromboembolic complications												
4	RCT	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	none	3/343 (0.82%)	1/343 (0.3%)	RD 0.01 (-0.01 to 0.02)	6 more per 1000 (from 10 fewer to 20 more)	VERY LOW	CRITICAL
Mortality												

4	RCT	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[3]	none	6/368 (1.6%)	9/325 (2.8%)	RD -0.01 (-0.03 to 0.01)	9 fewer per 1000 (from 30 fewer to 10 more)	VERY LOW	CRITICAL
Recurrent symptomatic AF (post blanking period)												
5	RCT	Very serious risk of bias[1]	Very serious inconsistency[2]	Serious indirectness[4]	No serious imprecision	none	101/331 (30.5%)	76.4%	Random RR 0.38 (0.25 to 0.58)	474 fewer per 1000 (from 321 fewer to 573 fewer)	VERY LOW	CRITICAL
hospitalisation with a primary diagnosis of AF												
2	RCT	Very serious risk of bias[1]	No serious inconsistency	Serious indirectness[5]	No serious imprecision	none	3/178 (1.7%)	27.8%	RR 0.18 (0.06 to 0.5)	228 fewer per 1000 (from 139 fewer to 261 fewer)	VERY LOW	CRITICAL
Redo of procedure												
0							-	0%	not pooled	not pooled		
HF incidence or exacerbation												
1	RCT	Very serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[3]	none	0/99 (0%)	0%	RD 0.00 (-0.02 to 0.02)	0 more per 1000 (from 20 fewer to 20 more)	VERY LOW	CRITICAL
Serious AEs												
6	RCT	Very serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[3]	none	32/523 (6.1%)	29/474 (6.1%)	RR 1.04 (0.64 to 1.69)	3 more per 1000 (from 21 fewer to 21 more)	VERY LOW	CRITICAL
Hospital length of stay (Better indicated by lower values)												
	RCT						0	-	-	not pooled		

[1] Risk of bias was graded as very serious if the majority of studies did not report allocation concealment and blinding of patients, carers and assessors was not possible / not carried out. Risk of bias was graded as serious if allocation concealment was reported as having been adequately done, but blinding of patients, carers and assessors was not possible / not carried out.

[2] Inconsistency was graded as serious if I^2 was between 50% and 74% and very serious if I^2 was 75% or higher.

[3] Imprecision was graded as very serious if the confidence intervals crossed both default 'minimum important differences' (MIDs), and as serious imprecision if the confidence intervals crossed one of the MIDs. If risk differences were used because of zero events in both arms, then imprecision was decided on the basis of the optimum information size (power<0.8=very serious, power 0.8-0.89=serious). For the SF36 physical and mental continuous outcomes, imprecision resulted from the 95% CIs crossing the single MID of +0.5 SDs (standardised MD used because one study used a different scale to the others despite labelling the outcome as SF36), and for the EQ5D, imprecision resulted from the upper 95% CI touching the single MID of +0.08.

[4] Indirectness was graded as serious because the majority of studies did not evaluate recurrence of symptomatic AF as specified in the protocol – instead most studies evaluated any AF (symptomatic or asymptomatic).

[5]Indirectness was graded as serious because hospitalisation was not specifically for AF

Table 39: Clinical evidence profile: RF multielectrode vs Cryoballoon [PAROXYSMAL] for AF

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RF multielectrode	Cryoballoon [PAROXYSMAL]	Relative (95% CI)	Absolute		
Health related quality of life (Better indicated by higher values)												
0	No evidence available					none	0	-	-	not pooled		
Stroke or thromboembolic complications												
1	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Very serious risk of imprecision[2]	none	0/15 (0%)	0/17 (0%)	RD 0.00 (-0.11 to 0.11)	0 fewer per 1000 (from 110 fewer to 110 more)	VERY LOW	CRITICAL
Mortality												
1	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Very serious risk of imprecision[2]	none	0/15 (0%)	0/17 (0%)	RD 0.00 (-0.11 to 0.11)	0 fewer per 1000 (from 110 fewer to 110 more)	VERY LOW	CRITICAL
Recurrent symptomatic AF (post blanking period)												
1	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Very serious risk of imprecision[2]	none	10/15 (66.7%)	59.1%	RR 1.13 (0.69 to 1.86)	77 more per 1000 (from 183 fewer to 508 more)	VERY LOW	CRITICAL
hospitalisation with a primary diagnosis of AF												

0	No evidence available					none	-	0%	not pooled	not pooled		
Redo of procedure												
0	No evidence available					none	-	0%	not pooled	not pooled		
HF incidence or exacerbation												
0	No evidence available					none	-	0%	not pooled	not pooled		
Serious AEs												
1	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Very serious risk of imprecision[2]	none	2/15 (6.7%)	11.8%	RR 1.13 (0.18 to 7.09)	15 more per 1000 (from 97 fewer to 719 more)	VERY LOW	CRITICAL
Hospital length of stay (Better indicated by lower values)												
0	No evidence available					none	-	-	-	not pooled		

[1] Risk of bias was graded as very serious because the majority of studies did not report allocation concealment and blinding of patients, carers and assessors was not possible / not carried out
[2] Imprecision was graded as very serious if the confidence intervals crossed both default 'minimum important differences' (MIDs), and as serious imprecision if the confidence intervals crossed one of the MIDs. If risk differences were used because of zero events in both arms, then imprecision was decided on the basis of the optimum information size (power<0.8=very serious, power 0.8-0.89=serious)

Table 40: Clinical evidence profile: RF multielectrode vs Thoracoscopy [PAROXYSMAL] for AF

Quality assessment						No of patients		Effect			Quality	Importance

No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**RF multielectrode**	**Thoracoscopy[PAROXYSMAL]**	**Relative (95% CI)**	**Absolute**		
Quality of life (Better indicated by higher values)												
0	No evidence available					none	0	-	-	not pooled		
Stroke or thromboembolic complications												
0	No evidence available					none	-	0%	not pooled	not pooled		
Mortality												
1	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Very serious risk of imprecision[2]	none	0/49 (0%)	5%	OR 0.03 (0 to 2.39)	48 fewer per 1000 (from 50 fewer to 62 more)	VERY LOW	CRITICAL
Recurrent symptomatic AF (post blanking period)												
1	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	No serious risk of imprecision	none	14/49 (28.6%)	0%	OR 5.7 (1.58 to 20.59)	290 more per 1000 (from 140 fewer to 430 more)	LOW	CRITICAL
hospitalisation with a primary diagnosis of AF												
0	No evidence available					none	-	0%	not pooled	not pooled		
Redo of procedure												
1	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	No serious risk of imprecision	none	13/49 (26.5%)	0%	OR 5.53 (1.48 to 20.7)	270 more per 1000 (from 130 fewer to 400 more)	LOW	CRITICAL

HF incidence or exacerbation												
0	No evidence available					none	-	0%	not pooled	not pooled		
Serious AEs												
1	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	No serious risk of imprecision	none	0/49 (0%)	30%	OR 0.02 (0 to 0.15)	292 fewer per 1000 (from 240 fewer to 300 fewer)	LOW	CRITICAL
Hospital length of stay (Better indicated by lower values)												
0	No evidence available					none	0	-	-	not pooled		

[1] Risk of bias was graded as very serious because the majority of studies did not report allocation concealment and blinding of patients, carers and assessors was not possible / not carried out
[2] Imprecision was graded as very serious if the confidence intervals crossed both default 'minimum important differences' (MIDs), and as serious imprecision if the confidence intervals crossed one of the MIDs. If risk differences were used because of zero events in both arms, then imprecision was decided on the basis of the optimum information size (power<0.8=very serious, power 0.8-0.89=serious)

Table 41: Clinical evidence profile: Laser versus cryoballoon [PAROXYSMAL] for AF

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Laser versus cryoballoon [PAROXYSMAL]**	**Control**	**Relative (95% CI)**	**Absolute**		
Health related quality of life												
0	No evidence available					none	-	0%	not pooled	not pooled		
Stroke or thromboembolic complications												

0	No evidence available					none	-	0%	not pooled	not pooled		
asymptomatic cerebral lesions on MRI												
1	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	Serious risk of indirectness[2]	Very serious risk of imprecision[3]	none	8/33 (24.2%)	18.2%	RR 1.33 (0.52 to 3.42)	60 more per 1000 (from 87 fewer to 440 more)	VERY LOW	CRITICAL
Mortality												
0	No evidence available					none	-	0%	not pooled	not pooled		
Recurrent symptomatic AF (post blanking period)												
0	No evidence available					none	-	0%	not pooled	not pooled		
Hospitalisation with a primary diagnosis of AF												
0	No evidence available					none	-	0%	not pooled	not pooled		
Redo												
0	No evidence available					none	-	0%	not pooled	not pooled		
HF incidence or exacerbation												
0	No evidence available					none	-	0%	not pooled	not pooled		
serious adverse events												
1	RCT	Very serious	No serious risk	No serious risk of	Very serious risk	none	0/33	0%	RD 0.00 (-	0 more per	VERY LOW	CRITICAL

		risk of bias[1]	of inconsistency	indirectness	of imprecision[3]		(0%)		0.06 to0.06)	1000 (from 60 less to 60 more)		
Hospital length of stay (Better indicated by lower values)												
0	No evidence available					none	0	-	-	not pooled		

[1] Risk of bias was graded as very serious because the majority of studies did not report allocation concealment and blinding of patients, carers and assessors was not possible / not carried out
[2] Indirectness was graded as serious because the outcome was not exactly as specified in the protocol. The protocol outcome is stroke/systemic thromboembolism, and whilst asymptomatic cerebral lesions fit into the category they are not the clinical outcome that would normally be regarded as clinically important.
[3] Imprecision was graded as very serious if the confidence intervals crossed both default 'minimum important differences' (MIDs), and as serious imprecision if the confidence intervals crossed one of the MIDs. If risk differences were used because of zero events in both arms, then imprecision was decided on the basis of the optimum information size (power<0.8=very serious, power 0.8-0.89=serious)

Table 42: Clinical evidence profile: Cryoballoon versus medical care [PAROXYSMAL] for AF

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Cryoballoon**	**Medical care [PAROXYSMAL]**	**Relative (95% CI)**	**Absolute**		
Health related quality of life												
0	No evidence available					none	0	-	-	not pooled		
Stroke or thromboembolic complications												
1	RCT	Very serious risk of bias[1]	No serious inconsistency	No serious indirectness	Serious imprecision[2]	none	7/163 (4.3%)	0%	Peto OR 4.67 (0.95 to 22.89)	40 more per 1000 (from 10 fewer to 80 more)	VERY LOW	CRITICAL
mortality												

1	RCT	Very serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	none	1/163 (0.61%)	0%	Peto OR 4.50 (0.07 to 286.16)	10 more per 1000 (from 20 fewer to 30 more)	VERY LOW	CRITICAL
Recurrent symptomatic AF (post blanking period)												
0	No evidence available					none	-	0%	not pooled	not pooled		
Hospitalisation with a primary diagnosis of AF												
0	No evidence available					none	-	0%	not pooled	not pooled		
Redo												
0	No evidence available					none	-	0%	not pooled	not pooled		
HF incidence or exacerbation												
0	No evidence available					none	-	0%	not pooled	not pooled		
serious adverse events												
0	No evidence available					none	0	-	-	not pooled		
Hospital length of stay (Better indicated by lower values)												
0	No evidence available					none	0	-	-	not pooled		

[1] Risk of bias was graded as very serious if the majority of studies did not report allocation concealment and blinding of patients, carers and assessors was not possible / not carried out. Risk of bias was graded as serious if allocation concealment was reported as having been adequately done, but blinding of patients, carers and assessors was not possible / not carried out.

