National Institute for Health and Care Excellence

Draft for consultation

Atrial Fibrillation

Antiarrhythmic drugs after ablation

NICE guideline

Intervention evidence review

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Draft for Consultation

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1

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Contents

1

1 Antiarrhythmic drugs after ablation

1.1 Review question: What is the clinical and cost-effectiveness of short-term (<6 months) antiarrhythmic drugs following ablation for preventing recurrence of atrial fibrillation?

1.2 Introduction

AF ablation is increasingly used as an effective invasive rhythm control treatment. Still, many patients experience recurrences of AF after ablation that requires treatment. Antiarrhythmic drugs have synergistic rhythm controlling effects in addition to AF ablation. Their effects are particularly useful in the first months after ablation or cardioversion, when the reversal of electrical remodelling and the healing of ablation wounds render recurrent AF likely. This chapter reviews the evidence and provides guidance on short-term antiarrhythmic drug therapy.

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 AF undergoing an ablative procedure
Intervention(s)	**Rhythm control medication** • Na+ channel blockers (such as amiodarone, procainamide, disopyramide, quinidine sulphate, flecainide, propafenone • K+ channel blockers (such as dronedarone, ibutilide, sotalol)
Comparison(s)	• Each other (both between and within classes) • Usual care/no treatment • Placebo
Outcomes	**Critical** • Health related quality of life • Mortality • Stroke or thromboembolic complications • Hospitalisation with a primary diagnosis of atrial arrhythmia • Cardioversion for AF **Important** • All cause hospitalisation • Study drug discontinuation • Repeat ablation procedure within 1 year • Any documented atrial arrhythmia
Study design	RCTs and SRs of RCTs

Post-ablation interventions were designated as ‘short-term’ and needed to be given for less than 6 months. Follow ups later than this were (of course) allowed provided the treatment had not exceeded 6 months. If the treatment exceeded 6 months, only data collected up to and including 6 months were included, and later follow ups were excluded.

Only eligible drugs given after the ablation were allowed. Studies evaluating drugs given during the ablation procedure itself were not included.

1.4 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual.[30] Methods specific to this review question are described in the review protocol in Appendix A:.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy.

This review was stratified into:

1) studies where an anti-arrhythmic drug was already being used prior to and up to ablation, and randomisation was a) to continue the drug or b) to not continue the drug, or

2) studies where AADs were not being used prior to and up to ablation, and randomisation was a) to start AADs or b) to not start AADs, or

3) studies where pre-ablation AAD status was unclear, or where there were a mixture of approaches.

1.5 Clinical evidence

1.5.1 Included studies

A search was conducted for randomised trials comparing the effectiveness of antiarrhythmic drugs used after ablation versus placebo, usual care or other antiarrhythmic drugs for preventing atrial fibrillation after ablation.

Seven randomised trials (9 RCTs) were included in the review.[1, 11, 12, 16, 20, 24, 26, 33, 38] A variety of antiarrhythmic drug approaches were used (see Table 2). The aim of all studies was to assess whether antiarrhythmic drugs are effective at preventing atrial fibrillation in people after ablation. The studies are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 3).

See also the study selection flow chart in Appendix C:, study evidence tables in Appendix D:, forest plots in Appendix E: and GRADE tables in Appendix H:.

1.5.2 Excluded studies

See the excluded studies list in Appendix I.

1.5.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Stratum	Inclusion and exclusion criteria	Type of AF	Existence of HF	Duration of AAD treatment	Type of ablation	LA diameter
Ad, 2016[1] N=97 USA	Amiodarone versus usual care - dosing details not provided	Unclear /mixed – No data on pre-ablation AAD use.	Inclusion: Age >=18; Persistent or long-standing persistent AF, according to HRS guidelines; Candidate to undergo the Cox maze procedure for AF; Left ventricular ejection fraction >=30%; Normally would be prescribed amiodarone as an AAD after surgical ablation; Exclusion: Emergent cardiac surgery (e.g., cardiogenic shock); Previous attempts at ablation procedure or other AF operation, including surgical or catheter ablation; NYHA class IV heart failure (truncated – see evidence tables for full details)	Mixed	No HF	3 months	Open surgical	>5cm
Darkner, 2014[11, 12] AMIO-CAT TRIAL N=212 Denmark	Amiodarone versus usual care 400mg on night of ablation, then 400mg bd for 13 days, then 200mg bd for 2 weeks,	Unclear / mixed - about half on non-amiodarone AADs pre-ablation (people using amiodarone in previous 3	Inclusion: patients with paroxysmal or persistent AF undergoing first time or repeat ablation Exclusion: age <18 years, contraindications to or previous side effects during oral amiodarone therapy,	Mixed	No HF	8 weeks	RF point to point	<5cm

Study	Intervention and comparison	Stratum	Inclusion and exclusion criteria	Type of AF	Existence of HF	Duration of AAD treatment	Type of ablation	LA diameter
	then 200mg od for 4 weeks	months excluded), (15% digoxin, 21% flecainide/propafenone, 1% sotalol, 13% dronedarone in intervention group).	amiodarone therapy within 3 months before the ablation procedure, sustained AF <1 year, other atrial arrhythmias than AF and typical atrial flutter, severe heart failure (New York Heart Association class III, IV, or LVEF ,35%), significant heart valve disease, previous participating in the study, thyroid disease, severe pulmonary or liver disease, and woman with child bearing potential.					
Kaitani, 2016[20] EAST-AF TRIAL N=2044 Japan	AAD[a] versus usual care AAD started on the day of the ablation procedure. Initial doses were 150 mg/day for pilsicainide, 100 mg/day for flecainide, 300 mg/day for cibenzoline, 450 mg/day for propafenone, 300 mg/day for disopyramide, 40 mg/day for aprindine, 100	Unclear / mixed – About 60% had used at least 1 prior ineffective AAD. It is unlikely that many of the 40% not using AADs had been using an *effective* AADs as otherwise they would have not needed the ablation. Thus overall there is probably a mixture	Inclusion: patients who were 21–79 years old undergoing first-time radiofrequency catheter ablation for paroxysmal, persistent, or long- lasting AF were eligible for the study. Exclusion: contraindication or intolerance to ATP or Vaughan Williams class I or III AADs including severe asthma, severe vasospastic angina and substantial bradycardia, renal insufficiency (serum creatinine ≥2.0 mg/dL or on haemodialysis), New York Heart Association class IV heart failure, left ventricular	Mixed	No HF	90 days	RF point to point	<5cm

Study	Intervention and comparison	Stratum	Inclusion and exclusion criteria	Type of AF	Existence of HF	Duration of AAD treatment	Type of ablation	LA diameter
	mg/day for bepridil, 200 mg/day for amiodarone, and 80 mg/day for sotalol.	(60:40) of previous AADs and no previous AADs	ejection fraction,40%, LA diameter >55 mm, very long-lasting (≥5 years) AF, intolerance for optimal anticoagulation, myocardial infarction within the past 6 months, prior or planned open heart surgery, severe valvular heart disease.					
Hayashi, 2014[16] N=126 JAPAN	Flecainide versus usual care Started on evening after ablation. Administered bd with daily dose of 150mg in those weighing ≥50Kg and 100mg in those under 50kg.	Unclear/mixed – not clear how many had used AADs previously. Mean AADs per patient was 1, which is ambiguous. Amiodarone in previous 3 months excluded but this does not mean all AADs excluded.	Inclusion: all patients referred to the Nippon Medical School Teaching Hospital for ablation of AF Exclusion: <18 years; had a history of RFCA or surgery for AF; were on amiodarone therapy within 3 months or on bepridil therapy within 1 month; suffered from congestive heart failure or hypertrophic cardiomyopathy; showed any symptoms, electrocardiographic abnormalities, or images suggesting ischaemic heart disease; showed a left ventricular ejection fraction of <0.50; had a diagnosis of sick sinus syndrome; had any syncopal episodes; showed a resting heart rate of <50 beats per minute or second- or third-degree	Mixed	No HF	3 months	RF point to point	<5cm

Study	Intervention and comparison	Stratum	Inclusion and exclusion criteria	Type of AF	Existence of HF	Duration of AAD treatment	Type of ablation	LA diameter
			atrioventricular block; underwent haemodialysis. They also were excluded if all pulmonary veins were not isolated.					
Lodzinski, 2014[26] N=210 POLAND	AAD[a] versus usual care Given amiodarone (n=30), or sotalol (n=32) if unable to tolerate amiodarone, or the last ineffective AAD (n=58). Initiated during the first 24 hours after the procedure	Unclear/mixed stratum. Although not definitively stated, almost all must have been on AADs pre-ablation. One randomised group was designated 'last ineffective pre-ablation AAD for post-ablation use' so this must have meant that all in study were having AADs pre-ablation (if everyone had an equal chance of being randomised to this group, they had to be on prior	Inclusion: patients undergoing first PVI for AF;>18 years; sinus rhythm during first 24 hours after PVI Exclusion: reversible causes of AF; pre-procedural LA appendage thrombus; HR <50bpm; AV or IV blocks; contraindications to AADs used in study (except amiodarone as sotalol could be used instead); PVI procedure with heart tamponade complication	Paroxysmal	No HF	2 months	RF point to point	<5cm

Study	Intervention and comparison	Stratum	Inclusion and exclusion criteria	Type of AF	Existence of HF	Duration of AAD treatment	Type of ablation	LA diameter
		AADs). However not clear if participants were on these drugs up to the point of ablation.						
Roux, 2009[24, 33] 5A Study trial N=110 USA	AADs[a] versus usual care AADs started on the night of the procedure. Class 1C drugs were used in the absence of structural heart disease (propafenone 150mg TID or flecainide 100mg BID). For patients with normal LV function but CAD, sotalol 80mg BID was used. For abnormal LV function sotalol 80 mg BID or dofetilide 500 micrograms BID were used.	Unclear /mixed – only 72% receiving an AAD pre-ablation	Inclusion: patients referred for ablation of paroxysmal AF. Exclusion: persistent AF or flutter; inability to tolerate any AAD, amiodarone therapy within 3 months of ablation; inability to follow up; participation in another trial.	Parox-ysmal	No HF	6 weeks	Unclear	<5cm
Turco,	AAD versus usual	Unclear/mixed	Inclusion: People with AF	Mixed	No HF	1 month	RF point to	<5cm

Study	Intervention and comparison	Stratum	Inclusion and exclusion criteria	Type of AF	Existence of HF	Duration of AAD treatment	Type of ablation	LA diameter
2007[38] N=107 ITALY	care. The antiarrhythmic drug preferentially administered was amiodarone. In patients with a history of amiodarone adverse effects or intolerance, a class IC antiarrhythmic drug was administered	stratum. The population ONLY includes those where they were intolerant of AADs or had been unsuccessful with 2 or more AADs. However not clear if participants were on these drugs up to the point of ablation.	who had previously failed at least 2 AADs Exclusion: not reported	AF		(longer treatment was given but data in review were collected at 1 month)	point	

(a) The specific AAD used was at the discretion of the treating electrophysiologist

See Appendix D:for full evidence tables.