[2] Imprecision was graded as very serious if the confidence intervals crossed both default 'minimum important differences' (MIDs), and as serious imprecision if the confidence intervals crossed one of the MIDs. If risk differences were used because of zero events in both arms, then imprecision was decided on the basis of the optimum information size (power<0.8=very serious, power 0.8-0.89=serious)

[3] Indirectness was graded as serious because the majority of studies did not evaluate recurrence of symptomatic AF as specified in the protocol – instead most studies evaluated any AF (symptomatic or asymptomatic).

Table 43: Clinical evidence profile: RF point by point vs Cryoballoon [MIXED] for AF

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RF point by point	Cryoballoon [MIXED]	Relative (95% CI)	Absolute		
Quality of life (Better indicated by higher values)												
0	No evidence available					none	0	-	-	not pooled		
Stroke or thromboembolic complications												
0	No evidence available					none	-	0%	not pooled	not pooled		
Mortality												
0	No evidence available					none	-	0%	not pooled	not pooled		
Recurrent symptomatic AF (post blanking period)												
1	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Very serious risk of imprecision[2]	none	6/30 (20%)	36.7%	RR 0.55 (0.23 to 1.28)	165 fewer per 1000 (from 283 fewer to 103 more)	VERY LOW	CRITICAL
hospitalisation with a primary diagnosis of AF												
0	No evidence available					none	-	0%	not pooled	not pooled		
Redo of procedure												

1	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Very serious risk of imprecision[2]	none	6/30 (20%)	33.3%	RR 0.6 (0.25 to 1.44)	133 fewer per 1000 (from 250 fewer to 147 more)	VERY LOW	CRITICAL
HF incidence or exacerbation												
0	No evidence available					none	-	0%	not pooled	not pooled		
Serious AEs												
1	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Very serious risk of imprecision[3]	none	0/30 (0%)	3.3%	OR 0.14 0 to 6.82)	28 fewer per 1000 (from 33 fewer to 156 more)	VERY LOW	CRITICAL
Hospital length of stay (Better indicated by lower values)												
0	No evidence available					none	0	-	-	not pooled		

[1] Risk of bias was graded as very serious because the majority of studies did not report allocation concealment and blinding of patients, carers and assessors was not possible / not carried out
[2] Imprecision was graded as very serious if the confidence intervals crossed both default 'minimum important differences' (MIDs), and as serious imprecision if the confidence intervals crossed one of the MIDs. If risk differences were used because of zero events in both arms, then imprecision was decided on the basis of the optimum information size (power<0.8=very serious, power 0.8-0.89=serious)

Table 44: Clinical evidence profile: RF point by point vs RF multielectrode [MIXED] for AF

Quality assessment						No of patients	Effect		Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RF point by point	RF multielectrode [MIXED]	Relative (95% CI)	Absolute		
Quality of life (Better indicated by higher values)												
0	No evidence available					none	0	-	-	not pooled		
Stroke or thromboembolic complications												
1	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Very serious risk of imprecision[3]	none	0/40 (0%)	0%	RD 0.00 (-0.05 to 0.05)	0 more per 100 (from 50 fewer to 50 more)	VERY LOW	CRITICAL
Mortality												
1	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Very serious risk of imprecision[3]	none	0/40 (0%)	0%	RD 0.00 (-0.05 to 0.05)	0 more per 100 (from 50 fewer to 50 more)	VERY LOW	CRITICAL
Recurrent symptomatic AF (post blanking period)												
1	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	Serious risk of indirectness[2]	Very serious risk of imprecision[3]	none	13/40 (32.5%)	27.5%	RR 1.18 (0.6 to 2.32)	49 more per 1000 (from 110 fewer to 363 more)	VERY LOW	CRITICAL
hospitalisation with a primary diagnosis of AF												
0	No evidence available					none	-	0%	not pooled	not pooled		
Redo of procedure												
1	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Very serious risk of imprecision[3]	none	4/40 (10%)	12.5%	RR 0.8 (0.23 to 2.76)	25 fewer per 1000 (from 96 fewer to 220 more)	VERY LOW	CRITICAL
HF incidence or exacerbation												
0	No evidence					none	-	0%	not pooled	not pooled		

	available											
Serious AEs												
1	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Very serious risk of imprecision[3]	none	2/40 (5%)	0%	OR 7.58 (0.4 to 123.37)	50 more per 100 (from 30 fewer to 130 more)	VERY LOW	CRITICAL
Hospital length of stay (Better indicated by lower values)												
0	No evidence available					none	0	-	-	not pooled		

[1] Risk of bias was graded as very serious because the majority of studies did not report allocation concealment and blinding of patients, carers and assessors was not possible / not carried out
[2] Indirectness was graded as serious because the majority of studies did not evaluate recurrence of symptomatic AF as specified in the protocol – instead most studies evaluated any AF (symptomatic or asymptomatic).
[3]Imprecision was graded as very serious if the confidence intervals crossed both default 'minimum important differences' (MIDs), and as serious imprecision if the confidence intervals crossed one of the MIDs. If risk differences were used because of zero events in both arms, then imprecision was decided on the basis of the optimum information size (power<0.8=very serious, power 0.8-0.89=serious)

Table 45: Clinical evidence profile: RF point by point vs medical care [MIXED] for AF

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**RF point by point**	**Medical care [mixed]**	**Relative (95% CI)**	**Absolute**		
Quality of life (Better indicated by lower values)												
0	RCT						0	-	-	not pooled		CRITICAL
Stroke or thromboembolic complications												
3	RCT	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	none	2/118 (1.7%)	1/1119 (0.8%)	RD 0.01 (-0.03 to 0.04)	9 more per 100 (from 30 fewer to 40 more)	VERY LOW	CRITICAL
Mortality												
1	RCT	Serious risk	No serious	No serious	Very serious	none	1/68	2.9%	RR 0.51	14 fewer per 1000 (from	VERY	CRITICAL

		of bias[1]	inconsistency	indirectness	imprecision[2]		(1.5%)		(0.05 to 5.47)	28 fewer to 130 more)	LOW	
Recurrent symptomatic AF (post blanking period)												
2	RCT	Serious risk of bias[1]	No serious inconsistency	Serious indirectness[3]	No serious imprecision	none	33/103 (32%)	74.2%	RR 0.4 (0.3 to 0.54)	445 fewer per 1000 (from 341 fewer to 519 fewer)	LOW	CRITICAL
hospitalisation with a primary diagnosis of AF												
1	RCT	Very serious risk of bias[1]	No serious inconsistency	Serious indirectness[4]	Serious imprecision[2]	none	3/35 (8.6%)	34.3%	RR 0.25 (0.08 to 0.81)	257 fewer per 1000 (from 65 fewer to 316 fewer)	VERY LOW	CRITICAL
Redo of procedure												
0	RCT						-	0%	not pooled	not pooled		
HF incidence or exacerbation												
0	RCT						-	0%	not pooled	not pooled		
Serious AEs												
3	RCT	Very serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	none	4/118 (3.4%)	0%	RR 0.69 (0.22 to 2.21)	27 fewer per 1000 (from 67 fewer to 104 more)	VERY LOW	CRITICAL
Hospital length of stay (Better indicated by lower values)												
0	RCT						0	-	-	not pooled		

[1] Risk of bias was graded as very serious if the majority of studies did not report allocation concealment and blinding of patients, carers and assessors was not possible / not carried out. Risk of bias was graded as serious if allocation concealment was reported as having been adequately done, but blinding of patients, carers and assessors was not possible / not carried out.
[2] Imprecision was graded as very serious if the confidence intervals crossed both default 'minimum important differences' (MIDs), and as serious imprecision if the confidence intervals crossed one of the MIDs. If risk differences were used because of zero events in both arms, then imprecision was decided on the basis of the optimum information size (power<0.8=very serious, power 0.8-0.89=serious)
[3] Indirectness was graded as serious because the majority of studies did not evaluate recurrence of symptomatic AF as specified in the protocol – instead most studies evaluated any AF (symptomatic or asymptomatic).
[4]Indirectness was graded as serious because hospitalisation was not specifically for AF
[5] Inconsistency serious if I^2 from 50-74% and very serious if 75% or higher.

Table 46: Clinical evidence profile: RF point by point vs Thoracoscopy [MIXED] for AF

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RF point by point	Thoracoscopy [MIXED]	Relative (95% CI)	Absolute		
Quality of life (Better indicated by higher values)												
0	No evidence available					none	0	-	-	not pooled		
Stroke or thromboembolic complications												
2	RCT	Very serious risk of bias[1]	Serious risk of inconsistency[4]	No serious risk of indirectness	Very serious risk of imprecision[2]	none	7/95 (7.4%)	15%	Random RR 0.48 (0.06 to 3.88)	65 fewer per 1000 (from 116 fewer to 61 more)	VERY LOW	CRITICAL
Mortality												
2	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Very serious risk of imprecision[2]	none	5/88 (5.7%)	5.2%	RR 0.98 (0.31 to 3.09)	1 fewer per 1000 (from 36 fewer to 109 more)	VERY LOW	CRITICAL
Recurrent symptomatic AF (post blanking period)												
3	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	Serious risk of indirectness[3]	No serious risk of imprecision	none	87/122 (71.3%	30.4%	RR 1.77 (1.4 to 2.23)	234 more per 1000 (from 122 more to 374 more)	VERY LOW	CRITICAL
Survival from recurrent AF												
1	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	Serious risk of indirectness[3]	Very serious risk of imprecision	none	-	-	HR 0.56 (0.26 to 1.21)	-	VERY LOW	CRITICAL
hospitalisation with a primary diagnosis of AF												
0	No evidence available					none	-	0%	not pooled	not pooled		

Redo of procedure											
2	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	No serious risk of imprecision	none	38/95 (40.0%)	8.1%	RR 4.11 (2.13 to 7.93)	252 more per 1000 (from 92 more to 561 more)	LOW	CRITICAL
HF incidence or exacerbation											
0	No evidence available					none	-	0%	not pooled	not pooled		
Serious AEs											
3	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	No serious risk of imprecision	none	8/121 (6.6%)	31.2%	RR 0.24(0.12 to 0.48)	237 fewer per 1000 (from 162 fewer to 275 fewer)	LOW	CRITICAL
Hospital length of stay (Better indicated by lower values)											
1	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Very serious risk of imprecision[2]	none	32	32	-	MD 2.8 lower (3.31 to 2.29 lower)	VERY LOW	IMPORTANT

[1] Risk of bias was graded as very serious because the majority of studies did not report allocation concealment and blinding of patients, carers and assessors was not possible / not carried out
[2] Imprecision was graded as very serious if the confidence intervals crossed both default 'minimum important differences' (MIDs), and as serious imprecision if the confidence intervals crossed one of the MIDs. If risk differences were used because of zero events in both arms, then imprecision was decided on the basis of the optimum information size (power<0.8=very serious, power 0.8-0.89=serious)
[3] Indirectness was graded as serious because the majority of studies did not evaluate recurrence of symptomatic AF as specified in the protocol – instead most studies evaluated any AF (symptomatic or asymptomatic).
[4]Inconsistency was graded as serious if I^2 was between 50% and 74% and very serious if I^2 was 75% or higher

Table 47: Clinical evidence profile: RF multielectrode vs Cryoballoon [MIXED] for AF

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**RF multielectrode**	**Cryoballoon [MIXED]**	**Relative (95% CI)**	**Absolute**		
Quality of life (Better indicated by higher values)												
0	No evidence available					none	0	-	-	not pooled		
Stroke or thromboembolic complications												
0	No evidence available					none	-	0%	not pooled	not pooled		
Mortality												
0	No evidence available					none	-	0%	not pooled	not pooled		
Recurrent symptomatic AF (post blanking period)												
1	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Serious risk of imprecision[2]	none	37/56 (62.5%)	54%	RR 1.22 (0.89 to 1.68)	119 more per 1000 (from 59 fewer to 367 more)	VERY LOW	CRITICAL
hospitalisation with a primary diagnosis of AF												
0	No evidence available					none	-	0%	not pooled	not pooled		
Redo of procedure												
1	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Very serious risk of imprecision[2]	none	10/56 (17.9%)	14%	RR 1.28 (0.53 to 3.1)	39 more per 1000 (from 66 fewer to 294 more)	VERY LOW	CRITICAL
HF incidence or exacerbation												

0	No evidence available					none	-	0%	not pooled	not pooled		
Serious AEs												
1	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Very serious risk of imprecision[2]	none	1/56 (1.8%)	4%	RR 0.45 (0.04 to 4.78)	22 fewer per 1000 (from 38 fewer to 151 more)	VERY LOW	CRITICAL
Hospital length of stay (Better indicated by lower values)												
0	No evidence available					none	0	-	-	not pooled		

[1] Risk of bias was graded as very serious because the majority of studies did not report allocation concealment and blinding of patients, carers and assessors was not possible / not carried out
[2] Imprecision was graded as very serious if the confidence intervals crossed both default 'minimum important differences' (MIDs), and as serious imprecision if the confidence intervals crossed one of the MIDs. If risk differences were used because of zero events in both arms, then imprecision was decided on the basis of the optimum information size (power<0.8=very serious, power 0.8-0.89=serious)

Table 48: Clinical evidence profile: RF multielectrode vs medical care [MIXED] for AF

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**RF multielectrode**	**Medical care [MIXED]**	**Relative (95% CI)**	**Absolute**		
Health related quality of life												
0	No evidence available					none	0	-	-	not pooled		
Stroke or thromboembolic complications												
1	RCT	Very serious risk of bias[1]	No serious inconsistency	No serious indirectness	Serious imprecision[2]	none	5/138 (3.6%)	0%	OR 4.72 (0.73 to 30.45)	40 more per 1000 (from 0 fewer to 70 more)	VERY LOW	CRITICAL

mortality												
1	RCT	Very serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	none	1/138 (0.72%)	0%	Peto OR 4.58 (0.07 to 284.55)	10 more per 1000 (from 20 fewer to 30 more)	VERY LOW	CRITICAL
Recurrent symptomatic AF (post blanking period)												
0	No evidence available					none	-	0%	not pooled	not pooled		
Hospitalisation with a primary diagnosis of AF												
0	No evidence available					none	-	0%	not pooled	not pooled		
Redo of procedure												
0	No evidence available					none	-	0%	not pooled	not pooled		
HF incidence or exacerbation												
0	No evidence available					none	-	0%	not pooled	not pooled		
Chronic serious AEs												
1	RCT	Very serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	none	8/138 (5.8%)	4.2%	RR 1.39 (0.38 to 5.08)	16 more per 1000 (from 26 fewer to 171 more)	VERY LOW	CRITICAL
Hospital length of stay												
0	No evidence available					none	0	-	-	not pooled		

[1] Risk of bias was graded as very serious if the majority of studies did not report allocation concealment and blinding of patients, carers and assessors was not possible / not carried out. Risk of bias was graded as serious if allocation concealment was reported as having been adequately done, but blinding of patients, carers and assessors was not possible / not carried out.

[2] Imprecision was graded as very serious if the confidence intervals crossed both default 'minimum important differences' (MIDs), and as serious imprecision if the confidence intervals crossed one of the MIDs. If risk differences were used because of zero events in both arms, then imprecision was decided on the basis of the optimum information size (power<0.8=very serious, power 0.8-0.89=serious)

[3] Indirectness was graded as serious because the majority of studies did not evaluate recurrence of symptomatic AF as specified in the protocol – instead most studies evaluated any AF (symptomatic or asymptomatic).

1

2 **Table 49: Clinical evidence profile: RF point by point vs Laser [PERSISTENT <1 YEAR] for AF**
3

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RF point by point	Laser [PERSISTENT]	Relative (95% CI)	Absolute		
Health related quality of life (Better indicated by higher values)												
0	No evidence available					none	0	-	-	not pooled		
Stroke or thromboembolic complications												
1	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Very serious risk of imprecision[2]	none	0/66 (0%)	4.4%	OR 0.14 (0.01 to 1.32)	38 fewer per 1000 (from 44 fewer to 13 more)	VERY LOW	CRITICAL
Mortality												
1	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Very serious risk of imprecision[2]	none	0/66 (0%)	0%	RD 0.00 (-0.03 to 0.03)	0 fewer per 1000 (from 30 fewer to 30 more)	VERY LOW	CRITICAL
Recurrent symptomatic AF (post blanking period)												
1	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	Serious risk of indirectness[3]	Very serious risk of imprecision[2]	none	19/62 (30.6%)	28.8%	RR 1.06 (0.62 to 1.81)	17 more per 1000 (from 109 fewer to 233 more)	VERY LOW	CRITICAL
hospitalisation with a primary diagnosis of AF												
0	No evidence available					none	-	0%	not pooled	not pooled		

Redo of procedure												
1	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Very serious risk of imprecision[2]	none	9/66 (13.6%)	11.8%	RR 1.16 (0.48 to 2.82)	19 more per 1000 (from 61 fewer to 215 more)	VERY LOW	CRITICAL
HF incidence or exacerbation												
0	No evidence available					none	-	0%	not pooled	not pooled		
Serious AEs												
1	RCT	Very serious risk of bias[1]	No serious risk of inconsistency	No serious risk of indirectness	Very serious risk of imprecision[2]	none	3/66 (4.5%)	2.9%	RR 1.55 (0.27 to 8.95)	16 more per 1000 (from 21 fewer to 231 more)	VERY LOW	CRITICAL
Hospital length of stay (Better indicated by lower values)												
0	No evidence available					none	0	-	-	not pooled		

[1] Risk of bias was graded as very serious because the majority of studies did not report allocation concealment and blinding of patients, carers and assessors was not possible / not carried out
[2] Imprecision was graded as very serious if the confidence intervals crossed both default 'minimum important differences' (MIDs), and as serious imprecision if the confidence intervals crossed one of the MIDs. If risk differences were used because of zero events in both arms, then imprecision was decided on the basis of the optimum information size (power<0.8=very serious, power 0.8-0.89=serious)
[3]Indirectness was graded as serious because the majority of studies did not evaluate recurrence of symptomatic AF as specified in the protocol – instead most studies evaluated any AF (symptomatic or asymptomatic).

Table 50: Clinical evidence profile: RF point by point vs medical care [PERSISTENT <1 YEAR] for AF

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RF point by point	Medical care [pers <1 yr]	Relative (95% CI)	Absolute		

Quality of life AF QoL (higher better)												
1	RCT	Very serious risk of bias[1]	No serious inconsistency	No serious indirectness	No serious imprecision	none	98	48	-	MD 3.8 (-5.80 to 13.40)	LOW	CRITICAL
Quality of life MLHFQ (lower better)												
1	RCT	Very serious risk of bias[1]	No serious inconsistency	No serious indirectness	Serious imprecision[2]	none	94	83	-	MD -5 (-10.3 to 0.3)	VERY LOW	CRITICAL
Stroke or thromboembolic complications												
1	RCT	Very serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	none	0/98 (0%)	0%	RD 0.00 (-0.03 to 0.03)	0 fewer per 1000 (from 30 fewer to 30 more)	VERY LOW	CRITICAL
Mortality												
2	RCT	Serious risk of bias[1]	Very serious inconsistency[5]	No serious indirectness	Very serious imprecision[2]	none	8/200 (4%)	18/149 (12%)	RD -0.05 (-0.23 to 0.14)	50 fewer per 1000 (from 230 fewer to 140 more)	VERY LOW	CRITICAL
Recurrent symptomatic AF (post blanking period)												
2	RCT	Serious risk of bias[1]	No serious inconsistency	Serious indirectness[3]	No serious imprecision	none	70/200 (30%)	68.6%	RR 0.50 (0.4 to 0.63)	343 fewer per 1000 (from 254 fewer to 412 fewer)	LOW	CRITICAL
hospitalisation with a primary diagnosis of AF												
2	RCT	Serious risk of bias[1]	No serious inconsistency	Serious indirectness[4]	No serious imprecision	none	34/200 (17%)	31.8%	RR 0.53 (0.38 to 0.74)	149 fewer per 1000 (from 83 fewer to 197 fewer)	LOW	CRITICAL
Redo of procedure												
0	RCT						-	0%	not pooled	not pooled		
HF incidence or exacerbation (change in LVEF% - higher better)												
1	RCT	Very serious risk of bias[1]	No serious inconsistency	No serious indirectness	Serious imprecision[2]	none	94	83	-	MD +1.9 (0.55 to 3.25)	VERY LOW	CRITICAL
Serious AEs												

2	RCT	Serious risk of bias[1]	Very serious inconsistency[5]	No serious indirectness	Very serious imprecision[2]	none	6/200 (3%)	1%	Random RR 0.58 (0.04 to 9.63)	19 fewer per 1000 (from 43 fewer to 388 more)	VERY LOW	CRITICAL
Hospital length of stay (Better indicated by lower values)												
0	RCT						-	-	-	not pooled		

[1] Risk of bias was graded as very serious if the majority of studies did not report allocation concealment and blinding of patients, carers and assessors was not possible / not carried out. Risk of bias was graded as serious if allocation concealment was reported as having been adequately done, but blinding of patients, carers and assessors was not possible / not carried out.
[2] Imprecision was graded as very serious if the confidence intervals crossed both default 'minimum important differences' (MIDs), and as serious imprecision if the confidence intervals crossed one of the MIDs. If risk differences were used because of zero events in both arms, then imprecision was decided on the basis of the optimum information size (power<0.8=very serious, power 0.8-0.89=serious). For the continuous outcome of Health related quality of life (Minnesota living with HF questionnaire), imprecision was serious because the 95% CIs crossed the single MID of -8.5 points. For the continuous outcome of HF incidence or exacerbation (change in LVEF), imprecision was serious because the 95% CIs crossed the single MID of +3.1%.
[3] Indirectness was graded as serious because the majority of studies did not evaluate recurrence of symptomatic AF as specified in the protocol – instead most studies evaluated any AF (symptomatic or asymptomatic).
[4]Indirectness was graded as serious because hospitalisation was not specifically for AF
[5] Inconsistency rated serious if I^2 50% to 74% or very serious if 75% or higher.