1.5.4 Quality assessment of clinical studies included in the evidence review

Table 3: Clinical evidence summary: AADs versus usual care [unclear/mixed 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 Amiodarone v usual care [unclear/mixed stratum] (95% CI)
Quality of life SF36 Physical	0 (0)	See comment	Not estimable	See comment	See comment
Mortality	2032 (1 study) 1year	⊕⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 1.5 (0.25 to 8.98)	2 per 1000	1 more per 1000 (from 2 fewer to 16 more)
Stroke or thromboembolic complications	2027 (1 study) 1year	⊕⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 3.01 (0.31 to 28.88)	1 per 1000	2 more per 1000 (from 1 fewer to 28 more)
Hospitalisation with a primary diagnosis of atrial arrhythmia	2034 (1 study) 1year	⊕⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 1.01 (0.25 to 4.03)	4 per 1000	0 more per 1000 (from 3 fewer to 12 more)
Cardioversion for AF	2134 (2 studies) 1 year	⊕⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision, inconsistency[c]	Random effects RR 0.72 (0.36 to 1.46)	237 per 1000	66 fewer per 1000 (from 152 fewer to 109 more)
All cause hospitalisation	0 (0)	See comment	Not estimable	See comment	See comment
Study drug discontinuation (and control switching)	2028 (1 study)	⊕⊕⊖⊖ LOW[a] due to risk of bias	RR 0.53 (0.40 to 0.68)	144 per 1000	68 fewer per 1000 (from 46 fewer to 86 fewer)

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 Amiodarone v usual care [unclear/mixed stratum] (95% CI)
	1year				
Repeat ablation within one year	2027 (1 study) 1 year	⊕⊕⊖⊖ LOW[a] due to risk of bias	RR 0.94 (0.78 to 1.14)	176 per 1000	11 fewer per 1000 (from 39 fewer to 25 more)
Any documented atrial arrhythmia	2415 (4 studies) 2 months – 1 year	⊕⊕⊖⊖ LOW[a] due to risk of bias	RR 0.94 (0.84 to 1.06)	340 per 1000	20 fewer per 1000 (from 54 fewer to 20 more)

[a] Risk of bias very serious due to selection and performance bias in studies
[b] If confidence intervals crossed one MID the imprecision was deemed serious. If the confidence intervals crossed two MIDS imprecision was deemed very serious
[c] Inconsistency serious if I2 from 50-74% and very serious if I2 >75%

Table 4: Clinical evidence summary: Amiodarone versus usual care [unclear/mixed 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 Amiodarone v usual care [unclear/mixed stratum] (95% CI)
Quality of life SF36 Physical	206 (1 study) 6 months	⊕⊕⊕⊖ MODERATE[a] due to risk of bias			The mean quality of life sf36 physical in the intervention groups was 0.7 higher (1.57 lower to 2.97 higher) [MID was deemed to be 4.3 points (based on 0.5 x median sd (8.6) in comparator group)]

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 Amiodarone v usual care [unclear/mixed stratum] (95% CI)
Quality of life SF36 Mental	206 (1 study) 6 months	⊕⊕⊕⊖ MODERATE[a] due to risk of bias			The mean quality of life sf36 mental in the intervention groups was 0.5 lower (3.14 lower to 2.14 higher) [MID was deemed to be 5 points (based on 0.5 x median sd (10) in comparator group)]
Mortality	296 (2 studies) 3 -6 months	⊕⊖⊖⊖ VERY LOW[b,c] due to risk of bias, imprecision	RR 0.59 (0.08 to 4.34)	Moderate	
				16 per 1000	7 fewer per 1000 (from 15 fewer to 53 more)
Stroke or thromboembolic complications	294 (2 studies) 3-6 months	⊕⊖⊖⊖ VERY LOW[b,c] due to risk of bias, imprecision	RR 0.93 (0.06 to 14.74)	Moderate	
				5 per 1000	0 fewer per 1000 (from 5 fewer to 69 more)
Hospitalisation with a primary diagnosis of atrial arrythmia	207 (1 study) 6 months	⊕⊕⊖⊖ LOW[a,c] due to risk of bias, imprecision	Rate ratio: 0.59 (0.32-1.09)	Moderate	
				-	-
Cardioversion for AF	87 (1 study) 3 months	⊕⊖⊖⊖ VERY LOW[a,c] due to risk of bias, imprecision	RR 0.73 (0.28 to 1.94)	Moderate	
				186 per 1000	50 fewer per 1000 (from 134 fewer to 175 more)
Cardioversion for AF (rate ratio)	207 (1 study) 6 months	⊕⊕⊖⊖ LOW[a,c] due to risk of bias, imprecision	Rate ratio: 0.53(0.30-0.94)	Moderate	
				-	-
All cause hospitalisation	206 (1 study) 6 months	⊕⊖⊖⊖ LOW[a,c] due to risk of bias,	Peto OR 7.06 (0.98 to	Moderate	
				0 per 1000	40 fewer per 1000 (from 0 fewer to 80 more)

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 Amiodarone v usual care [unclear/mixed stratum] (95% CI)
		imprecision	50.9)		
Study drug discontinuation (and control switching)	293 (2 studies) 3-6 months	⊕⊕⊖⊖ LOW[a,c] due to risk of bias, imprecision	RR 0.83 (0.55 to 1.27)	Moderate	
				280 per 1000	48 fewer per 1000 (from 126 fewer to 76 more)
Repeat ablation within one year	278 (2 studies) 3-6 months	⊕⊕⊖⊖ LOW[a,d] due to risk of bias, imprecision	RD -0.03 (-0.06 to 0.00)	Moderate	
				29 per 1000	30 fewer per 1000 (from 60 fewer to 0 fewer)
Any documented atrial arrythmia	293 (2 studies) 3-6 months	⊕⊕⊖⊖ LOW[a,c] due to risk of bias, imprecision	RR 0.67 (0.5 to 0.89)	Moderate	
				504 per 1000	166 fewer per 1000 (from 55 fewer to 252 fewer)

[a] Serious risk of bias due to selection bias or performance bias
[b] Very serious risk of bias due to selection bias and attrition bias
[c] Serious imprecision if confidence intervals crossed one MID and very serious if the confidence intervals crossed two MIDS
[d] Very serious imprecision because OIS<0.80

Table 5: Clinical evidence summary: flecainide versus usual care [unclear/mixed 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 Flecainide v usual care [unclear/mixed stratum] (95% CI)

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 Flecainide v usual care [unclear/mixed stratum] (95% CI)
Quality of life SF36 Physical	0 (0)	See comment	Not estimable	See comment	See comment
Mortality	0 (0)	See comment	Not estimable	See comment	See comment
Stroke or thromboembolic complications	0 (0)	See comment	Not estimable	See comment	See comment
Hospitalisation with a primary diagnosis of atrial arrythmia	0 (0)	See comment	Not estimable	See comment	See comment
Cardioversion for AF	125 (1 study) 3 months	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 4.06 (0.47 to 35.35)	Moderate	
				16 per 1000	49 more per 1000 (from 8 fewer to 550 more)
All cause hospitalisation	125 (1 study) 3 months	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 0.14 (0 to 6.93)	Moderate	
				16 per 1000	14 fewer per 1000 (from 16 fewer to 85 more)
Study drug discontinuation (and control switching)	125 (1 study) 3 months	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.72 (0.37 to 1.37)	Moderate	
				270 per 1000	76 fewer per 1000 (from 170 fewer to 100 more)
Repeat ablation within one year	0 (0)	See comment	Not estimable	See comment	See comment
Any documented atrial arrythmia	125 (1 study) 3 months	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias,	RR 0.9 (0.51 to 1.61)	Moderate	
				286 per 1000	29 fewer per 1000 (from 140 fewer to 174 more)

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 Flecainide v usual care [unclear/mixed stratum] (95% CI)
		imprecision			

[a] Very serious risk of bias due to selection and performance bias
[b] Imprecision serious if confidence intervals crossed one MID and very serious if confidence intervals crossed two MIDS

See Appendix F: for full GRADE tables.

1.6 Economic evidence

1.6.1 Included studies

No health economic studies were included.

1.6.2 Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

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

1.6.3 Unit costs

Relevant drug unit costs are provided in Table 6 to aid consideration of cost effectiveness.

Note, the Na+ channel blocker procainamide is only available from 'special-order' manufacturers or specialist importing companies and so has not been costed below.

Table 6: Drug unit costs

Class	Drug (preparation)	Dose range	Cost range per day	Cost range per year
Class IC (Na+ channel blockers)	Disopyramide (capsules)	300mg to 800 mg daily in divided doses	£0.79 to £2.10	£287.22 to £765.92
	Flecainide acetate (tablet)	50mg bd to 300mg daily	£0.16 to £0.26	£59.13 to £93.26
	Propafenone hydrochloride (tablet)	150mg tid to 300mg tid	£0.25 to £0.49	£89.67 to £179.34
Class II & III (beta blockers/K+ channel blocker)	Sotalol hydrochloride (tablet)	80 mg to 320 mg daily in 2 divided doses	£0.08 to £0.28	£28.94 to £102.98
Class III (K+ channel blocker)	Amiodarone (tablet)	200mg od	£0.12	£42.50
	Amiodarone (IV infusion)	Maximum 1.2 g per day	£5.87	N/A
	Dronedarone (tablet)	400mg bd	£2.25	£821.25

Source of cost and dose: BNF[5], last accessed January 2020.
Abbreviations: bd: twice daily;IV: intravenous; N/A: not applicable; od: once daily; tid: three times daily.

1.7 The committee's discussion of the evidence

1.7.1 Interpreting the evidence

1.7.1.1 The outcomes that matter most

Quality of life, stroke/systemic embolism, mortality, hospitalisation with a primary diagnosis of AF were regarded as 'critical' by the committee, whilst repeat ablation, any documented atrial arrhythmia, study drug discontinuation, and hospitalisation were regarded as relatively less critical and designated 'important'.

1.7.1.2 The quality of the evidence

Risk of bias was generally serious or very serious, as most outcomes were at high risk of selection, performance and attrition bias. A small number of outcomes exhibited serious heterogeneity, and these were sub-grouped according to the predefined protocol strategies, but resolution of heterogeneity was not achieved. In one outcome serious heterogeneity was observed, but because both studies showed the same direction of effect the heterogeneity was not addressed by sub-grouping and a fixed effect model was retained. The other main contributor to overall grading was imprecision. Overall, most outcomes were graded 'low' or 'very low'.

Although the protocol dictated stratification of studies into those where most patients had been on AADs until the ablation (and who were therefore randomised to continuing AADs or stopping AADs) or those where patients were not on AADs prior to the ablation (and who were therefore randomised to starting AADs or not starting AADs), no studies fitted into either category. This was either because the studies contained insufficient information to allow a decision on the most relevant stratum to be made, or because the study contained a mixture of patients (some were on AADs until ablation, but some were not). Hence all included studies were compiled into a single 'mixed/unclear' stratum.

1.7.1.3 Benefits and harms

Within the solitary 'mixed/unclear' stratum, three comparisons were meta-analysed: 1) Specific AADs given at the discretion of the physician versus usual care after ablation, 2) amiodarone versus placebo or usual care after ablation and 3) flecainide versus usual care after ablation. The usual care groups were poorly described but did not involve the provision of AADs. The benefits and harms within each of these comparisons are given below.

Specific AADs given at the discretion of the physician versus usual care after ablation

No clinical benefits or harms were evident for AADs over usual care for any outcomes. Because of the very small quantity of evidence (four trials) covering this comparison this was regarded as 'absence of evidence' rather than 'evidence of absence' by the committee.

Amiodarone versus usual care after ablation

Amiodarone led to a clinical benefit in terms of a lower rate of DC cardioversion and a reduction in the number of people developing subsequent atrial arrhythmia. However, amiodarone also led to the clinical harm of increased all-cause hospitalisation. This harm was deemed important by the committee. Overall the committee agreed that amiodarone was effective at reducing atrial fibrillation after ablation but carried risks of occasionally severe side-effects. These adverse effects were described as potentially life-threatening, but their rarity was emphasised.

The committee were also reminded that the absolute effect for *amiodarone versus usual care* implied that 6 people would need to be treated with amiodarone for one to obtain a benefit that would not otherwise have been obtained with usual care [a number needed to treat (NNT) of 6]. The patient members of the group felt this NNT was an unexpectedly large number indicating a surprisingly low benefit.

The committee noted that for the outcome of developing atrial arrhythmia, much of the effect in the 2-study meta-analysis was from the study using usual care as the comparator. The other study using placebo as the comparator showed a much more modest effect. Thus the committee were cautioned that some of the overall effect may have been driven by performance bias (although the possibility of the heterogeneity being due to other causes was also discussed).

In view of the above considerations, and the paucity of the evidence, the committee as a whole were not fully convinced by the efficacy of amioadarone in reducing AF recurrence after ablation, and they were also concerned about the potential side effects. The committee noted that the evidence was insufficient to change what they deemed current practice - which was *not* to begin AADs if the patient had not been taking them prior to the ablation. It was also suggested that current practice for patients taking AADs up to ablation is to continue them for 3 months post-ablation, and, equally, the committee did not feel that the review evidence opposed this practice. These views were not consensus views, however, with some members stating that these descriptions of current practice did not cover the entire UK and that practice varied widely.

Overall, the committee felt that amiodarone should not be discarded as an option but that it should not be freely recommended either. A recommendation was made to consider the use of AADs only after an assessment of the patients' likely risks and benefits as well as consideration of the patients' views. This suggestion was welcomed by the committee as a useful 'middle ground' that would allow suitably considered use of a potentially useful drug by recognising the potential of AADs to reduce AF recurrence whilst carefully considering the risks, benefits and patient views.

Flecainide versus usual care after ablation

No clinical benefits or harms were evident for flecainide over usual care for any outcomes. Because of the very small quantity of evidence (1 trial) covering this comparison this was regarded as 'absence of evidence' rather than 'evidence of absence' by the committee.