Table 51: Clinical evidence profile: RF point by point vs medical care [PERSISTENT >1 YEAR] for AF

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**RF point by point**	**Medical care [pers >1 yr]**	**Relative (95% CI)**	**Absolute**		
Health related quality of life SF 36 Physical												
1	RCT	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Serious imprecision[2]	none	53	51		MD: 3.36 (-1.0 to 6.82)	LOW	CRITICAL
Health related quality of life SF 36 mental												
1	RCT	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Serious imprecision[2]	none	53	51		MD: -1.86 (-8.81 to 5.10)	LOW	CRITICAL
Stroke or thromboembolic complications												

2	RCT	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	none	1/58 (1.7%)	0%	RD 0.02 (-0.04 to 0.07)	20 fewer per 1000 (from 40 fewer to 70 more)	VERY LOW	CRITICAL
Mortality												
3	RCT	Very serious risk of bias[1]	Serious inconsistency[4]	No serious indirectness	Very serious imprecision[2]	none	1/83 (1.2%)	0%	RD 0.00 (-0.05 to 0.05)	0 fewer per 1000 (from 50 fewer to 50 more)	VERY LOW	CRITICAL
Recurrent symptomatic AF (post blanking period)												
1	RCT	Very serious risk of bias[1]	No serious inconsistency	Serious indirectness[5]	Serious imprecision[2]	none	12/20 (60%)	100%	RR 0.61 (0.43 to 0.88)	390 fewer per 1000 (from 120 fewer to 570 fewer)	VERY LOW	CRITICAL
hospitalisation with a primary diagnosis of AF												
1	RCT	Serious risk of bias[1]	No serious inconsistency	Serious indirectness[3]	Serious imprecision[2]	none	0/33 (0%)	12.1%	Peto OR 0.12 (0.02 to 0.91)	105 fewer per 1000 (from 10 fewer to 118 fewer)	VERY LOW	CRITICAL
Redo of procedure												
0	RCT						-	0%	not pooled	not pooled		
HF incidence or exacerbation												
1	RCT	Very serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	none	3/20 (15%)	0%	Peto OR 7.45 (0.72 to 76.61)	150 more per 1000 (from 20 fewer to 320 more)	VERY LOW	CRITICAL
Change in LVEF (Better indicated by lower values)												
1	RCT	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	none	20	18	-	MD 1.7 higher (4.07 lower to 7.47 higher)	VERY LOW	CRITICAL
Change in NYHA grade												
1	RCT	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	No serious imprecision[2]	none	33	33	-	MD 0.82 lower (1.13 lower to 0.51 lower)	MODERATE	CRITICAL
Serious AEs												

3	RCT	Serious risk of bias[1]	Serious inconsistency	No serious indirectness	Very serious imprecision	none	9/79 (11.4%)	0%	Random RR: 2.18 (0.28 to 17.21)	61 more per 1000 (from 37 fewer to 842 more)	VERY LOW	CRITICAL
Hospital length of stay (Better indicated by lower values)												
0	RCT						0	-	-	not pooled		

[1] Risk of bias was graded as very serious if the majority of studies did not report allocation concealment and blinding of patients, carers and assessors was not possible / not carried out. Risk of bias was graded as serious if allocation concealment was reported as having been adequately done, but blinding of patients, carers and assessors was not possible / not carried out.

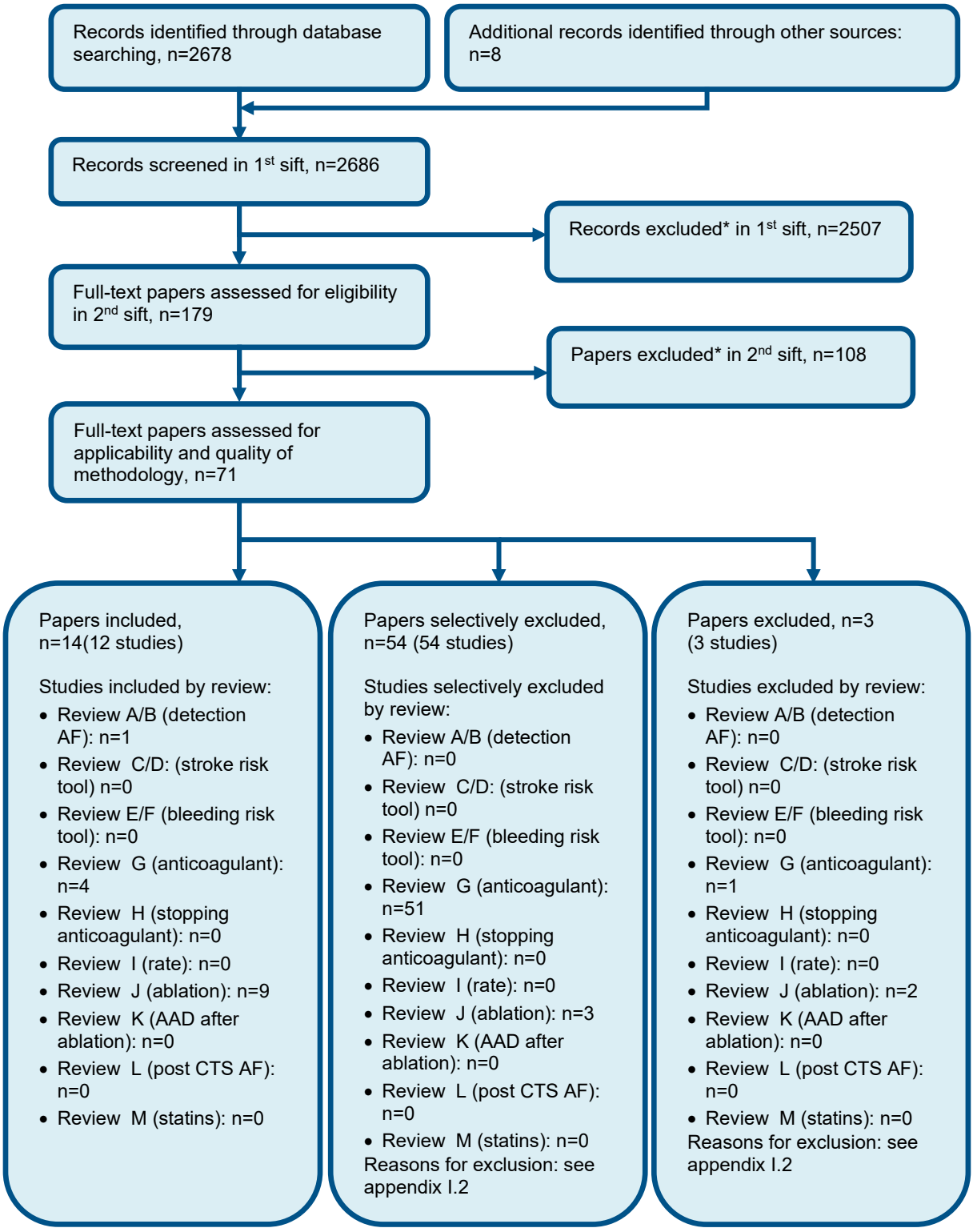
[2] Imprecision was graded as very serious if the confidence intervals crossed both default 'minimum important differences' (MIDs), and as serious imprecision if the confidence intervals crossed one of the MIDs. If risk differences were used because of zero events in both arms, then imprecision was decided on the basis of the optimum information size (power<0.8=very serious, power 0.8-0.89=serious). For the continuous outcomes of Health related quality of life SF36 physical and Health related quality of life SF36 mental, imprecision was serious because the 95% CIs crossed the single MIDs of +3.9 and +4.35 points respectively. For the continuous outcome of change in LVEF imprecision was very serious because the 95% Cis crossed both MIDs of +3.35 and -3.35.

[3]Inconsistency was graded as serious if I^2 was between 50% and 74% and very serious if I^2 was 75% or higher

[4] Indirectness was graded as serious because the majority of studies did not evaluate recurrence of symptomatic AF as specified in the protocol – instead most studies evaluated any AF (symptomatic or asymptomatic).

[5] Indirectness was graded as serious because the majority of studies did not evaluate recurrence of symptomatic AF as specified in the protocol – instead most studies evaluated any AF (symptomatic or asymptomatic).

Appendix G: Health economic evidence selection



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix H: Health economic evidence tables

H.1 First line

Study	Aronsson 2015[16]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Probabilistic decision analytic model **Approach to analysis:** Markov model. Health states include AF, normal sinus rhythm, thromboembolic events (ischaemic and haemorrhagic stroke), MI, bleeding, toxicity (adverse drug events), and death (cardiac and non-cardiac). Depending on AF status, patients were able to crossover from antiarrhythmic drugs to radiofrequency ablation or have repeat ablations (up to three times). 1 month cycle duration. **Perspective:** Swedish	**Population:** Patients with symptomatic paroxysmal AF with at least two episodes of documented AF within the preceding 6 months and where rhythm-control therapy was considered appropriate. **Cohort settings:** Start age: Intervention 1: 54 (SD: 10) Intervention 2: 56 (SD: 9) Male: Intervention 1: 72% Intervention 2: 68% **Intervention 1:** Antiarrhythmic drug therapy: either flecainide 200mg OD or propafenone 600mg OD. Class III agents also allowed.	**Total costs (mean per patient):** Intervention 1: NR Intervention 2: NR Incremental (2−1): £2,722 (95% CI: NR; p=NR) **Currency & cost year:** 2012 Euros (presented here as 2012 UK pounds[(b)]) **Cost components incorporated:** Ablation procedure, hospitalisation, stroke care first year (by stroke type) and subsequent years, cardioversion, electrocardiography, transthoracic echocardiogram, transoesophageal echocardiogram, X-Ray, Holter monitoring, computed tomography warfarin, antiarrhythmic	**QALYs (mean per patient):** Intervention 1: NR Intervention 2: NR Incremental (2−1): 0.06 (95% CI: NR; p=NR)	**ICER (Intervention 2 versus Intervention 1):** £45,385 per QALY gained (pa) 95% CI: Probability Intervention 2 cost effective (£20K/30K threshold): NR. **Analysis of uncertainty:** When visualising 1,000 samples from probabilistic sensitivity analysis on the cost effectiveness plane, samples are spread across all four quadrants indicating uncertainty. Results of lifetime model also presented stratified by age, this was done due to differences in outcomes observed between two age groups in MANTRA PAF trial (including incidence of hospital visits number of ablation procedures and AF burden) : • ≤50 years ICER 2 vs 1: £3,082 per QALY. Probability Intervention 2 cost effective (£45K threshold): 90% • >50 years ICER 2 vs. 1: £97,768 per QALY One way sensitivity analyses conducted

health care **Time horizon:** lifetime **Treatment effect duration:**[(a)] 2 years **Discounting:** Costs: 3%; Outcomes: 3%	**Intervention 2:** Radiofrequency ablation	drugs		for each age strata. Both groups sensitive to the readiness of offering crossovers and changes in the cost of ablation. Older strata sensitive to recurrence of AF and discount rates.
Data sources				
Health outcomes: AF stroke risk taken from RELY RCT, normal sinus rhythm stroke risk taken from AFFIRM trial. Effectiveness data taken from published and unpublished data from MANTRA-PAF RCT.[56, 253] Probability of experiencing AF at 24 months was 0.29 and 0.15 for antiarrhythmic drugs and ablation respectively and probability of those receiving antiarrhythmic drugs crossing over to ablation was 0.36 over 2 years. Beyond two years recurrence rate of AF following ablation was based on a meta-analysis of studies with time horizon ≥5 years (0.8), and for antiarrhythmic drugs was based on a longitudinal observational study Pappone 2003. **Quality-of-life weights:** EQ-5D from MANTRA-PAF trial with UK tariff applied, 24 month QALY weights from MANTRA-PAF, adjusted for age as the individuals became older were use in model. Utility decrements applied for symptomatic AF and stroke. Unclear methodological reporting, potential double counting. **Cost sources:** Resource use from MANTRA-PAF. Unit costs from Linkoping University Hospital and Southeast Healthcare region of Sweden.				
Comments				
Source of funding: Danish heart foundation and Biosense Webster. **Limitations:** Swedish health care payer perspective may not reflect current NHS context, does not include all comparators. Baseline and relative treatment effects not based on systematic review of the literature. Effectiveness based on a single RCT and may not reflect full body of evidence. Unclear methodological reporting. Potential financial conflict of interest funded by manufacturer of ablation instruments. **Other:**				
Overall applicability:[(c)] Partially applicable		**Overall quality:**[(d)] Potential serious limitations		

Abbreviations: 95% CI= 95% confidence interval; AF= atrial fibrillation; CUA= cost–utility analysis; da= deterministic analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER= incremental cost-effectiveness ratio; MI= myocardial infarction; NR= not reported; OD= once daily; pa= probabilistic analysis; SD= standard deviation; QALYs= quality-adjusted life years

For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(a) Converted using 2012 purchasing power parities[182]

(b) Directly applicable / Partially applicable / Not applicable

(c) Minor limitations / Potentially serious limitations / Very serious limitations

H.2 Second line

Study	**Eckard 2009[72]**			
Study details	**Population &**	**Costs**	**Health outcomes**	**Cost effectiveness**

	interventions			
Economic analysis: CUA (health outcome: QALYs) **Study design:** Probabilistic decision analytic model **Approach to analysis:** Decision tree feeding into a Markov model with health states of controlled AF, uncontrolled AF, stroke and death. **Perspective:** Swedish societal perspective quoted in the paper, however from the inputs listed this model takes a payer perspective **Time horizon:** Lifetime **Treatment effect duration:**[a] Lifetime **Discounting:** Costs: 3%; Outcomes: 3%	**Population:** Patients with paroxysmal or persistent drug refractory AF **Cohort settings:** Start age: NR Male: NR **Intervention 1:** ADD (0.090 probability of being AF free at 12 months) **Intervention 2:** RFA (0.780 probability of being AF free at 12 months)	**Total costs (mean per patient):** Intervention 1: £19,073 Intervention 2: £15,953 Incremental (2−1): saves £3,120 (95% CI: NR; p=NR) **Currency & cost year:** 2006 US dollars (presented here as 2006 UK pounds[b]) **Cost components incorporated ($):** Single RFA procedure = 9860 (inc. 3-4 hospital days, diagnostic examinations and disposables such as catheters) Complications inc. tamponade, bleeding, pulmonary vein stenosis, stroke, oesophageal fistula = 2190 Annual ADD treatment = 1640 Annual anticoagulation (inc. monitoring and loss of production) = 770 Annual cost of stroke (year 1) = 19180 Annual cost of stroke (post year 1) = 4380	**QALYs (mean per patient):** Intervention 1: 8.68 Intervention 2: 9.46 Incremental (2−1): 0.78 (95% CI: NR; p=NR)	**ICER (Intervention 2 versus Intervention 1):** In the base case where benefits are sustained over a life time (assuming no rate of reversion post year 1), RFA was less costly and more beneficial than antiarrhythmic therapy, and therefore was the dominant option (deterministic analysis) Probability Intervention 2 cost effective (£20K/30K threshold): NR. **Analysis of uncertainty:** Probabilistic sensitivity analysis was performed and inspection of cost effectiveness plane suggests the majority of simulations showed RFA to be a dominant strategy (no probability reported). One way deterministic analyses: • Annual reversion to AF for those receiving ablation (post 12 months) of 5%, 10% and 15% gave cost per QALY estimates of £5,888, £16,580 and £30,271 respectively. • An elevated stroke risk in the AF state disfavoured the ADD strategy as a greater proportion of these patients remained in that state for longer than in the RFA strategy (this was not quantified in the study).

Data sources
Health outcomes: Studies (including RCTs) of drug refractory AF patients were used to inform treatment effect [Krittayaphong (2007); Stabile (2006), Pappone (2006) and Cauchmez (2008)]. Probability of being AF recurrence at 12 months, 0.22 for ablation and 0.91 for AAD. Assumed no further reversion to AF thereafter in basecase. **Quality-of-life weights:** Age adjusted QALY weights based on a Swedish population were applied as a reference and a decrement of 0.1 for uncontrolled AF and 0.25 for stroke was applied. **Cost sources:** Unclear – sources quoted in Swedish.
Comments
Source of funding: NR. **Limitations:** Quality of life was reviewed; however it is unclear how the literature informed quality of life decrements or how the treatment effect and resource use estimates were derived. Assumed no further reversion to AF thereafter in basecase, an assumption that does not represent current understanding and evidence of ablation. It is unclear whether the best source of unit cost was used. Although the model was constructed probabilistically, the results were only reported graphically. Results were only reported for only one deterministic sensitivity analysis in an incremental manner. It is unclear how a different stroke risk in the AF state would have impacted results in this analysis. **Other:** All effectiveness data used in the model used RFA as a second line treatment to ADD.
Overall applicability:[(c)] Partially applicable **Overall quality:**[(d)] Potentially serious limitations

Abbreviations: AF = Atrial fibrillation; Ami = Amiodarone, ASA = aspirin; ADD = Anti arrhythmic drug; CHADS2 = Congestive heart failure, hypertension, age 75, diabetes mellitus and prior stroke; CI = 95% confidence interval; CUA = cost-utility analysis; da = deterministic analysis; EQ-5D = Euroqol five dimensions (scale: 0.0 [death] to 1.0 [full health]; <0.0 = worse than death); ICER = incremental cost-effectiveness ratio; INR = International Normalized Ratio; LACA = Left atrial catheter ablation; NR = not reported; NSR=normal sinus rhythm; pa = probabilistic analysis; PVI = Pulmonary Vein Isolation ; QALYs = quality-adjusted life years; RC = Rate control; RFCA = radiofrequency catheter ablation; W = Warfarin

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Converted using 2006 purchasing power parities[182]

(c) Directly applicable / Partially applicable / Not applicable

(d) Minor limitations / Potentially serious limitations / Very serious limitations

Study	**McKenna 2009; [154] Rogers 2009[215]**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Probabilistic decision analytic model **Approach to analysis:**	**Population:** Adults with AF refractory to at least one ADD (majority had paroxysmal) **Cohort settings:** Start age: 52 years Male: 80%	**Total costs (mean per patient):** Lifetime treatment effect Intvn 1: CHADS2 0 = £14,417 CHADS2 1 = £15,367 CHADS2 2 = £16,517 CHADS2 3 = £18,107	**QALYs (mean per patient):** Lifetime treatment effect Intvn 1: CHADS2 0 = 10.98 CHADS2 1 = 10.77 CHADS2 2 = 10.52 CHADS2 3 = 10.19	**ICER (Intervention 2 versus Intervention 1), probability 2 cost-effective (£20K/30K threshold):** Lifetime treatment effect CHADS2 0 = £7,763 per QALY gained (98.3%/99.6%) CHADS2 1 = £7,780 per QALY gained

Decision tree capturing short term clinical outcomes and costs (12 months) and a Markov model which extrapolates over a lifetime. At end of decision tree model established proportion of people entering AF or NSR health states. Complications/toxicity captured in decision tree. Health states in Markov model include: NSR, AF, stroke, post stroke and dead. Additional states capture AAD adverse events. Annual cycle duration. **Perspective:** UK NHS **Time horizon:** lifetime **Treatment effect duration:**[(a)] lifetime (alternative basecase analysis 5 years) **Discounting:** Costs: 3.5%; Outcomes: 3.5%	**Intervention 1:** Long term antiarrhythmic drug (AAD) therapy: Amiodarone (200mg daily, pa) **Intervention 2:** Radiofrequency catheter ablation (RFCA)	Intvn 2: CHADS2 0 = £25,240 CHADS2 1 = £26,027 CHADS2 2 = £26,987 CHADS2 3 = £28,343 Incremental (Invn 1-2): CHADS2 0 = £10,823 CHADS2 1 = £10,660 CHADS2 2 = £10,470 CHADS2 3 = £10,236 5 year treatment effect Intvn 1: CHADS2 0 = £14,429 CHADS2 1 = £15,352 CHADS2 2 = £16,499 CHADS2 3 = £18,133 Intvn 2: CHADS2 0 = £25,251 CHADS2 1 = £26,016 CHADS2 2 = £26,972 CHADS2 3 = £28,366 Incremental (Invn 1-2): CHADS2 0 = £10,822 CHADS2 1 = £10,664 CHADS2 2 = £10,473 CHADS2 3 = £10,233 (95% CI: NR; p=NR) **Currency & cost year:** 2006 UK pounds **Cost components incorporated:**	Intvn 2: CHADS2 0 = 12.37 CHADS2 1 = 12.14 CHADS2 2 = 11.87 CHADS2 3 = 11.49 Incremental (Invn 1-2): CHADS2 0 = 1.39 CHADS2 1 = 1.37 CHADS2 2 = 1.35 CHADS2 3 = 1.30 5 year treatment effect Intvn 1: CHADS2 0 = 10.96 CHADS2 1 = 10.76 CHADS2 2 = 10.52 CHADS2 3 = 10.18 Intvn 2: CHADS2 0 = 11.35 CHADS2 1 = 11.18 CHADS2 2 = 10.97 CHADS2 3 = 10.67 Incremental (Invn 1-2): CHADS2 0 = 0.39 CHADS2 1 = 0.42 CHADS2 2 = 0.45 CHADS2 3 = 0.49 (95% CI: NR; p=NR)	(98.1%/99.6%) CHADS2 2 = £7,765 per QALY gained (98.6%/99.9%) CHADS2 3 = £7,910 per QALY gained (99.2%/100%) 5 year treatment effect CHADS2 0 = £27,745 per QALY gained (9.1%/57.7%) CHADS2 1 = £25,510 per QALY gained (16.5%/68.8%) CHADS2 2 = £23,202 per QALY gained (26.5%/78.6%) CHADS2 3 = £20,831 per QALY gained (41.8%/88.1%) **Analysis of uncertainty:** Scenario Analyses: Use of different effectiveness evidence, equality in prognosis for NSR and AF states, no differential impact of treatment and change in annual probability of reversion back to AF did not change the conclusion of the analysis using the 20K threshold for either the lifetime or 5 year treatment effect analyses. However, the ICER increased above the 30K threshold in some scenarios with a 5 year treatment effect analysis e.g. a change in the prognosis of the NSR state; increasing the probability of recurrent AF to above 15% and no differential utility between the states increased the ICER above £30k in the 5 year treatment effect analysis. Duration of benefits is likely to be a key

		RFCA accumulated cost: £9810 (total consumables, £5687, 2 day ward stay, £182, 200 minutes lab time, £1979, plus VAT and administration); Complications from: cardiac tamponade: £815; PV stenosis: £3217; Outpatient initiation of amiodarone: £154; Amiodarone pa: £32; AF and NSR health states pa: £646; Stroke (year 1): £9431 Stroke (year 2+): £2488; Warfarin (5mg daily pa): £19; Aspirin (75mg daily, pa): £20; Toxic event: £1497; Reversible toxicity (per day): £0.43; Irreversible toxicity (50mg daily): £158; Major bleeding event: £1573; Minor bleeding event: £87		determinant of cost effectiveness.
Data sources				
Health outcomes: Three USA RCTS: Kittayaphong 2006; Pappone (2006); Wazni (2005). A range of case series and survey data was considered to estimate RFCA UK baseline event rate. Probability of AF recurrence at 1 year, RFCA= 0.16 and AAD=0.64. Annual probability of recurrence of AF post 1 year for those receiving ablation was estimated to be 0.035 (Pappone 2003) and for those receiving AAD 0.29. Assume reduction in stroke risk for AF symptom free. **Quality-of-life weights:** Quality-of-life weights: EQ5D UK tariff used for baseline utility; Other AAD and RFCA states used utilities derived from Sf36 scores mapped to the EQ5D. Utility decrements estimated from baseline of 1 day were applied to clinical adverse events. Utility associated with stroke from published source applied. Following utility decrements unreferenced: utility decrement for AF symptoms RFCA = 0.0034 and AAD = 0.0925 and utility decrement for AAD in symptoms free state (NSR) = 0.0199. **Cost sources:** Procedural costs from NHS reference costs, otherwise estimates derived from expert opinion and 2 costing studies were used.				
Comments				

Source of funding: National Institute of Health Research, UK. **Limitations:** Does not include all relevant comparators. Some QoL estimates based on assumption (no references provided) and others mapped from SF36 to EQ5D (detail of estimation not specified); extrapolation of clinical effect of RFCA post 5 years; stroke risk estimated from population which did not have RFCA; population predominantly paroxysmal AF. **Other:**

Overall applicability:[b] Partially applicable **Overall quality:**[c] Potential serious limitations

Abbreviations: AF = Atrial fibrillation; Ami = Amiodarone, ASA = aspirin; ADD = Anti arrhythmic drug; CHADS2 = Congestive heart failure, hypertension, age 75, diabetes mellitus and prior stroke; CI = 95% confidence interval; CUA = cost-utility analysis; da = deterministic analysis; EQ-5D = Euroqol five dimensions (scale: 0.0 [death] to 1.0 [full health]; <0.0 = worse than death); ICER = incremental cost-effectiveness ratio; INR = International Normalized Ratio; LACA = Left atrial catheter ablation; NR = not reported; NSR=normal sinus rhythm; pa = probabilistic analysis; PVI = Pulmonary Vein Isolation ; QALYs = quality-adjusted life years; RC = Rate control; RFCA = radiofrequency catheter ablation; W = Warfarin;

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.In this instance they assumed that the utility improvements with RFCA compared to AADs are either maintained for a lifetime or maintained for a maximum of 5 years only.