Overall decision

The committee decided to recommend reassessment of the need for AADs, and, conditional on that careful reassessment and consideration of the patients' views, to permit up to three months treatment with AADs after ablation. Some of the committee were concerned that the evidence was only in favour of amiodarone, and that recommending all AADs in this way ignored this. However, following further discussion, the committee agreed that as most of the evidence was for amiodarone and only one study used an alternative AAD, with no comparisons between the different AADs, there was insufficient evidence to recommend one specific AAD following ablation in all cases. It was noted that flecainide is also used fairly commonly in current practice and that in those that were already receiving AADs prior to their ablation procedure, the drug that was being used prior to ablation would most likely be continued in current practice. In addition, no distinction between people who had been on AADs up to ablation and people who had not been using AADs prior to ablation was made. This was discussed by the committee and although there was some disagreement as to whether in current practice those who had not been on AADs prior to ablation would be started on AADs following ablation as a strategy of reducing recurrence following ablation, it was clear that in many cases this would be considered. The committee agreed that the current wording of the recommendations, where AAD use should be considered after taking into account the potential benefits, harms and patient preferences, allowed this option for

those that had not been on AADs prior to ablation as well as those that were already on AADs prior to ablation. The committee noted that AADs can be associated with potentially severe adverse events and that these should be made clear to patients as part of the shared decision-making process when deciding whether to consider AADs following ablation.

1.7.2 Cost effectiveness and resource use

No relevant health economic analyses were identified for this review. The unit costs of antiarrhythmic drugs were presented. The recommendation is a weaker 'consider' recommendation reflecting the limited clinical evidence and lack of economic evidence. The committee discussed the clinical evidence which indicated that that amiodarone was effective at reducing atrial fibrillation after ablation but carried risks of occasionally severe side-effects. The committee discussed the serious adverse effects associated with the use of amiodarone (including thyroid, lung and nerve damage), many of which are irreversible. They noted amiodarone requires intensive monitoring (such as annual cardiology appointment and 6-monthly liver and thyroid function tests) which has an associated cost. Furthermore, if a person experiences these serious adverse events then there would be a significant cost to both the patient in terms of prognosis and NHS in terms of treatment and long-term management. The committee noted that these are more common with long term use but can occur with short term use, although very rarely. Amiodarone also has some more common adverse events, but these are reversible and would have minimal impact in terms of costs to the NHS. The committee discussed that the trade-off is the cost of amiodarone, monitoring and rare serious adverse events versus reduced atrial fibrillation hospitalisations and cardioversion, and felt that the costs were likely to be offset.

The committee also discussed current practice and how these recommendations may alter current practice. Currently it was thought that if the person had not been taking AADs prior to the ablation then they would not be given AADs post ablation, and if a person was taking AADs up to ablation then they would continue for 3-months post ablation, that is until their first review post ablation. This would mean that these new recommendations would change current practice, because it would mean that some people previously on AADs could be removed from them, and some not previously on AADs might be started on them. The effects of these recommendations on the quantity of AAD provision are difficult to predict, but might lead to an increase in provision from current levels.

1.7.3 Other factors the committee took into account

The committee discussed whether the evidence suggested that very early recurrence of AF (<3 months) may be associated with a worse long-term outcome, and that successful prevention of such early AF re-occurrence through treatment may therefore improve long-term outcomes. The committee noted that the use of the longest available follow up in the meta-analyses did not allow the committee to observe the more pronounced and significant benefits in terms of reducing AF recurrence that occurred after a shorter 3 month follow up for amiodarone, that could imply the possibility of better outcomes in the longer term. The committee agreed that the assumed links between better short-term suppression of recurrence and improved long-term outcomes were not sufficiently strong to take precedence over the direct evidence (from the longest available follow up in our meta-analyses) of modest longer-term effects on recurrence and no discernible benefits in other outcomes.

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Appendices

Appendix A: Review protocols

Table 7: Review protocol: Antiarrhythmic drugs after 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 short-term (<6 months) antiarrhythmic drugs following ablation for preventing recurrence of atrial fibrillation
2.	Review question	What is the clinical and cost effectiveness of short-term (<6 months) antiarrhythmic drugs following ablation for preventing recurrence of atrial fibrillation?
3.	Objective	To identify the clinical effects of short-term antiarrhythmic drugs on recurrence of AF after ablation
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 AF undergoing an ablative procedure. Exclusion: People with AF due to severe valvular disease
7.	Intervention/Exposure/Test	Rhythm control medication Na+ channel blockers, such as – amiodarone, procainamide, disopyramide, quinidine sulphate, flecainide, propafenone

ID	Field	Content
		K+ channel blockers, such as – dronedarone, ibutilide, sotalol RCTs where patients in the intervention group are given different Na+ or K+ blockers to each other on the basis of clinical indication (but each patient only receives one specific drug) will also be included.
8.	Comparator/Reference standard/Confounding factors	All compared to: each other (both within and across classes) Placebo Usual Care / 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 hospitalisation with a primary diagnosis of atrial arrhythmia Cardioversion for AF.
13.	Secondary outcomes (important outcomes)	All cause hospitalisation Study drug discontinuation Repeat ablation procedure within 1 year Any documented atrial arrhythmia
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 a third reviewer where necessary).
15.	Risk of bias	Risk of bias will be assessed using the appropriate checklist as

ID	Field	Content
	(quality) assessment	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 The only stratification strategy will be by previous use of AADs. The strata will be: Studies where anti-arrhythmic drugs are already being used pre-ablation, and the randomisation is to a group that continues on the anti-arrhythmic drugs after ablation and a group that stops anti-arrhythmic drugs after ablation. Studies where there are no anti-arrhythmic drugs being used pre-ablation, and the randomisation is to a group that commences arrhythmic drugs after ablation and a group that does not commence them after ablation. Studies where it is unclear if an AAD regimen was in use pre-ablation, or where the patients varied in terms of previous AADs The above stratification is performed unconditionally and ‘up-front’. Sub-grouping If serious or very serious heterogeneity (I2>50%) is present within

ID	Field	Content		
		each stratum, sub-grouping within each stratum will occur according to the following strategies: Type of AF (persistent > 1 year, persistent < 1 year, paroxysmal, mixed or unclear) Existence of HF (yes/No) Duration of treatment (<1 month/1-3months / >3-6 months) Type of ablation (thoracoscopic surgical ablation / open surgical ablation / hybrid (catheter - surgical) ablation / point by point radiofrequency catheter ablation / multi-electrode radiofrequency catheter ablation / cryoballoon catheter ablation/ laser catheter ablation / mixed or unclear Left atrial size (< 5cm vs > 5cm)		
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		

ID	Field	Content
		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 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, rate-limiting drugs
33.	Details of existing review of same topic by same authors	N/A
34.	Current review	☒ Ongoing

ID	Field	Content	
	status	☐	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

2 **Table 8: 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.[30] **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.

1

Appendix B: Literature search strategies

This literature search strategy was used for the following reviews;

- **What is the clinical and cost effectiveness of short-term (<6 months) antiarrhythmic drugs following ablation for preventing recurrence of atrial fibrillation?**

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[30]

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 9: 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
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

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)

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)

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 Health Economics literature search strategy

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

Table 10: Database date parameters and filters used

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

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.	24 and 41

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.	22 and 36

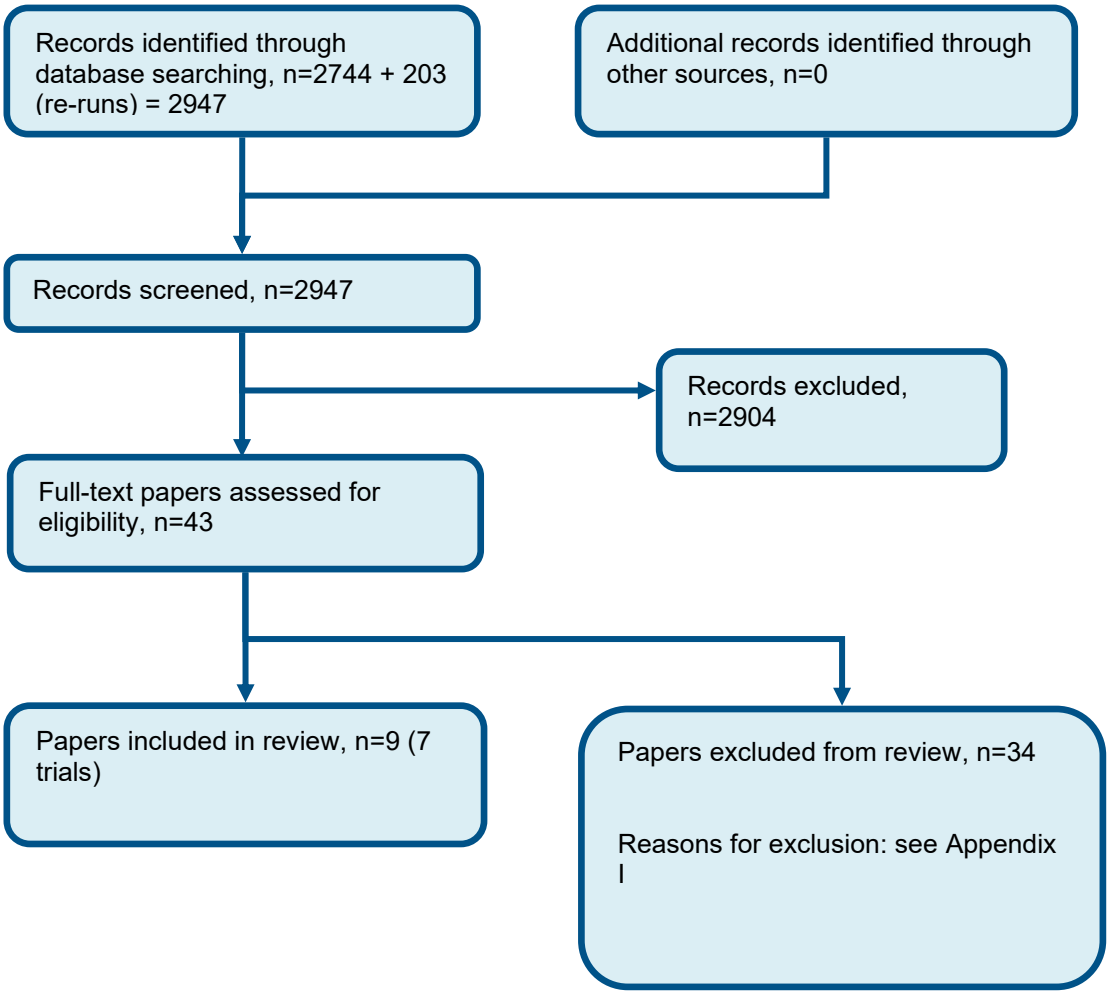
1 **NHS EED and HTA (CRD) search terms**

#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)

2
3

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of AF



Appendix D: Clinical evidence tables

Study	AD, 2016 trial: Ad 2016[1]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=97)
Countries and setting	Conducted in USA; Setting: unclear
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	Unclear or mixed
Subgroup analysis within study	Not applicable
Inclusion criteria	Age >=18; Persistent or long-standing persistent AF, according to HRS guidelines; Candidate to undergo the Cox maze procedure for AF; Left ventricular ejection fraction >=30%; Normally would be prescribed amiodarone as an AAD after surgical ablation; Able and willing to provide written informed consent; Able and willing to comply with all study requirements including attending follow-up visits; Life expectancy of>=1y
Exclusion criteria	Emergent cardiac surgery (e.g., cardiogenic shock); Previous attempts at ablation procedure or other AF operation, including surgical or catheter ablation; NYHA class IV heart failure; Documented myocardial infarction within 6 weeks before study enrolment; Accessory-pathways disorder (e.g., Wolff-Parkinson-White syndrome); Carotid artery stenosis>80%; Current diagnosis of active systemic infection; Pregnant, planning to become pregnant within 12-14 months, or lactating; Preoperative intra-aortic balloon pump or intravenous inotropes; Renal failure requiring dialysis; Hepatic failure; Taking antiarrhythmic drug therapy for ventricular arrhythmia; Known connective tissue disorder; Previous or current therapy that could compromise tissue integrity, including thoracic radiation, chemotherapy, or long-term oral or injected steroids; Intravenous drug and/or alcohol abuse; Participation in concomitant research

	studies of investigational products.
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Range of means: 63.4 to 63.8. Gender (M:F): 65:25. Ethnicity: Unclear
Further population details	1. existence of HF: No HF (LVEF over 54%). 2. left atrial size: >=5cm (Both groups with mean at 5/5.1cm). 3. Type of ablation: open surgical (defined as surgical ablation). 4. type of AF: mixed (<75% of any type) (55/90 persistent < 1 year and 35/90 persistent > 1 year - so mixed rather than either sub-group).
Extra comments	Amiodarone/ no amiodarone: LVEF 55.2%/54.4%; CHF 22%/27%; DM 18%/7%; Hypertension 60%/67%; PVD 2%/9%; CPD 20%/24%; L atrial size 5/5.1 cm; duration AF 23mo/20 mo; long standing persistent AF 44%/33%; EUROSCORE II 2.4/2.9; Concomitant mitral valve surgery 51%/60%; concomitant aortic valve surgery 20%/18%; concomitant CABG 13%/18%
Indirectness of population	No indirectness
Interventions	(n=45) Intervention 1: Na+ channel blockers - amiodarone. No details on dose. Amiodarone given immediately post-op. . Duration 3 months. Concurrent medication/care: Cox maze III/IV lesion set. Both groups received post-operative beta-blockers. Allowed to stop amiodarone if side-effects occurred. Indirectness: No indirectness Further details: 1. Duration of treatment: (n=45) Intervention 2: usual care. Same background treatment of beta-blockers after Cox Maze procedure, but no treatment with amiodarone. Duration 3 months. Concurrent medication/care: NA. Indirectness: No indirectness Further details: 1. Duration of treatment:
Funding	Equipment / drugs provided by industry (CardioNet provided the Dual Alert Afib Event Monitors)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AMIODARONE versus USUAL CARE

Protocol outcome 1: Stroke or thromboembolic complications
- Actual outcome for Unclear or mixed : Stroke or TIA at 3 months; Group 1: 0/44, Group 2: 0/43
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: 7, Reason: did not receive surgical ablation + 1 death + 1 non responder; Group 2 Number missing: 3, Reason: did not receive ablation + 1 death Protocol outcome 2: Mortality - Actual outcome for Unclear or mixed : mortality at 3 months; Group 1: 1/44, Group 2: 1/45; Comments: operative mortality 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: 6, Reason: did not receive surgical ablation + non responder; Group 2 Number missing: 2, Reason: did not receive ablation Protocol outcome 3: cardioversion for AF - Actual outcome for Unclear or mixed : Electrical cardioversions at 3 months; Group 1: 6/44, Group 2: 8/43 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, Reason: did not receive surgical ablation; Group 2 Number missing: 5, Reason: did not receive ablation Protocol outcome 4: Repeat ablation within 1 year - Actual outcome for Unclear or mixed : Follow up catheter ablations within 12 weeks at 3 months; Group 1: 0/43, Group 2: 0/44 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: 7, Reason: did not receive surgical ablation + death + non responder; Group 2 Number missing: 3, Reason: did not receive ablation + death Protocol outcome 5: Any documented atrial arrythmia - Actual outcome for Unclear or mixed : AF recurrence at 3 months; Group 1: 8/43, Group 2: 23/44 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, Reason: did not receive surgical ablation; Group 2 Number missing: 5, Reason: did not receive ablation Protocol outcome 6: study drug discontinuation - Actual outcome for Unclear or mixed : Switching to other group (stopping amiodarone versus starting amiodarone) at 3 months; Group 1: 18/43, Group 2: 18/44; Comments: Cross-over from amiodarone to no amiodarone was because of side effects; cross-over from usual care to amiodarone was because of AF recurrence. 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, Reason: did not receive surgical ablation; Group 2 Number missing: 5, Reason: did not receive ablation
Protocol outcomes not reported by the study	Quality of life ; hospitalisation with primary diagnosis of AF ; Hospitalisation ; Length of stay

Study (subsidiary papers)	AMIO-CAT TRIAL, 2014 trial: Darkner 2014[11] (Diederichsen 2016[12])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=212)
Countries and setting	Conducted in Denmark
Line of therapy	1st line
Duration of study	Follow up (post intervention): 6 months (but treatment only 8 weeks)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Unclear/mixed
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with paroxysmal or persistent AF undergoing first time or repeat ablation
Exclusion criteria	Exclusion criteria were age <18 years, contraindications to or previous side effects during oral amiodarone therapy, amiodarone therapy within 3 months before the ablation procedure, sustained AF <1 year, other atrial arrhythmias than AF and typical atrial flutter, severe heart failure (New York Heart Association class III, IV, or LVEF <35%), significant heart valve disease, previous participating in the study, thyroid disease, severe pulmonary or liver disease, and woman with child bearing potential.
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Range of means: 61-62. Gender (M:F): 76:36. Ethnicity: unclear
Further population details	1. existence of HF: No HF (all NYHA I or II). 2. left atrial size: <5 cm (44mm). 3. Type of ablation: RF point by point (no evidence that multielectrode devices used). 4. type of AF: mixed (<75% of any type) (50% persistent).
Extra comments	amiodarone/placebo: AF duration 78mo/76mo; previous AADs 1.2/1/1; previous ablation 30%/28%; persistent AF

	50%/49%; LVEF 51/50; LA diam 44/44; Hypertension 37%/42%; CAD 6%/8%; Stroke or TIA 6%/7%; DM 9%/8%; Number on AADs (none on amiodarone) at baseline: beta 58%/62%; Ca blockers 15%/10%; digoxin 15%/12%; flecainide/profenone 21%/24%; sotalol 1%/2%; dronedarone 13%/12%
Indirectness of population	No indirectness
Interventions	(n=108) Intervention 1: Na+ channel blockers - amiodarone. The loading regimen was inspired from the EMIAT trial. Amiodarone was initiated on the night of the ablation with a dose of 400 mg, thereafter 400 mg twice daily for 13 days, then 200 mg twice daily for 2 weeks and finally 200 mg once daily for 4 weeks. Patients weighing ,60 kg were individually dosed. Other antiarrhythmic medications were discontinued 3–5 days before ablation except rate controlling medication given for other indications (e.g. hypertension, ischaemic heart disease, and systolic dysfunction). Rate controlling medication could be started within the study-medication period if needed. Duration 8 weeks. Concurrent medication/care: Patients underwent transthoracic echocardiography before the ablation and no longer than 3 months prior to the ablation procedure. Thoracic X-ray, thyroid, and liver parameters were tested within 3 days before ablation to reveal possible exclusion criteria. All patients underwent trans-oesophageal echocardiography within 48 h of the ablation and were on continuous oral anticoagulation (OAC) with a vitamin K antagonist for at least 4 weeks pre-ablation and 3 months post-ablation. All patients underwent pulmonary vein (PV) isolation by radiofrequency ablation. A three-dimensional mapping system was used in all patients (NavX or CARTO). Procedural end-point was PV isolation by wide antral circumferential ablation assessed by meticulous remapping (centre 1) or by a circular mapping catheter (centre 2). If atrial tachyarrhythmias occurred, they were mapped and ablated by standard approaches. Additional substrate modification (linear ablations or complex fractionated electrogram-guided ablations) was left to the discretion of the operating electrophysiologist. Complex fractionated electrogram-guided ablations were considered in patients with longer lasting persistent AF (i.e. patients with episodes of persistent AF lasting for months) or targeted if electrical cardioversion failed following PV isolation. A fairly conservative strategy for additional ablations was followed. Cavotricuspid isthmus block was performed in patients with documented typical atrial flutter. Patients undergoing re-ablation where the PVs were found already isolated were not randomized in the study. Each patient only underwent a single ablation procedure during their participation in the trial. Indirectness: No indirectness Further details: 1. Duration of treatment: 1-3 months (8 weeks). (n=104) Intervention 2: placebo. Identical matched placebo. Duration 8 weeks. Concurrent medication/care: Patients underwent transthoracic echocardiography before the ablation and no longer than 3 months prior to the ablation procedure. Thoracic X-ray, thyroid, and liver parameters were tested within 3 days before ablation to reveal possible exclusion criteria. All patients underwent trans-oesophageal echocardiography within 48 h of the ablation and were on continuous oral anticoagulation (OAC) with a vitamin K antagonist for at least 4 weeks pre-ablation and 3 months post-ablation. All patients underwent pulmonary vein (PV) isolation by radiofrequency ablation. A three-dimensional mapping system was used in all patients (NavX or CARTO). Procedural end-point was PV isolation by wide antral

	circumferential ablation assessed by meticulous remapping (centre 1) or by a circular mapping catheter (centre 2). If atrial tachyarrhythmias occurred, they were mapped and ablated by standard approaches. Additional substrate modification (linear ablations or complex fractionated electrogram-guided ablations) was left to the discretion of the operating electrophysiologist. Complex fractionated electrogram-guided ablations were considered in patients with longer lasting persistent AF (i.e. patients with episodes of persistent AF lasting for months) or targeted if electrical cardioversion failed following PV isolation. A fairly conservative strategy for additional ablations was followed. Cavotricuspid isthmus block was performed in patients with documented typical atrial flutter. Patients undergoing re-ablation where the PVs were found already isolated were not randomized in the study. Each patient only underwent a single ablation procedure during their participation in the trial. Indirectness: No indirectness Further details: 1. Duration of treatment: 1-3 months (8 weeks).
Funding	Academic or government funding (Danish heart foundation and the heart centre research committee)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AMIODARONE versus PLACEBO

Protocol outcome 1: Quality of life
- Actual outcome for Study where same AADs are not being used pre-ablation : SF36 physical at 6 months; Group 1: mean 51 points (SD 8); n=107, Group 2: mean 50.3 points (SD 8.6); n=99; Comments: Similar at baseline 47.1 vs 46.8 but could explain half the change seen
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: withdrawn to start open amiodarone; Group 2 Number missing: 5, Reason: 2 withdrawn to start open amiodarone, 1 died, 1 withdrew consent 1 day after randomisation, 1 excluded due to pre-existing thyroid disease
- Actual outcome for Study where same AADs are not being used pre-ablation : SF36 mental at 6 months; Group 1: mean 52.5 points (SD 9.3); n=107, Group 2: mean 53 points (SD 10); n=99; Comments: Not similar at baseline 46.4 vs 48.9. This would more than explain the difference at FU
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: withdrawn to start open amiodarone; Group 2 Number missing: 5, Reason: 2 withdrawn to start open amiodarone, 1 died, 1 withdrew consent 1 day after randomisation, 1 excluded due to pre-existing thyroid disease

Protocol outcome 2: Stroke or thromboembolic complications
- Actual outcome for Study where same AADs are not being used pre-ablation : stroke or TIA at 6 months; Group 1: 1/107, Group 2: 1/100
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: possibly related to outcome; Group 2 Number missing: 4, Reason: possibly related to outcome

Protocol outcome 3: Mortality

- Actual outcome for Study where same AADs are not being used pre-ablation : Death at 3 months; Group 1: 0/107, Group 2: 1/100
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 4

Protocol outcome 4: hospitalisation with primary diagnosis of AF
- Actual outcome for Study where same AADs are not being used pre-ablation : AF/AT related hospitalisations at 6 months; (95%CI 0.32 to 1.06); Comments: Rate ratio (amiodarone v placebo) for all patients over total study duration
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: withdrawn to start open amiodarone; Group 2 Number missing: 5, Reason: 2 withdrawn to start open amiodarone, 1 died, 1 withdrew consent 1 day after randomisation, 1 excluded due to pre-existing thyroid disease

Protocol outcome 5: cardioversion for AF
- Actual outcome for Study where same AADs are not being used pre-ablation : Cardioversions at 6 months; (95%CI 0.3 to 0.92); Comments: Rate ratio (amiodarone v placebo) for all patients over whole duration of study
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: withdrawn to start open amiodarone; Group 2 Number missing: 5, Reason: 2 withdrawn to start open amiodarone, 1 died, 1 withdrew consent 1 day after randomisation, 1 excluded due to pre-existing thyroid disease

Protocol outcome 6: Repeat ablation within 1 year
- Actual outcome for Study where same AADs are not being used pre-ablation : Re-ablation within 8 weeks of randomisation at 8 weeks; Group 1: 0/98, Group 2: 4/93
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 10, Reason: Those that discontinued medication early for other reasons - side effects (6), use of open-label AAD due to recurrent AF (4); Group 2 Number missing: 11, Reason: Those that discontinued medication early for other reasons - side effects (2), lost to follow-up (2), use of open-label AAD due to recurrent AF (7)

Protocol outcome 7: Any documented atrial arrhythmia
- Actual outcome for Study where same AADs are not being used pre-ablation : documented (symptomatic or asymptomatic) episode of AF or AT>30 s at 6 months; Group 1: 42/107, Group 2: 48/99
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: withdrawn to start open amiodarone; Group 2 Number missing: 5, Reason: 2 withdrawn to start open amiodarone, 1 died, 1 withdrew consent 1 day after randomisation, 1 excluded due to pre-existing thyroid disease

Protocol outcome 8: study drug discontinuation
- Actual outcome for Study where same AADs are not being used pre-ablation : Premature discontinuation of study drug at 8 weeks; Group 1: 10/107, Group 2: 15/99; Comments:
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;

Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 9: Hospitalisation - Actual outcome for Study where same AADs are not being used pre-ablation : Hospitalisation due to high INR at 6 months; Group 1: 4/107, Group 2: 0/99 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 4	
Protocol outcomes not reported by the study	Length of stay