(b) Directly applicable / Partially applicable / Not applicable

(c) Minor limitations / Potentially serious limitations / Very serious limitations

Study	**Blackhouse 2013[27] / Assasi 2012[18]**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Probabilistic decision analytic model **Approach to analysis:** Two part model includes short term model (1 year decision tree), long term model (Markov model). Decision tree, a proportion of those having ablation will experience operative complications: cardiac tamponade, pulmonary	**Population:** Men with paroxysmal AF previously unsuccessful with antiarrhythmic drugs. CHADS2 = 2. **Cohort settings:** Start age: 65 Male: 100% **Intervention 1:** Amiodarone 200mg OD **Intervention 2:** Catheter ablation (type not specified, assumed to be radiofrequency)	**Total costs (mean per patient):** Intervention 1: £7,141 Intervention 2: £11,976 Incremental (2−1): £4,835 (95% CI: NR; p=NR) **Currency & cost year:** 2010 Canadian dollars (presented here as 2010 UK pounds[(b)]) **Cost components incorporated:** • Ablation procedure including inpatient stay, physician fees and follow up in the first year	**QALYs (mean per patient):** Intervention 1: 3.272 Intervention 2: 3.416 Incremental (2−1): 0.144 (95% CI: NR; p=NR)	**ICER (Intervention 2 versus Intervention 1):** £33,576 per QALY gained (pa) 95% CI: Probability catheter ablation cost effective (£14K/28K/57K threshold): 3%/30%/89% **Analysis of uncertainty:** One way sensitivity analyses undertaken. • There was little change when discounting rate of 0% and 3% for both costs and outcomes applied or when the annual probability of AF recurrence was adjusted. • Results varied according to age, gender and CHADS2 score. • Changing the time horizon had a large

vein stenosis, ischaemic stroke, TIA. Those without a stroke will either end up with normal sinus rhythm (NSR) or AF at the end of the short term model. The Markov model includes the following health states: NSR, AF, ischaemic stroke, post ischaemic stroke, major bleed, ICH, post-ICH, other major bleeds (GI) and dead. 3 month cycle. **Perspective:** Canadian health care payer **Time horizon:** 5 years **Treatment effect duration:**[(a)] 3 years **Discounting:** Costs: 5%; Outcomes: 5%		(3 cardiologist consultations and CT scan) • Procedural complications (cardiac tamponade, PV stenosis, stroke and TIA) • Drug costs: amiodarone (200mg OD) (given to all those in that arm in all cycles), warfarin for those with AF only • Stroke and major bleeding		impact on results: ○ 3 years: £74.014 per QALY ○ 10 years: £8,082 per QALY ○ 20 years: ablation dominant (less costly and more effective) • When it was assumed restoration of NSR had no impact on stroke risk, ICER increased to £48,770 per QALY • Increasing the disutility of having AF compared to NSR reduced (from 0.043 to 0.08) the ICER to £21,738 per QALY • Decreasing the disutility of having AF: (0.02) increased the ICER to £57,237 per QALY
Data sources				
Health outcomes: Targeted literature reviews undertaken for model inputs. Stroke risk based on US registry data (by CHADs2 score), adjustment of stroke risk for NSR applied (based on post-hoc study). Major bleeds, taken from registry data and published systematic reviews of literature/meta-analyses. Mortality taken from Canadian life tables. Mortality adjusted for specific events, data taken from various published sources (primarily Canadian). Probability of being in NSR at 1 year derived from systematic review of literature undertaken by same authors as part of HTA: meta-analysis if 5 RCTs (Forleo 2009, Jais 2008, Pappone 2006, Krittayaphong 2003, Wilber 2010), probability of being iAF recurrence at 1 year estimated to be 0.25 and 0.74 for ablation and antiarrhythmic drugs respectively. Recurrence of AF taken from long term observational study of recurrence for antiarrhythmic drugs or ablation at 1, 2 and 3 years (Pappone 2003), annual probability of AF recurrence estimated to be 0.036 and 0.221 for ablation and antiarrhythmic drugs respectively. Procedural complications taken from systematic review of RCT and non-RCT studies evaluating catheter ablation. Antiarrhythmic drug adverse events taken from systematic review/meta-analysis. **Quality-of-life weights:** UK EQ-5D general population data used for NSR. Disutilities taken from various sources of published literature. Some are mapped from SF12 data or modified Rankin Score. Populations Canadian or other. **Cost sources:** Resource use based on literature or assumptions. Estimated 1.27 ablations per patient based on published survey. Follow up in year following ablation based on assumptions. Unit costs primarily from Canadian national/regional published costs. Procedural complications and stroke from Canadian				

published costing studies.

Comments

Source of funding: NR. **Limitations:** Canadian Health care perspective. Includes 2 of the 7 interventions of interest. QALY's derived from EQ-5D as well as other mapped from other measures of quality of life and not all from UK representative population. Discounting incorrect. Baseline effects not based on systematic reviews of the literature. Relative treatment effects based on 5 RCTs, and may not reflect full body of evidence available. Unit costs from Canadian published sources and may not reflect UK NHS unit costs. **Other:** Model assumptions: Ablation patients are assumed to discontinue warfarin 3 months after procedure, therefore resulting in a different bleeding risk vs. antiarrhythmic drugs patients who are still being anticoagulated. Ablation patients who do not achieve NSR at 1 year or who have a subsequent recurrence of AF are assumed to switch to antiarrhythmic drugs.

Overall applicability:[c] Partially applicable **Overall quality:**[d] Potentially serious limitations

Abbreviations: CCA= cost–consequences analysis; CEA= cost-effectiveness analysis; 95% CI= 95% confidence interval; CUA= cost–utility analysis; da= deterministic analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER= incremental cost-effectiveness ratio; NR= not reported; NSR = normal sinus rhythm; pa= probabilistic analysis; QALYs= quality-adjusted life years

(e) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(f) Converted using 2010 purchasing power parities[182]

(g) Directly applicable / Partially applicable / Not applicable

(h) Minor limitations / Potentially serious limitations / Very serious limitations

Study	Reynolds 2014 [210]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Probabilistic decision analytic model **Approach to analysis:** Markov model. Health states include sinus rhythm post ablation, sinus rhythm on antiarrhythmic drugs (health states for each line of antiarrhythmic	**Population:** Paroxysmal AF patients unsuccessfully treated with ≥1 antiarrhythmic drug (patient characteristics based on STOP-AF trial (Packer 2013) [183] **Cohort settings:** Start age: NR Male: NR **Intervention 1:**	**Total costs (mean per patient):** Intervention 1: £17,627 Intervention 2: £21,162 Incremental (2−1): £3,535 (95% CI: NR; p=NR) **Currency & cost year:** 2011 UK pounds **Cost components incorporated:** Ablation procedure, cryoballoon, freezer catheter, drugs	**QALYs (mean per patient):** Intervention 1: 3.404 Intervention 2: 3.565 Incremental (2−1): 0.161 (95% CI: NR; p=NR)	**ICER (Intervention 2 versus Intervention 1):** £21,957 per QALY gained (da) 95% CI: Probability Intervention 2 cost effective (£20K/30K threshold): ~40%/86% **Analysis of uncertainty:** In addition to the probabilistic sensitivity analysis, a number of one-way sensitivity analyses were conducted. Results were sensitive to the following: • Time horizon (2,10 years) (ICER: ~£90,000 per QALY and ~£3,000 per

drug given), AF post recurrence (rate control only), disabling and non-disabling stroke and dead. Procedural complications for ablation patients included in model: ischaemic stroke, cardiac tamponade, phrenic nerve palsy, PV stenosis, arteriovenous fistula, bleeding requiring transfusion, femoral artery pseudoaneurysm and subclavian vein rupture. Once in stroke states it is assumed that patients stop taking antiarrhythmic drugs and begin rate control therapy. Assumed all take warfarin when AF recurs. Major and minor bleeding was modelled and switch to aspirin applied following major bleed. Repeat ablation included. 6 month cycle with half cycle correction. **Perspective:** UK NHS **Time horizon:** 5 years **Treatment effect duration:**[(a)] 1 year trial	Antiarrhythmic drugs. Sequence of drugs modelled : • first line propafenone • second line sotalol • third line amiodarone • finally rate control therapy alone (metoprolol) **Intervention 2:** Cryoballoon ablation	(antiarrhythmic drugs, rate control, warfarin, aspirin), ischaemic stroke (non-disabling and disabling), bleeding (disabling haemorrhagic stroke, non-disabling haemorrhagic stroke, major gastrointestinal bleed, minor bleed, warfarin monitoring), procedural AEs, drug related serious AEs, initiation of amiodarone and monitoring.		QALY respectively) • Cost of follow up care in patients with recurrent AF (more expensive the care, lower the ICER) • Total initial procedure cost (more expensive the procedure the higher the ICER)

data used. Other data sources used for extrapolation. **Discounting:** Costs: 3.5%; Outcomes: 3.5%				

Data sources

Health outcomes: Stroke risk based on baseline CHADS2 score from STOP-AF trial and published literature as well as UK regional registry data. Stroke risk reduction for warfarin and bleeding risk based on published literature. UK life tables used for mortality, stroke mortality from published literature. Efficacy data (recurrence of atrial fibrillation at 12 months) taken from STOP-AF trial[183]. Probabilities of recurrence were 0.227 and 0.866 at 0-6 months and 0.063 and 0.454 at 6-12 months for ablation and antiarrhythmic drugs respectively. Beyond 12 months, taken from other published literature including case series for ablation (Vogt 2013) and longitudinal observational study for antiarrhythmic drugs (Pappone 2003), with annual probabilities of 0..98 and 0.220 for ablation and AAD respectively. Procedural complications taken from a published meta-analysis of cryoballoon studies. Antiarrhythmic drug AEs taken from large study of sotalol in paroxysmal AF patients, OR from a published meta-analysis applied to this for other antiarrhythmic drugs. AEs for rate control therapy from published study. Stroke risk reduction of 1.6 applied to AF symptom free health state for ablation arm only. (AFFIRM data). OAC initiated after first AF recurrence only. **Quality-of-life weights:** STOP AF trial SF36 data mapped to SF6D utility weights for first 12 months. Other sources of utility values used for other health states and AEs. Utility decrement for AF symptoms 0.08. **Cost sources:** Resource use taken primarily from STOP-AF trial. Unit costs from NHS PBR tariffs, UK national drug price lists, personal and social care costs, and existing HE analyses and costing studies.