Study	EAST-AF trial, 2016 trial: Kaitani 2016[20]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=2044)
Countries and setting	Conducted in Japan; Setting: Cardiovascular centres in Japan
Line of therapy	1st line
Duration of study	Intervention time: 90 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Unclear or mixed
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients who were 21–79 years old undergoing first-time radiofrequency catheter ablation for paroxysmal, persistent, or long- lasting AF were eligible for the study.
Exclusion criteria	contraindication or intolerance to ATP or Vaughan Williams class I or III AADs including severe asthma, severe vasospastic angina and substantial bradycardia, renal insufficiency (serum creatinine ≥2.0 mg/dL or on haemodialysis), New York Heart Association class IV heart failure, left ventricular ejection fraction,40%, LA diameter >55 mm, very long-lasting (≥5 years) AF, intolerance for optimal anticoagulation, myocardial infarction within the past 6 months, prior or planned open heart surgery, severe valvular heart disease, inability to be followed at the outpatient clinic for 1 year, unwillingness to sign the consent form for participation, and patients whom the attending physician considered inappropriate to enrol in the study.
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Range of means: 65.9 to 60.7. Gender (M:F): 1530:514. Ethnicity: unclear
Further population details	1. existence of HF: No HF (LVEF over 64%), 2. left atrial size: <5 cm (38-39mm), 3. Type of ablation: RF point by point

	(irrigation catheter). 4. type of AF: mixed (<75% of any type) (paroxysmal 66.9 to 68.1%).
Extra comments	AAD/control: history of AF 24.2m/23.9m; Paroxysmal 68.1%/66.9%; CHADS2 >2 11.1%/7.4%; hypertension 55.2%/51.5%; DM 15.2%/11.5%; HF 8.7%/7.1%; LVEF 64.5/64.2; LA diam 38.9/39mm; moderate valvular heart disease 8.5%/4.9%; stroke or TIA 8%/8.4%; MI 2.3%/1.2%;
Indirectness of population	No indirectness
Interventions	(n=1018) Intervention 1: Mixed Na+ channel or K+ channel regimen - mixed regimen. Vaughan Williams class I or III AAD was started on the day of the ablation procedure. The choice and dosage of AADs were to be determined according to the Japanese AF guidelines and the reimbursement approval in Japan. The initial doses or standard maintenance doses of AADs approved by the reimbursement were 150 mg/day for pilsicainide, 100 mg/day for flecainide, 300 mg/day for cibenzoline, 450 mg/day for propafenone, 300 mg/day for disopyramide, 40 mg/day for aprindine, 100 mg/day for bepridil, 200 mg/day for amiodarone, and 80 mg/day for sotalol. Usage of amiodarone for AF was approved only in patients with heart failure, reduced left ventricular function, and/or hypertrophic cardiomyopathy. Sotalol was approved only for ventricular tachyarrhythmias. Neither dronedarone nor dofetilide was commercially available. For safety reason, the actual choice and dosage of the AADs were left to the discretion of the attending physician. Duration 90 days. Concurrent medication/care: All patients had prior RF ablation. No information on AAD use prior to ablation. . Indirectness: No indirectness Further details: 1. Duration of treatment: (n=1026) Intervention 2: usual care. No details given. Duration 90 days. Concurrent medication/care: All patients had prior RF ablation. No information on AAD use prior to ablation. . Indirectness: No indirectness Further details: 1. Duration of treatment:
Funding	Academic or government funding (Research Institute for Production development, Kyoto, Japan)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MIXED REGIMEN versus USUAL CARE

Protocol outcome 1: Stroke or thromboembolic complications
- Actual outcome for Unclear or mixed : Ischaemic stroke at 1 year; Group 1: 3/1012, Group 2: 1/1015
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: 3, Reason: unclear; Group 2 Number missing: 9, Reason: unclear

Protocol outcome 2: Mortality
- Actual outcome for Unclear or mixed : Death at 1 year; Group 1: 3/1015, Group 2: 2/1017
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: 3, Reason: unclear; Group 2 Number missing: 9, Reason: unclear

Protocol outcome 3: cardioversion for AF
- Actual outcome for Unclear or mixed : cardioversion at 1 year; Group 1: 113/1012, Group 2: 117/1015
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: 6, Reason: unclear for 3 + 3 deaths; Group 2 Number missing: 11, Reason: unclear for 9 + 2 deaths

Protocol outcome 4: Repeat ablation within 1 year
- Actual outcome for Unclear or mixed : Repeat ablation at 1 year; Group 1: 168/1012, Group 2: 179/1015
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: 6, Reason: unclear for 3 + 3 deaths; Group 2 Number missing: 11, Reason: unclear for 9 + 2 deaths

Protocol outcome 5: Any documented atrial arrythmia
- Actual outcome for Unclear or mixed : Recurrence of AF at 1 year at 1 year; Group 1: 309/1012, Group 2: 327/1015
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: 6, Reason: unclear for 3 + 3 deaths; Group 2 Number missing: 11, Reason: unclear for 9 + 2 deaths
- Actual outcome for Unclear or mixed : Recurrence of AF at 90 days at 90 days; Group 1: 417/1016, Group 2: 490/1022
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, Reason: unclear ; Group 2 Number missing: 4, Reason: unclear

Protocol outcome 6: study drug discontinuation
- Actual outcome for Unclear or mixed : Discontinuation of study drug (or commencement of AADs for control groups) at 90 days; Group 1: 77/1016, Group 2: 146/1012
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, Reason: unclear ; Group 2 Number missing: 4, Reason: unclear

Protocol outcome 7: Hospitalisation
- Actual outcome for Unclear or mixed : Hospitalisation for HF at 1 year; Group 1: 4/1012, Group 2: 4/1022
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: 3, Reason: unclear; Group 2 Number missing: 9, Reason: unclear

Protocol outcomes not reported by the study	Quality of life ; hospitalisation with primary diagnosis of AF ; Length of stay

Study	HAYASHI, 2014 trial: Hayashi 2014[16]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=126)
Countries and setting	Conducted in Japan; Setting: Teaching Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up: 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Unclear or mixed
Subgroup analysis within study	Not applicable
Inclusion criteria	All patients referred to the Nippon Medical School Teaching Hospital for ablation of AF
Exclusion criteria	<18 years; had a history of RFCA or surgery for AF; were on amiodarone therapy within 3 months or on bepridil therapy within 1 month; suffered from congestive heart failure or hypertrophic cardiomyopathy; showed any symptoms, electrocardiographic abnormalities, or images suggesting ischaemic heart disease; showed a left ventricular ejection fraction of ,0.50; had a diagnosis of sick sinus syndrome; had any syncopal episodes; showed a resting heart rate of <50 beats per minute or second- or third-degree atrioventricular block; underwent haemodialysis; were unable to be followed-up at the study site; were participating in another clinical trial evaluating AAD efficacy; or were unwilling to provide informed consent. They also were excluded if all pulmonary veins were not isolated.
Recruitment/selection of patients	Consecutive
Age, gender and ethnicity	Age - Range of means: 62-64. Gender (M:F): 77:23. Ethnicity: unclear
Further population details	1. existence of HF: No HF (LVEF 68-69%). 2. left atrial size: <5 cm (38mm). 3. Type of ablation: RF point by point (4mm tip irrigated ablation catheter used). 4. type of AF: mixed (<75% of any type) (71-72% paroxysmal).

Extra comments	Flecainide/control: history of AF 5.2yrs/4.4yrs; paroxysmal AF 71%/72%; number of failed AADs 1/1; LA diam 38/38mm; LVEF 69/68; history of stroke 8%/6%; hypertension 65%/61%; sleep apnoea 8%/5%; DM 5%/9%; COPD 0/2%
Indirectness of population	No indirectness
Interventions	(n=62) Intervention 1: Na+ channel blockers - flecainide. Flecainide was started on the evening after the ablation procedure, and administered bd with a daily dose of 150 mg in those weighing ≥50 kg and 100 mg in those weighing <50 kg. The treating electrophysiologists continued flecainide with the same dose during the early period unless there were observable side effects, such as symptomatic hypotension (systolic blood pressure of <90 mm Hg), bradycardia during sinus rhythm (heart rate of<50 beats per minute) or after restoration of sinus rhythm from AF (sinus pause of >4 s), dyspnoea, presyncope, syncope, or episodes of ventricular tachyarrhythmia developed. Flecainide was changed to another AAD if there were at least three episodes of AF/AT or the development of the secondary endpoint, which was a clinically significant AT. The choice of the alternative AAD depended on the treating electrophysiologists. Mean dose was 143 mg per day (2.2 mg/kg/day). Duration 3 months. Concurrent medication/care: RF point to point given. Atrial rhythm continuously measured with telemetry monitoring. (n=64) Intervention 2: No treatment. No AADs given. Administration of class I or III AADs was avoided unless there was a patient request to take AADs, at least 3 episodes of ATs, or occurrence of secondary endpoint (24 hrs of AF or AF requiring hospitalisation). Duration 3 months. Concurrent medication/care: RF point to point given. AF measured continuously with telemetry until discharge. Indirectness: No indirectness
Funding	Academic or government funding (Japanese National Grant)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FLECAINIDE versus NO TREATMENT

Protocol outcome 1: cardioversion for AF
- Actual outcome for Unclear or mixed : Electrical cardioversion at 3 months; Group 1: 4/62, Group 2: 1/63
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: 1, Reason: unknown

Protocol outcome 2: Any documented atrial arrythmia - Actual outcome for Unclear or mixed : AF recurrence at 3 months; Group 1: 19/62, Group 2: 20/63 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: 1, Reason: unknown - Actual outcome for Unclear or mixed : AT recurrence at 17 months; Group 1: 16/62, Group 2: 18/63 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: 1, Reason: unknown Protocol outcome 3: study drug discontinuation - Actual outcome for Unclear or mixed : Stopping or changing drug (or starting AADs for control group) at 3 months; Group 1: 12/62, Group 2: 17/63 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: 1, Reason: unknown Protocol outcome 4: Hospitalisation - Actual outcome for Unclear or mixed : Emergency admission (reason not stated) at 3 months; Group 1: 0/62, Group 2: 1/63 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: 1, Reason: unknown	
Protocol outcomes not reported by the study	Quality of life ; Stroke or thromboembolic complications ; Mortality ; hospitalisation with primary diagnosis of AF ; Repeat ablation within 1 year ; Length of stay

Study	LODZINSKI, 2014 trial: Lodzinski 2014[26]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=210)
Countries and setting	Conducted in Poland; Setting:
Line of therapy	1st line
Duration of study	Intervention time: 2 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Unclear or mixed
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients undergoing first PVI for AF;>18 years; sinus rhythm during first 24 hours after PVI
Exclusion criteria	Reversible causes of AF; pre-procedural LA appendage thrombus; HR <50bpm; AV or IV blocks; contraindications to AADs used in study (except amiodarone as sotalol could be used instead); PVI procedure with heart tamponade complication
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Mean (SD): 50.2(11.2). Gender (M:F): 123:87. Ethnicity: unclear
Further population details	1. existence of HF: No HF (LA diam 42mm). 2. left atrial size: <5 cm (42mm). 3. Type of ablation: RF point by point (irrigated tip). 4. type of AF: paroxysmal (20% persistent so 80% paroxysmal).
Extra comments	Persistent AF 20%; LA diam 42mm; CAD 10%; hypertension 46.1%; DM 6.1%; CHF 1.1%, previous AADs 5(2); AF duration 79.2 months

Indirectness of population	No indirectness
Interventions	(n=120) Intervention 1: Mixed Na+ channel or K+ channel regimen - mixed regimen. There were two AAD groups, but they have been merged for the purposes of this review. The first group were given amiodarone (n=30), or sotalol (n=32) if unable to tolerate amiodarone. The second group were given the last ineffective AAD (n=58). Initiated during the first 24 hours after the procedure. Duration 2 months. Concurrent medication/care: AADs withdrawn 7 days before the procedure in case of amiodarone, beta-blockers, propafenone and sotalol, with gradual dosage reduction stopped 2 days before PVI. PVI done with 4mm irrigated tip RF catheter with 30-35 W power. Indirectness: No indirectness Further details: 1. Duration of treatment: (n=60) Intervention 2: usual care. No AADs. Duration 2 months. Concurrent medication/care: AADs withdrawn 7 days before the procedure in case of amiodarone, beta-blockers, propafenone and sotalol, with gradual dosage reduction stopped 2 days before PVI. PVI done with 4mm irrigated tip RF catheter with 30-35 W power. Indirectness: No indirectness Further details: 1. Duration of treatment:
Funding	Funding not stated (Reported that no conflicts of interest)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MIXED REGIMEN versus USUAL CARE

Protocol outcome 1: Any documented atrial arrhythmia
- Actual outcome for Unclear or mixed : Recurrence of AF at 2 months; Group 1: 61/114, Group 2: 26/57
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: 6, Reason: not stated; Group 2 Number missing: 3, Reason: not stated

Protocol outcomes not reported by the study	Quality of life ; Stroke or thromboembolic complications ; Mortality ; hospitalisation with primary diagnosis of AF ; cardioversion for AF ; Repeat ablation within 1 year ; study drug discontinuation ; Hospitalisation ; Length of stay

Study (subsidiary papers)	5A Study trial: Roux 2009[33] (Leong-sit 2011[24])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=110)
Countries and setting	Conducted in USA; Setting: Patients at a Teaching Hospital in USA
Line of therapy	1st line
Duration of study	Intervention + follow up: 6 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Unclear or mixed
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients referred for ablation of paroxysmal AF
Exclusion criteria	Persistent AF or flutter; inability to tolerate any AAD, amiodarone therapy within 3 months of ablation; inability to follow up; participation in another trial.
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Mean (range): 55-56. Gender (M:F): 78:32. Ethnicity: unknown
Further population details	1. existence of HF: No HF (LVEF 61/62). 2. left atrial size: <5 cm (43/41mm). 3. Type of ablation: Not stated / Unclear (PVI but no description of actual technique). 4. type of AF: paroxysmal (persistent excluded).
Extra comments	AAD/control: AF duration 71m/81m; mean number of previous AADs 1.7/1.5; previous ablation 25%/25%; LVEF 61/62; LA diam 4.3/4.1cm; hypertension 47%/53%; CAD 13%/12%; DM 8%/4%; COPD 4%/2%. At the time of the procedure, 72% of patients were receiving an AAD (74% in the AAD group, 70% in the no-AAD group). Overall, 60% of patients were started on a class IC agent, 36% of the patients were started on sotalol, and only 2 patients received dofetilide.