Comments

Source of funding: Medtronic. **Limitations:** Study does not include all treatment options. QALYs derived from utility scores mapped from other measures of quality of life, not clear if tariff is from a UK representative population. Baseline and relative treatment effects not based on a systematic reviews of the evidence. Analysis is based on a single RCT and so may not reflect full body of available evidence for this comparison. Potential financial conflict of interest funded by industry: Medtronic. **Other:**

Overall applicability:[(b)] Partially applicable **Overall quality:**[(c)] Potentially serious limitations

Abbreviations: AEs= adverse events; CCA= cost–consequences analysis; CEA= cost-effectiveness analysis; 95% CI= 95% confidence interval; CUA= cost–utility analysis; da= deterministic analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER= incremental cost-effectiveness ratio; NR= not reported; pa= probabilistic analysis; QALYs= quality-adjusted life years

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Directly applicable / Partially applicable / Not applicable

(c) Minor limitations / Potentially serious limitations / Very serious limitations

Study	**Chun 2017[53]**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis:	**Population:**	**Total costs (mean per**	**All cause**	**ICER (Intervention 2 versus**

CCA (health outcome: multiple) **Study design:** Within trial analysis (FIRE AND ICE RCT, associated clinical paper Kuck 2016[122, 123]) **Approach to analysis:** Analysis of individual level data for health outcomes and resource use. Unit costs applied. **Perspective:** UK NHS **Follow-up:** 1.54 years (trial period) **Treatment effect duration:**[(a)] n/a **Discounting:** Costs: n/a; Outcomes: n/a	Patients with drug refractory symptomatic paroxysmal atrial fibrillation **Cohort settings:** Start age: Intervention 1: 60.1 (SD: 9.2) Intervention 2: 59.9 (SD: 9.8) Male: Intervention 1: 63% Intervention 2: 59% **Intervention 1:** Point-to-point radiofrequency ablation **Intervention 2:** "Single shot" cryoballoon ablation	**patient):** Intervention 1: £1,827 Intervention 2: £1,464 Incremental (2−1): saves £363.50 (95% CI: NR; p=NR) **Currency & cost year:** 2014-2015 UK pounds **Cost components incorporated:** Cardiovascular rehospitalisation: repeat ablation, AF related cardiovascular rehospitalisation, non-AF related cardiovascular rehospitalisation, cardioversion; non-cardiovascular rehospitalisation. Cost of interventions and adverse events related to interventions not included as authors reported no difference between comparators.	**rehospitalisation**: Incremental (2−1): 21% fewer **Cardiovascular rehospitalisation:** Incremental (2−1): 34% fewer **Repeat ablation:** Incremental (2−1): 33% fewer No difference observed between arms in quality of life metrics (SF-12 and EQ-5D-3L).	**Intervention 1):** "Single shot" cryoballoon ablation dominates point-to-point radiofrequency ablation (lower costs better health outcomes) **Analysis of uncertainty:** Bootstrapping analysis was undertaken. 97% and 98% probability of cost saving in the all cause rehospitalisation and cardiovascular rehospitalisation analyses. One way sensitivity analyses demonstrated that the size of the cost saving was most sensitive to payment level for a repeat ablation (higher payment associated with higher saving) and least sensitive to changes in the individual payment levels for other types of health care utilisation.
Data sources				
Health outcomes: Within trail analysis (FIRE AND ICE RCT, associated clinical paper Kuck 2016[122, 123]). **Quality-of-life weights:** n/a. **Cost sources:** NHS reference costs.				
Comments				
Source of funding: Medtronic. **Limitations:** QALYs were not used as the health outcome measure. Study does not include all treatment options. Analysis is based on a single RCT and so may not reflect full body of available evidence for this comparison; Kuck 2016 is 1 of 11 studies included in the clinical review for catheter ablation versus radiofrequency ablation. Potential financial conflict of interest funded by industry: Medtronic. **Other:**				

Overall applicability:[(b)] Partially applicable **Overall quality:**[(c)] Potentially serious limitations

Abbreviations: CCA= cost–consequences analysis; 95% CI= 95% confidence interval; da= deterministic analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER= incremental cost-effectiveness ratio; NR= not reported; pa= probabilistic analysis; QALYs= quality-adjusted life years

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Directly applicable / Partially applicable / Not applicable

(c) Minor limitations / Potentially serious limitations / Very serious limitations

Study	**Murray 2018[167]**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Decision analytic model **Approach to analysis:** Short-term decision tree model was developed to depict the probabilities, utilities and costs of CB compared to RF therapy. Data from a conducted systematic literature review and meta-analysis of only RCTs were used to evaluate clinical outcomes of CB and RF treatments, including success rates after one year, complications and recurrence of atrial fibrillation. **Perspective:** UK NHS	**Population:** Patients with paroxysmal atrial fibrillation **Cohort settings:** Start age: n/a Male: n/a **Intervention 1:** Point-by-point ablation using radiofrequency (RF) **Intervention 2:** Single shot cryoballoon ablation (CB)	**Total costs (mean per patient):** Intervention 1: £25,922 Intervention 2: £27,669 Incremental (2−1): £1,747 (95% CI: NR; p=NR) **Currency & cost year:** 2015/16 UK pounds **Cost components incorporated:** Variable hospital costs for the ablation visits (procedure costs, supplies and medication) and Complication events.	**Total QALYs (mean per patient):** Intervention 1: 0.98752 Intervention 2: 0.99895 Incremental (2−1): 0.01143 (95% CI: NR; p=NR)	**ICER (Intervention 2 versus Intervention 1):** £152,836 per QALY gained (da) 95% CI: n/a Probability Intervention 2 cost effective (£20K/30K threshold): n/a **Analysis of uncertainty:** One way sensitivity analyses was conducted on the following parameters, cost of CB treatment, and cost of complications with CB and the probability of AF recurrence after CB ablation. The results were most sensitive to the changes in the cost of CB (if the CB cost is reduced to £15,000, the incremental cost per QALY ablation compared to RF ablation would be £-158,005). Furthermore, if the probability of AF recurrence is assumed to be 0.15 or 0.35, the cost per QALY becomes £57,881 and £429,832, respectively. The cost of CB complications had a relatively small impact on results.

Time horizon: 1 year **Treatment effect duration:**[(a)] n/a **Discounting:** Costs: n/a; Outcomes: n/a				
Data sources				
Health outcomes: Data from a conducted systematic literature review and meta-analysis (4 RCTs). **Quality-of-life weights:** Published studies after a comprehensive literature review[16, 210]. **Cost sources:** NHS Payment by Results (PbR) tariffs, further cost estimates were based on existing economic analysis, personal and social care costs and resource use estimates from large databases, cost for CB ablation were estimated using data from a previous published study[210]. Procedural complications were valued based on national tariffs. The average cost for procedural complications were £950 in the CB group and £1500 in the RF group. The main reasons for the cost difference were the higher rate of cardiac tamponade and groin-side complications caused by RF ablation.				
Comments				
Source of funding: None. **Limitations:** It is unclear whether the utilities are representative of UK population as the RCTs included in the meta-analysis are from different perspectives. Study does not include all treatment options. Short time horizon therefore long-term effects are not captured. The possibility of mortality was not included. Cost year is unclear. Complication rates including stroke unclearly reported. Reports that stroke will impact quality adjusted life expectancy but this is not clearly reported in model. Model does not include cost adjustment for other comorbidities and PbR tariffs may not reveal the true complexity and cost of a patient episode. **Other:**				
Overall applicability:[(b)] Partially applicable **Overall quality:**[(c)] Potentially serious limitations				

Abbreviations: CUA= cost–utility analysis; 95% CI= 95% confidence interval; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER= incremental cost-effectiveness ratio; n/a= not applicable; NR= not reported; pa= probabilistic analysis; QALYs= quality-adjusted life years

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Directly applicable / Partially applicable / Not applicable

(c) Minor limitations / Potentially serious limitations / Very serious limitations

1 Appendix I: Excluded studies

I.1 2 Excluded clinical studies

3 **Table 52: Studies excluded from the clinical review**

Study	Exclusion reason
Ad 2017[1]	SR - REFERENCES CHECKED
Agasthi 2019[3]	SR - REFERENCES CHECKED
Albrecht 2004[4]	concomitant cardiac surgery
Alhede 2017[5]	Non-protocol outcomes
Alturki 2019[6]	SR - REFERENCES CHECKED
Amit 2017[7]	review
Ammar-busch 2017[8]	RF v cardioversion in patients already treated with PVI and CFAE ablation
Andrade 2012[11]	SR - REFERENCES CHECKED
Andrade 2012[12]	Both groups RF pt to pt
Andrade 2017[10]	protocol
Aras 2017[15]	SR - REFERENCES CHECKED
Aryana 2016[17]	Non-randomised
Atienza 2014[19]	Both groups using pt to pt RF
Bauer 2006[20]	Both groups RF pt to pt; comparing circumferential v segmental
Baykaner 2018[21]	cost effectiveness study; non randomised
Beaver 2016[22]	Involves appendage ligation
Berger 2019[24]	SR - REFERENCES CHECKED
Blandino 2013[28]	non randomised
Blomstrom-Lundqvist, 2019[29]	Pooled catheter treatments together
Bonanno 2010[33]	SR - REFERENCES CHECKED
Bordignon 2013[34]	No evidence of randomisation; patients 'prospectively assigned' to groups but no mention is made of any randomisation.
Briceno 2018[35]	SR - REFERENCES CHECKED

Buiatti 2017[36]	SR - REFERENCES CHECKED
Buist 2018[38]	non randomised (stated in limitations sections despite using the term 'randomised' in abstract)
Buist, 2019[37]	Involved left atrial appendage ligation
Calo 2006[40]	LA vs biatrial ablation with both groups using pt/pt RF
Cardoso 2016[41]	SR - REFERENCES CHECKED
Chang 2009[43]	non randomised
Chen 2011[46]	CFE v PVAI with both groups having pt/pt RF
Chen 2017[45]	SR - REFERENCES CHECKED
Chen 2017[47]	SR - REFERENCES CHECKED
Chen 2018[44]	SR - REFERENCES CHECKED
Cheng 2014[49]	SR - REFERENCES CHECKED
Cheng 2015[48]	SR - REFERENCES CHECKED
Chevalier 2007[50]	conference abstract
Chilukuri 2011[51]	Conv PVI vs box isolation with same RF in both groups
Choi 2010[52]	non randomised
Ciconte 2015[54]	non randomised
Conti 2018[55]	Both groups used RF pt to pt; CFS guided v CFS blinded
Das 2017[57]	The sample had already had a PVI and the study aimed to assess the benefit of reablation regardless of symptoms. The sample were therefore not the same as the protocol sample - people with symptoms requiring treatment
De greef 2014[59]	non randomised
Deisenhofer 2009[60]	PVI vs PVI + electrogram guided substrate ablation
Deneke 2001[61]	Not in English
Di biase 2009[63]	Comparison of strategies all using same RF cather (pt/pt)
Dixit 2006[65]	cool tip vs 8mm tip with both gps pt/pt RF
Dixit 2008[66]	Both groups RF pt to pt;
Dixit 2012[67]	Comparisons of PVI using 3 strategies that all used pt/pt RF
Dong 2009[68]	COMPARISON OF SINGLE VS DOUBLE CATHETER APPROACH

Dong 2015[69]	2C3L vs stepwise approach with both groups using pt/pt RF
Earley 2006[71]	compared different mapping strategies
Edgerton 2012[73]	SR - REFERENCES CHECKED
Elayi 2008[74]	both groups RF pt to pt
Erdogan 2001[75]	Not in English
Estner 2011[76]	CFAE vs linear ablation with both having pt to pt RF
Faustino 2015[77]	Stepwise ablation v PVI in 2 groups both using RF pt/pt
Fiala 2008[78]	both groups used RF pt to pt; segmental v circumferential
Gaita 2008[80]	PVI vs PVI plus left linear lesions in 2 gps using pt/pt RF
Gao, 2019 #1930[83]	cost effectiveness analysis
Garg 2016[84]	SR - REFERENCES CHECKED
Hachem 2018[88]	SR - REFERENCES CHECKED
Hakalahti 2015[89]	SR - REFERENCES CHECKED
Ito 2007[94]	unipolar vs unipolar + bipolar recordings during ablation
Jiang 2017[97]	SR - REFERENCES CHECKED
Jiang 2018[98]	SR - REFERENCES CHECKED
Jons 2009[100]	protocol
Kaba 2014[101]	review of Morillo 2014
Kabunga 2016[102]	SR - REFERENCES CHECKED
Kearney 2014[103]	SR - REFERENCES CHECKED
Khan 2008[105]	ablate and pace trial
Khan 2018[106]	SR - REFERENCES CHECKED
Khargi 2001[107]	mitral valve disease
Khaykin 2009[109]	Both groups used pt point RF
Kim 2015[111]	RF pt to pt with posterior wall isolation v RF pt to pt without
Kimman 2006[112]	Not an AF population
Kimura 2014[113]	contact guided vs not guided in 2 groups both using RF pt pt

Kircher 2018[115]	individually tailored vs standardised substrate modification sin 2 groups both having RF pt/pt
Kong 2010[118]	SR - REFERENCES CHECKED
Kozluk 2019[119]	Both groups using multielectrode RF - nMARQ vs PVAC
Kress 2017[120]	not randomised
Kuck 2016[124]	complete vs incomplete circumferential lines around PV with both gps using pt/pt RF
Kuck, 2019[125]	Type of catheter ablation unspecified.
Lee 2016[126]	RF pt to pt both groups; single ring isolation v wide antral isolation
Lee 2019[127]	Complex fractionated linear ablation vs complex fractionated focal ablation with both gps using pt/pt RF
Liakishev 2008[128]	Not in English
Lin 2012[131]	Mod PVI vs conventional PVI with point by point in both groups
Lin 2014[130]	limited vs extensive ablation with both groups using pt/pt RF
Lin 2019[129]	both groups RF pt to pt
Liu 2006[132]	both groups RF pt to pt
Liu 2006[133]	circumferential PVI vs stepwise segmental PVI in 2 groups with RF pt/pt
Liu 2010[134]	r. Rheumatic heart disease patients
Liu 2016[135]	SR - REFERENCES CHECKED
Looi 2013[136]	non randomised
Ma 2015[141]	SVT population
Ma 2017[139]	SR - REFERENCES CHECKED
Ma 2018[140]	SR - REFERENCES CHECKED
Malik 2018[143]	SR - REFERENCES CHECKED / NMA
Malmborg 2013[144]	no protocol outcomes (biomarkers only)
Mark, 2019 #1923[146]	Pooled catheter treatments together
Marrouche 2007[148]	Two types of point by point Rf delivery compared
Marrouche 2018[147]	Variety of ablation methods used in ablation group. therefore not able to compare the specific protocol interventions

Masuda 2018[149]	contact force guided PVI vs contact force guided PVI followed by pace-capture-guided ablation in 2 groups using pt/pt RF
Matsuo 2010[151]	steerable vs non-steerable sheath
Matsuo 2011[150]	steerable vs non-steerable sheath. sterable vs non-steerable sheath
Mcclure 2018[152]	SR - REFERENCES CHECKED
Mclellan 2015[155]	minimal vs maximal ablation for 2 gps using pt/pt RF
Mikhaylov 2010[156]	both groups RF pt to pt; additional septal line vs no additional septal line
Mohanty 2013[158]	AF vs AFL ablation with both gps using pt/pt RF
Mohanty 2015[159]	non-AF population (Flutter only)
Mohanty 2016[157]	Retracted paper
Morady 1993[161]	Ablate and pace trial
Mortsell 2018[164]	single cryoballoon vs standard cryoballoon application strategy
Mortsell 2019[163]	non randomised comparison of paroxysmal v persistent groups
Muneretto 2017[165]	non randomised
Murray 2018[166]	SR - REFERENCES CHECKED
Murray, 2018[167]	cost effectiveness analysis
Nakamura 2015[168]	contact forced guided vs not contact force guided
Narayan 2014[169]	Non randomised
Nashef 2018[170]	Concomitant cardiac surgery (including valvular)
Natale 2000[171]	Atrial flutter population (not atrial fibrillation)
Natale 2014[172]	non randomised
Naymushin 2017[174]	Not in English
Neumann 2011[175]	non randomised
Nyong 2016[179]	SR - REFERENCES CHECKED
Oral 2005[181]	both groups RF pt to pt; encircling v nonencircling
Oral 2008[180]	Comparison of RF v no treatment for right LA after failed LA ablation
Packer 2018[184]	protocol

Packer, 2019[185]	Pooled catheter treatments together
Pappone 2018[188]	CPVA vs CPVA + RRas with both groups using pt/pt RF
Pappone, 2006[186]	Not in English
Park 2018[190]	impedance-guided and contact force guided ablation both using pt/pt RF
Patel 2018[191]	SR - REFERENCES CHECKED
Pavlovic 2016[192]	NR
Pearman 2017[193]	SR - REFERENCES CHECKED
Pedrote 2016[194]	contact force monitoring vs no contact force monitoring
Phan 2016[196]	SR - REFERENCES CHECKED
Piccini 2009[197]	SR - REFERENCES CHECKED
Piorkowski 2011[198]	comparison of sheath type (steerable v non-steerable)
Pires 2010[199]	mitral valve disease
Pokushalov 2009[205]	both groups RF pt to pt; selective GPA v regional GPA
Pokushalov 2013[204]	both groups RF pt to pt
Raatikainen 2015[207]	Non randomised on-treatment analysis of trial data
Rajappan 2009[208]	steerable vs non steerable sheath during ablation
Reddy 2015[209]	Force sensing vs no force sensing during ablation
Reynolds 2018[212]	SR - REFERENCES CHECKED
Rillig 2013[213]	Review
Rillig 2017[214]	robotic navigation vs manual ablation with both using pt/pt RF
Rolf 2019[216]	flouroscopic vs no flouroscopic catheter visualisation with both groups using pt to pt RF
Romanov 2016[217]	PVI +box lesion vs PVI + box lesion +LAA excision in 2 groups treated with thoracoscopy
Scara 2017[218]	comparing differing navigation systems
Schmidt 2008[222]	Atrial flutter post PVI population
Schneider 2015[223]	Not an AF population; did not answer review question
Schumacher 2000[224]	Not in English

Shao 2018[225]	SR - REFERENCES CHECKED
Shi 2015[226]	SR - REFERENCES CHECKED
Shim 2017[227]	virtual ablation vs empirical ablation (both used pt to pt RF)
Smer 2018[228]	SR - REFERENCES CHECKED
Sohara 2016[229]	Incorrect interventions. Uses HotBalloon catheter, that utilises RF energy but not point by point or multielectrode
Srivastava 2008[230]	patients with valvular heart disease
Steinberg 2014[232]	non AF population (AFL only)
Steven 2013[233]	PVI v PVI with application of an additional acute procedural endpoint of unexcitability along the ablation line
Stevenhagen 2010[234]	comparison of different guiding techniques
Tada 2002[236]	bipolar vs bipolar + unipolar recordings
Tamborero 2010[237]	both groups RF pt to pt; circular mapping catheter vs without
Tang 2016[238]	Not in English
Terasawa 2009[240]	SR - REFERENCES CHECKED
Theis 2015[241]	PVI with induced AF vs PVI without induced AF
Tsyganov 2015[243]	Not available
Turagam 2019[244]	SR - REFERENCES CHECKED
Ullah 2014[246]	Robotic vs manual navigation in 2 groups using RF pt to pt
Ullah 2016[247]	contact force data vs no contact force data during ablation
Van der heijden 2019[248]	SR - REFERENCES CHECKED
Verma 2014[249]	comparison of strategies within one intervention class
Virk 2018[250]	SR - REFERENCES CHECKED
Vogler 2015[251]	PVI v defragmentation in 2 groups both having pt/pt RF
Vroomen 2016[252]	SR - REFERENCES CHECKED
Wang 2008[257]	PVI + SVCI vs PVI
Wang 2011[254]	Not in English
Wang 2017[255]	ablation vs cardioversion
Wasserlauf 2015[258]	Non randomised

Willems 2000[263]	Not in English
Willems 2006[262]	PVI vs PVI + substrate mod in 2 groups both using pt/pt RF
Wong 2015[264]	addition of CFAE to PVI/Linear ablation vs PVI/linear ablation in 2 groups using pt/pt RF
Wynn 2014[266]	SR - REFERENCES CHECKED
Wynn 2015[265]	Incorrect reanalysis of data from Mont
Xu, 2019[267]	Both arms using same type of ablation (RF pt by point) but with differing location of ablation
Yamagata 2018[269]	comparison of venipuncture techniques
Yi 2019[270]	SR - REFERENCES CHECKED
Yokokawa 2011[271]	non randomised
Yu 2017[274]	PVI vs PVI + linear ablation
Zhang 2017[276]	PVI with 3D ,mapping and X ray vs 3D mapping only
Zhang 2019[275]	SR - REFERENCES CHECKED
Zhu 2016[277]	SR - REFERENCES CHECKED

I.21 Excluded health economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2003 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

Table 53: Studies excluded from the health economic review

Reference	Reason for exclusion
Khaykin 2007[108]	Comparative costing of ablation versus anti-arrhythmic and rate control strategies using Canadian registry data and supplementing with data from published studies. No quality of life data collated. Overall assessed to have partial applicability. Due to use of registry data to estimate resource use, the comparators are poorly specified and treatment effect is uncertain. **Selectively excluded** due to having very serious limitations in comparison to available literature included in the review.
Khaykin 2009[110]	Comparative costing of ablation versus anti-arrhythmic and rate control strategies using Canadian registry data and supplementing with data from published studies. No quality of life data collated. Overall assessed to have partial applicability. Due to use of registry data to estimate resource use, the comparators are poorly specified and treatment effect is uncertain. **Selectively excluded** due to having very serious limitations in comparison to available literature included in the review.

Reference	Reason for exclusion
Kimura 2017[114]	This study comparing catheter ablation (type not specified) to no ablation was assessed as partially applicable (did not include all comparators; Japanese setting may not reflect current UK context) and judged to have potentially serious limitations (baseline risks and relative treatment effects based on non-RCT data; model structure does not include adverse events or all-cause mortality within model). However, developers felt this study was superseded by other available evidence in terms of its applicability and methodological quality, and therefore this study was **selectively excluded**.
Klein 2015[116]	This comparative cost study comparing the procedural time of point by point catheter ablation versus anatomical catheter ablation was **excluded** as it had very serious limitations. No health outcomes incorporated in analysis, the cost of procedure complications were not included, the resource use data was based on retrospective data and the study was funded by manufacturer ablation appliances. In addition, this study was partially applicable (German health care payer perspective may not reflect current UK context, no quality of life data included in analysis)
Noro 2011[178]	Model evaluating the cost of radiofrequency catheter ablation from a Japanese payer perspective, and as such no quality of life data was evaluated. Overall assessed to have partial applicability. Many of the sources for the unit costs and estimates of resource consumption were unclear, and unlikely to be from the best source (as they indicated RCT data had been excluded due to lack of applicability to the Japanese population). The probability of adverse events which incurred cost was not detailed. This study was **excluded** due very serious limitations.

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