	Sixty-six percent of patients were restarted on the same AAD they were taking just before ablation, and 85% of patients were started on a drug that was previously tolerated. Therefore, only 15% of patients were naïve to the AAD that was used as part of the study protocol.
Indirectness of population	No indirectness
Interventions	(n=53) Intervention 1: Mixed Na+ channel or K+ channel regimen - mixed regimen. For patients in the AAD group, an antiarrhythmic agent was started on the night of the procedure in combination with an atrioventricular (AV) nodal blocking agent. Class 1C drugs were recommended as first-line agents for most patients in the absence of structural heart disease (propafenone 150mg TID or flecainide 100mg BID). For patients with normal LV function but CAD, sotalol 80mg BID was used. For abnormal LV function sotalol 80 mg BID or dofetilide 500 micrograms BID were used. However, the final choice of agent and dosage was left to the discretion of the treating electrophysiologist. Duration 6 weeks. Concurrent medication/care: In both groups, AF ablation consisted of proximal antral pulmonary vein isolation and elimination of non-pulmonary vein triggers of AF guided by intracardiac echocardiogram and circular multipolar electrode catheter recording. All patients discharged with an auto-trigger transtelephonic monitor for 30 days. Indirectness: No indirectness Further details: 1. Duration of treatment: (n=57) Intervention 2: usual care. Only AV nodal blocking agents were used, and clinicians were asked to avoid using AADs unless patients developed atrial arrhythmias associated with severe symptoms or lasted >24 hrs. Duration 6 weeks. Concurrent medication/care: In both groups, AF ablation consisted of proximal antral pulmonary vein isolation and elimination of non-pulmonary vein triggers of AF guided by intracardiac echocardiogram and circular multipolar electrode catheter recording. All patients discharged with an auto-trigger transtelephonic monitor for 30 days. Indirectness: No indirectness Further details: 1. Duration of treatment:
Funding	Funding not stated (Stated that there are no disclosures)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MIXED REGIMEN versus USUAL CARE

Protocol outcome 1: Any documented atrial arrhythmia
- Actual outcome for Unclear or mixed : arrhythmia lasting >24 hours or requiring AAD initiation/change at 6 weeks; Group 1: 2/53, Group 2: 15/57
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 Unclear or mixed : non sustained atrial arrhythmias on TTM strip at 6 weeks; Group 1: 28/53, Group 2: 29/57 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 Unclear or mixed : organised atrial arrhythmias (atrial flutter or atrial tachycardia) on TTM strip at 6 weeks; Group 1: 15/53, Group 2: 6/57 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 Unclear or mixed : Lack of freedom from symptomatic and asymptomatic atrial arrhythmias at 6 months; Group 1: 15/53, Group 2: 18/57; Comments: Note, of those that were AF-free some either did not cease treatment at the designated 6 week time point (3/53 in AAD mixed regimen group) or were started on AAD after the 6 week time-point (4/57 in no AAD usual care group). Similar proportions between groups. Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Similar proportion in the two groups either continued/started AAD past the designated 6-week treatment period.; 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 or thromboembolic complications ; Mortality ; hospitalisation with primary diagnosis of AF ; cardioversion for AF ; Repeat ablation within 1 year ; study drug discontinuation ; Hospitalisation ; Length of stay

Study	Turco 2007[38]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=107)
Countries and setting	Conducted in Italy; Setting:
Line of therapy	Mixed line
Duration of study	Intervention time: 13 months post-ablation
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Unclear or mixed
Subgroup analysis within study	Not applicable
Inclusion criteria	Define
Exclusion criteria	Define
Recruitment/selection of patients	Consecutive
Age, gender and ethnicity	Age - Mean (SD): 57 (10) years. Gender (M:F): Define. Ethnicity: Not reported
Further population details	1. existence of HF: No HF (Mean ± SD LVEF: 57 ± 7%.). 2. left atrial size: <5 cm (Mean ± SD left atrium diameter: 48 ± 6 mm). 3. Type of ablation: RF point by point (RF pulses delivered using a 3.5 mm cooled-tip catheter). 4. type of AF: mixed (<75% of any type) (60% paroxysmal and 40% permanent AF).
Extra comments	60% with paroxysmal AF and 40% with persistent AF. Duration of AF history (mean, ± SD), 4.5 ± 4.2 years. 57% with hypertension, 6% with valvular disease, 5% with ischemic heart disease, 2% with dilated cardiomyopathy. No significant differences between two groups for any clinical characteristics

Indirectness of population	Serious indirectness: 6% with concomitant valvular disease
Interventions	(n=54) Intervention 1: Mixed Na+ channel or K+ channel regimen - mixed regimen. Ablation + an antiarrhythmic drug. The antiarrhythmic drug preferentially administered was amiodarone. In patients with a history of amiodarone adverse effects or intolerance, a class IC antiarrhythmic drug was administered. Antiarrhythmic drugs received included 38 (71%) on amiodarone, 10 (19%) on flecainide, 3 (6%) on propafenone and 2 (4%) on sotalol. Duration 13 months post-ablation. Concurrent medication/care: All patients underwent cavo-tricuspid and left inferior pulmonary vein-mitral isthmus ablation plus circumferential pulmonary vein ablation. All patients received oral anticoagulation with warfarin sodium to achieve an INR of 2-3. After 1 month run-in period, patients received a transtelephonic ECG recorder and a weekly 30-second ECG was scheduled for 12 months. Patients also instructed to obtain an ECG if they experienced palpitations. Indirectness: Serious indirectness; Indirectness comment: Unclear whether antiarrhythmic drugs initiated during ablation or after ablation. Also no details of doses of drugs used. Further details: 1. Duration of treatment: 1-3 months (13 month treatment period, but outcomes at 1 month post-ablation extracted). (n=53) Intervention 2: No treatment. Ablation alone. No AAD administered. Duration 13 months post-ablation. Concurrent medication/care: All patients underwent cavo-tricuspid and left inferior pulmonary vein-mitral isthmus ablation plus circumferential pulmonary vein ablation. All patients received oral anticoagulation with warfarin sodium to achieve an INR of 2-3. After 1 month run-in period, patients received a transtelephonic ECG recorder and a weekly 30-second ECG was scheduled for 12 months. Patients also instructed to obtain an ECG if they experienced palpitations. Indirectness: No indirectness Further details: 1. Duration of treatment:
Funding	Funding not stated (No conflicts of interest to declare)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MIXED REGIMEN versus NO TREATMENT

Protocol outcome 1: cardioversion for AF
- Actual outcome for Study where same AADs are not being used pre-ablation : Electrical cardioversion at 1 month post-ablation; Group 1: 2/54, Group 2: 7/53
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Any documented atrial arrhythmia

- Actual outcome for Study where same AADs are not being used pre-ablation : Recurrence of atrial arrhythmia at 1 month post-ablation; Group 1: 9/54, Group 2: 19/53; Comments: The authors note that recurrence of atrial tachyarrhythmias within the first month after ablation may be transient, so these results were not included in their main analysis at 13 months. However, this was extracted for our review as it was the only time-point reported after ≤6 months of treatment. Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - 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 or thromboembolic complications ; Mortality ; hospitalisation with primary diagnosis of AF ; Repeat ablation within 1 year ; study drug discontinuation ; Hospitalisation ; Length of stay

Appendix E: Forest plots

AADs versus usual care [mixed/unclear stratum]

Figure 2: Health-related quality of life

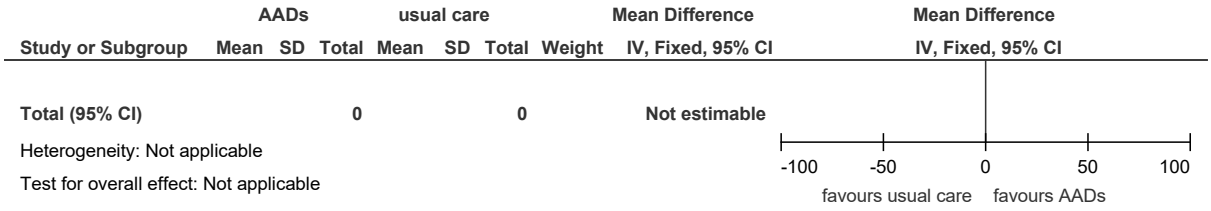


Figure 3: Mortality

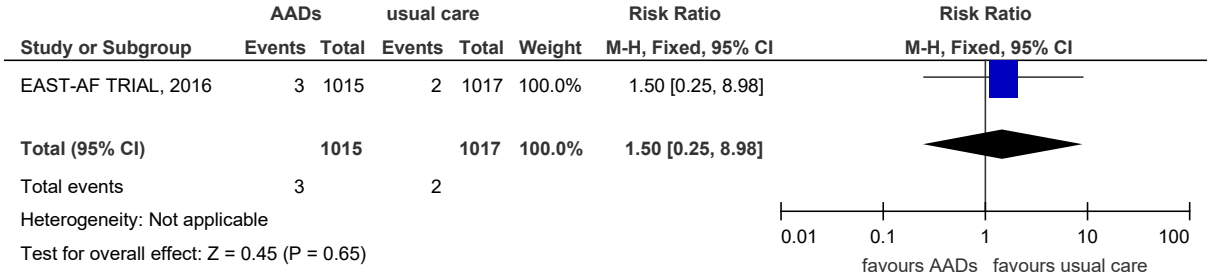


Figure 4: Stroke or thromboembolic complications

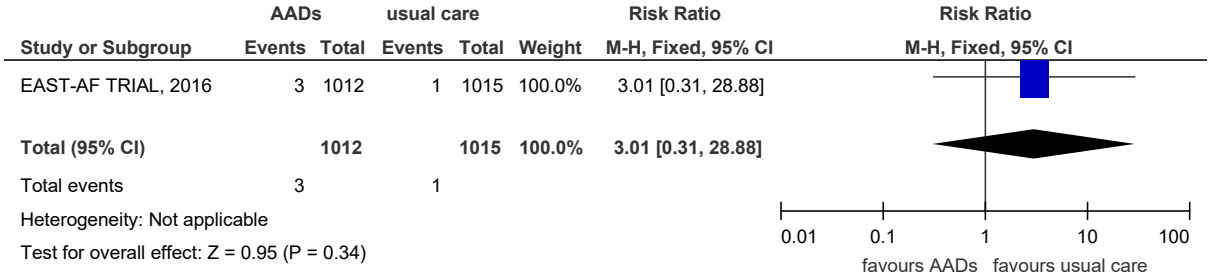


Figure 5: Hospitalisation with a primary diagnosis of atrial arrhythmia

Study or Subgroup	AADs Events	AADs Total	usual care Events	usual care Total	Weight	Risk Ratio M-H, Fixed, 95% CI
EAST-AF TRIAL, 2016	4	1012	4	1022	100.0%	1.01 [0.25, 4.03]
Total (95% CI)		**1012**		**1022**	**100.0%**	**1.01 [0.25, 4.03]**
Total events	4		4			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.01 (P = 0.99)

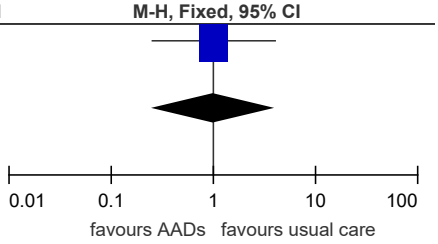


Figure 6: Cardioversion for AF

Study or Subgroup	AADs Events	AADs Total	usual care Events	usual care Total	Weight	Risk Ratio M-H, Random, 95% CI
EAST-AF TRIAL, 2016	113	1012	117	1015	60.3%	0.97 [0.76, 1.24]
Turco, 2007	9	54	19	53	39.7%	0.46 [0.23, 0.93]
Total (95% CI)		**1066**		**1068**	**100.0%**	**0.72 [0.36, 1.46]**
Total events	122		136			

Heterogeneity: Tau² = 0.20; Chi² = 3.80, df = 1 (P = 0.05); I² = 74%

Test for overall effect: Z = 0.90 (P = 0.37)

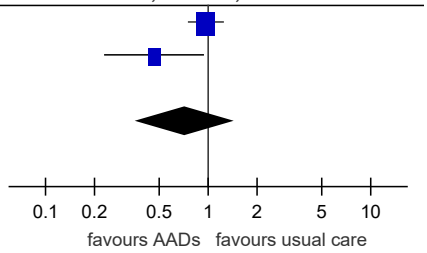


Figure 7: All-cause hospitalisation

Study or Subgroup	AADs Events	AADs Total	usual care Events	usual care Total	Weight	Odds 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

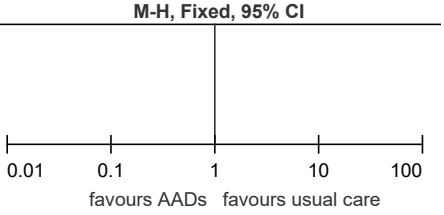


Figure 8: Study drug discontinuation (and control switching)

Figure 9: Repeat ablation within 1 year

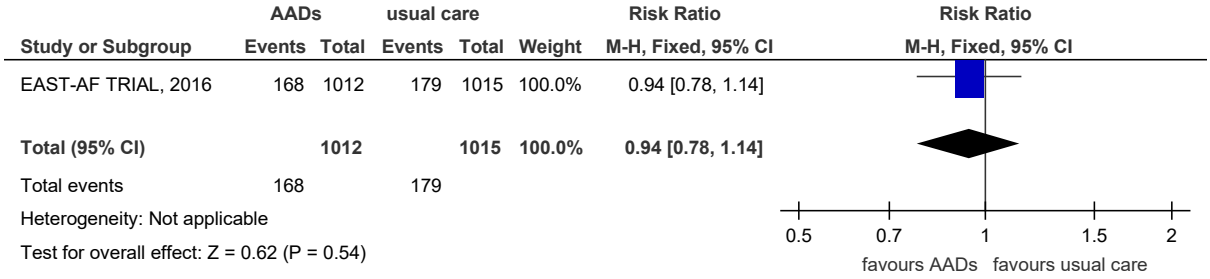
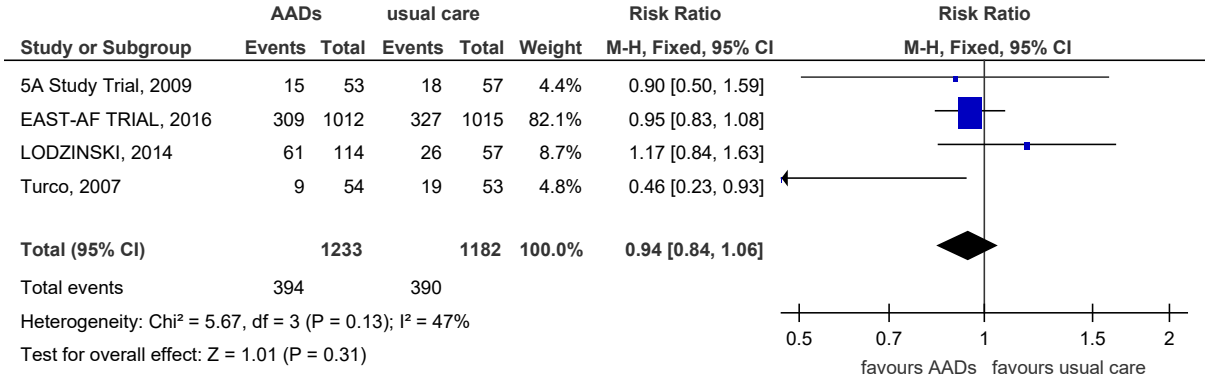


Figure 10: Any documented atrial arrhythmia



Amiodarone versus usual care [mixed/unclear stratum]

Figure 11: Quality of life SF36 Physical

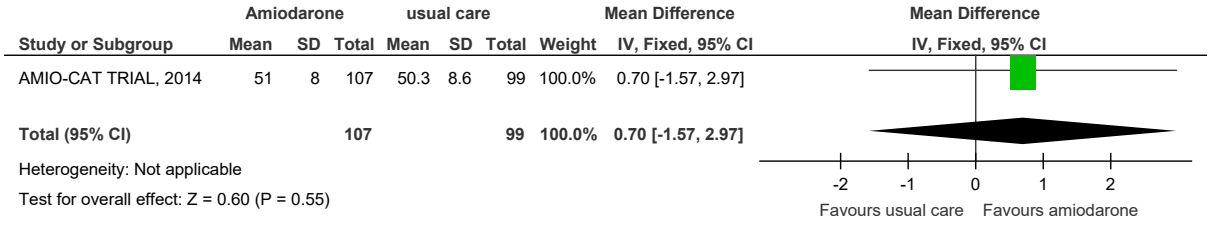


Figure 12: Quality of life SF36 Mental

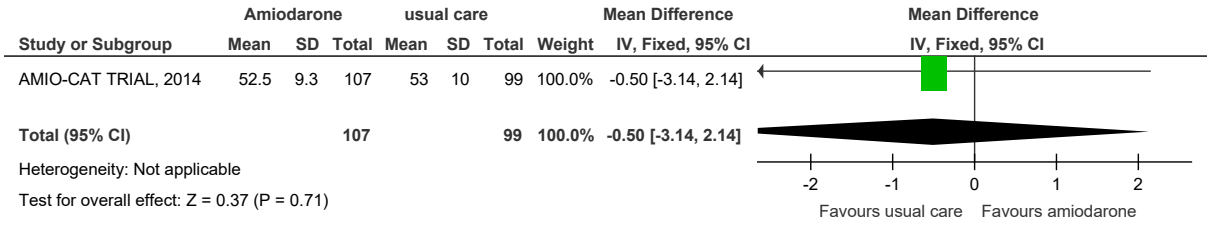


Figure 13: Mortality

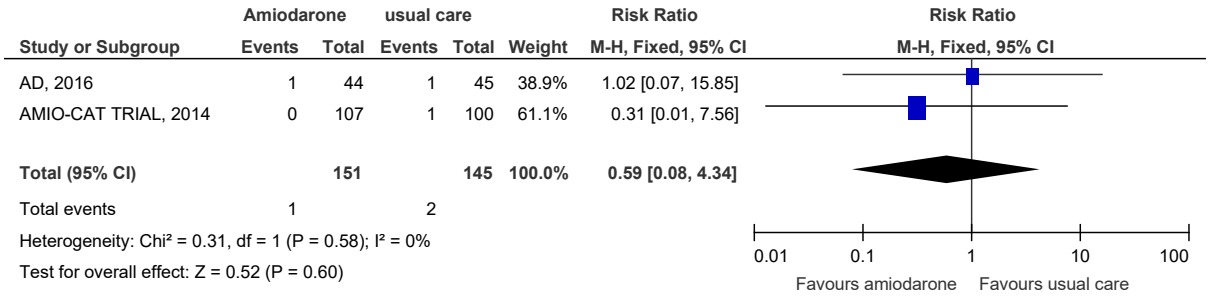
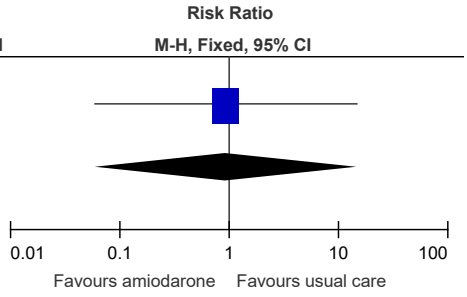


Figure 14: Stroke or thromboembolic complications

Study or Subgroup	Amiodarone Events	Amiodarone Total	usual care Events	usual care Total	Weight	Risk Ratio M-H, Fixed, 95% CI
AD, 2016	0	44	0	43		Not estimable
AMIO-CAT TRIAL, 2014	1	107	1	100	100.0%	0.93 [0.06, 14.74]
Total (95% CI)		**151**		**143**	**100.0%**	**0.93 [0.06, 14.74]**
Total events	1		1			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.05 (P = 0.96)



1

Figure 15: Hospitalisation with a primary diagnosis of atrial arrhythmia

Study or Subgroup	log[Rate Ratio]	SE	Weight	Rate Ratio IV, Fixed, 95% CI
AMIO-CAT TRIAL, 2014	-0.5276	0.3121	100.0%	0.59 [0.32, 1.09]
Total (95% CI)			**100.0%**	**0.59 [0.32, 1.09]**

Heterogeneity: Not applicable

Test for overall effect: Z = 1.69 (P = 0.09)

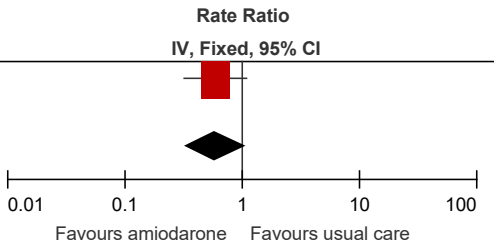


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Figure 16: Cardioversion for AF (risk ratio)

Study or Subgroup	Amiodarone Events	Amiodarone Total	usual care Events	usual care Total	Weight	Risk Ratio M-H, Fixed, 95% CI
AD, 2016	6	44	8	43	100.0%	0.73 [0.28, 1.94]
Total (95% CI)		**44**		**43**	**100.0%**	**0.73 [0.28, 1.94]**
Total events	6		8			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.63 (P = 0.53)

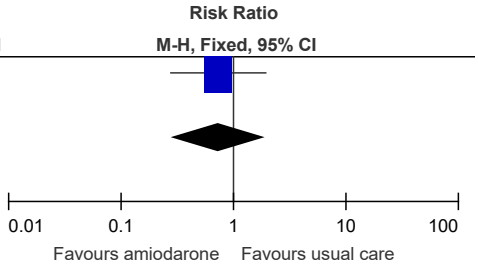

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Figure 17: Cardioversion for AF (rate ratio)

Study or Subgroup	log[Rate Ratio]	SE	Weight	Rate Ratio IV, Fixed, 95% CI
AMIO-CAT TRIAL, 2014	-0.6349	0.2904	100.0%	0.53 [0.30, 0.94]
Total (95% CI)			**100.0%**	**0.53 [0.30, 0.94]**

Heterogeneity: Not applicable

Test for overall effect: Z = 2.19 (P = 0.03)

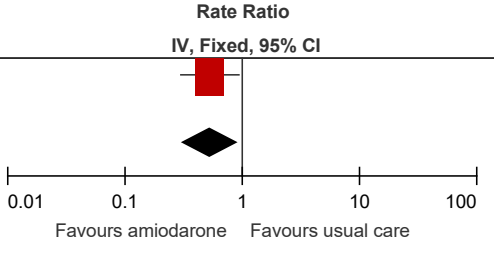


Figure 18: All cause hospitalisation

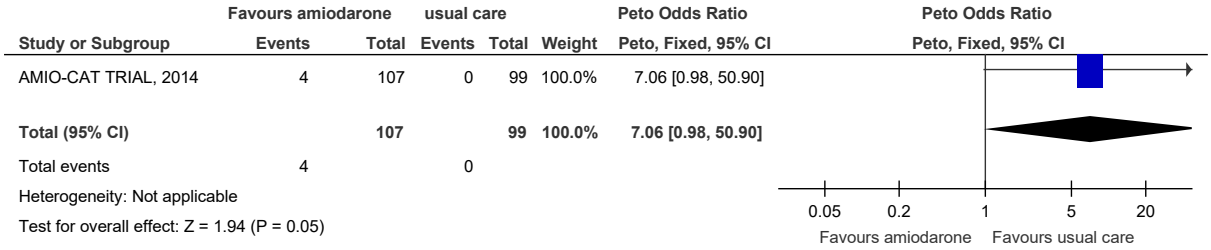


Figure 19: Study drug discontinuation (and control switching)

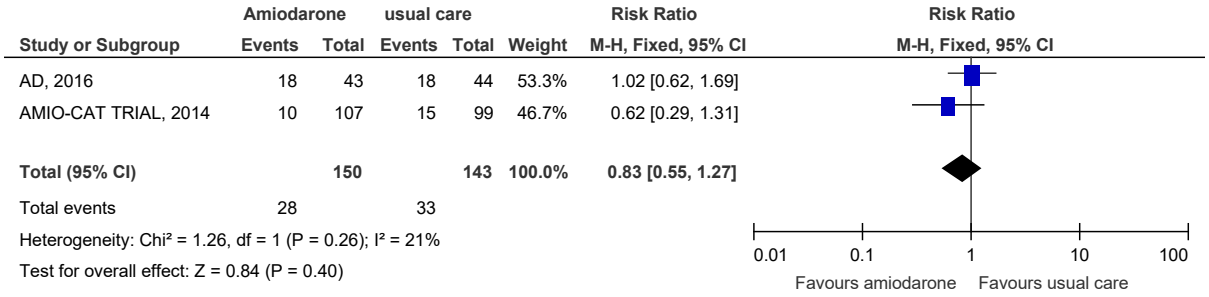


Figure 20: Repeat ablation within 1 year

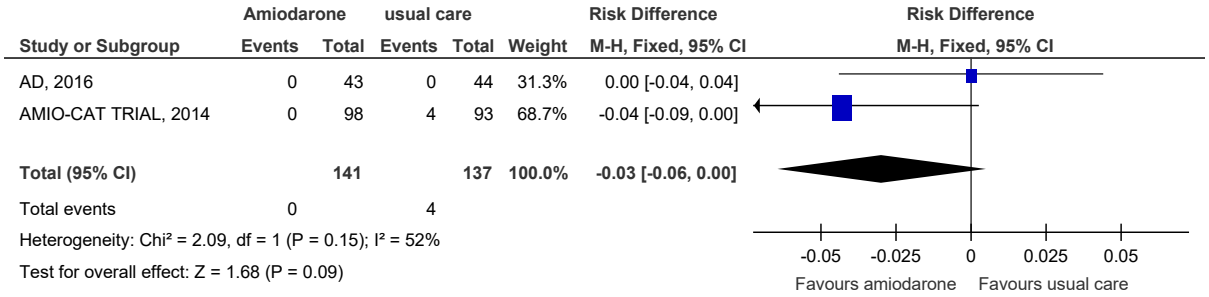
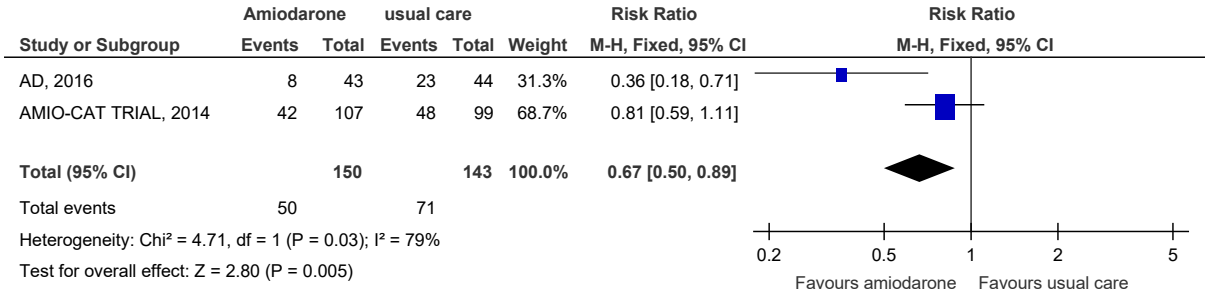


Figure 21: Any documented atrial arrhythmia



Flecainide versus usual care [mixed/unclear stratum]

Figure 22: Health-related quality of life

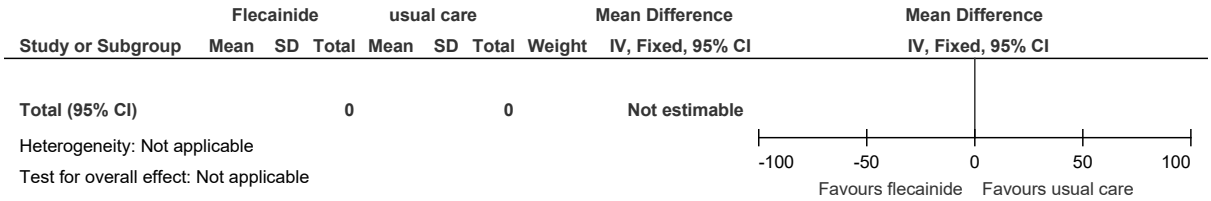


Figure 23: Mortality

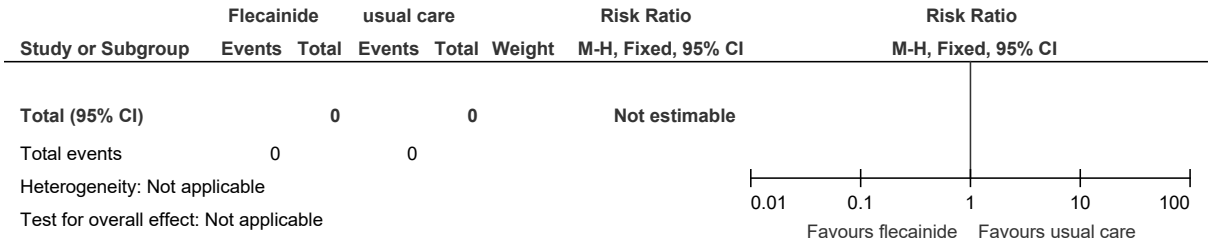


Figure 24: stroke or thromboembolic complications

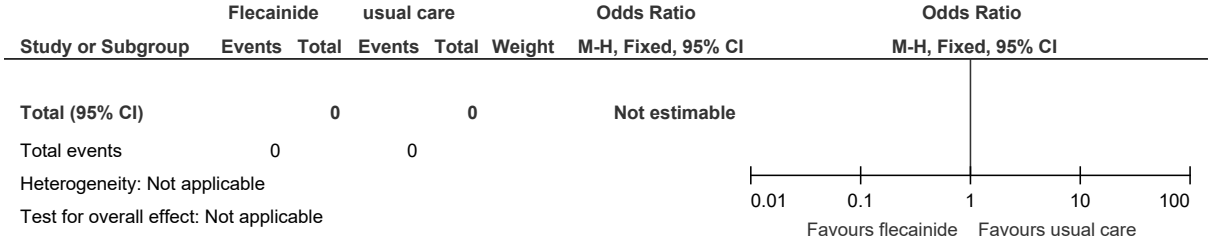


Figure 25: Hospitalisation with a primary diagnosis of atrial arrythmias

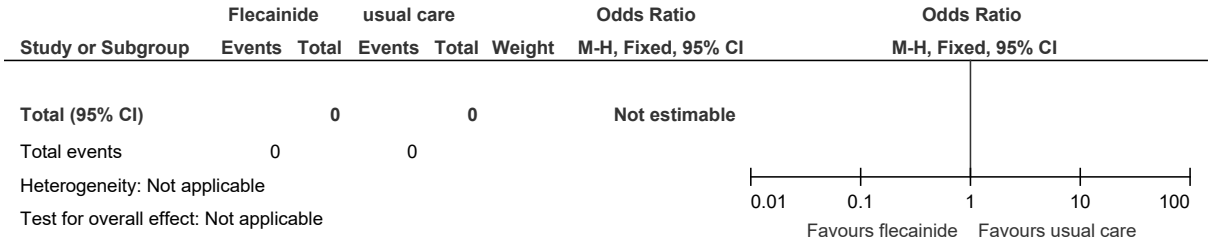


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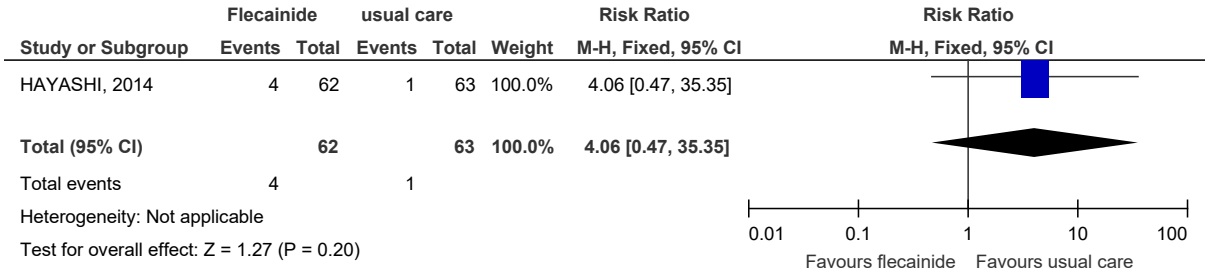
Figure 26: Cardioversion for AF



2

Figure 27: All cause hospitalisation

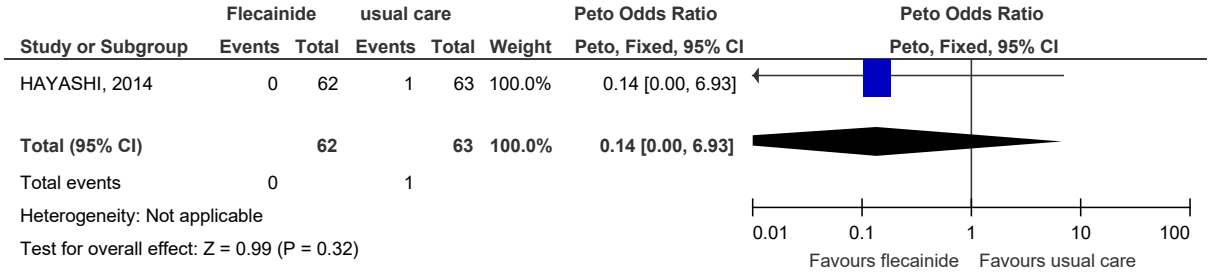


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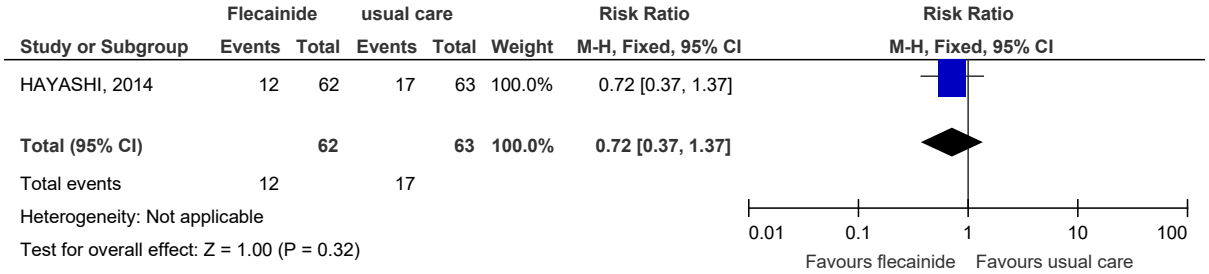
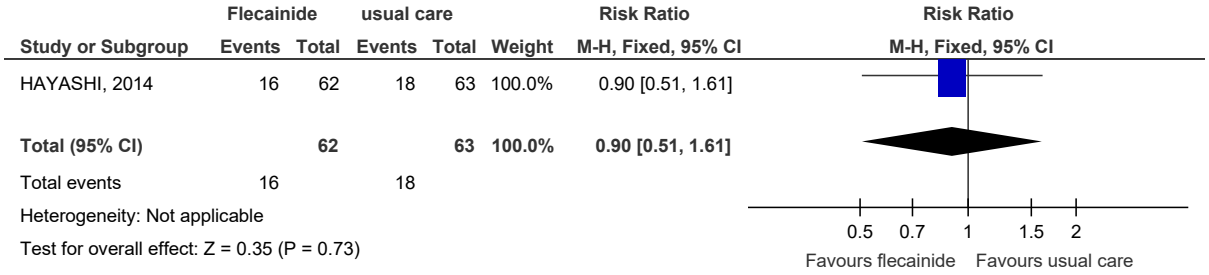
Figure 28: Study drug discontinuation (and control switching)



1

2

Figure 29: Any documented atrial arrhythmia



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Appendix F: GRADE tables

Table 11: Clinical evidence profile: Mixed AAD v usual care [unclear/mixed stratum]

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mixed AAD v usual care [unclear/mixed stratum]	Control	Relative (95% CI)	Absolute		
Quality of life SF36 Physical (Better indicated by lower values)												
0	No evidence available					none	0	-	-	not pooled		CRITICAL
Mortality												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/1015 (0.3%)	0.2%	RR 1.5 (0.25 to 8.98)	1 more per 1000 (from 2 fewer to 16 more)	⊕OOO VERY LOW	CRITICAL
Stroke or thromboembolic complications												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/1012 (0.3%)	0.1%	RR 3.01 (0.31 to 28.88)	2 more per 1000 (from 1 fewer to 28 more)	⊕OOO VERY LOW	CRITICAL
Hospitalisation with a primary diagnosis of atrial arrhythmia												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/1012 (0.4%)	0.4%	RR 1.01 (0.25 to 4.03)	0 more per 1000 (from 3 fewer to 12 more)	⊕OOO VERY LOW	CRITICAL
Cardioversion for AF												
2	randomised trials	very serious[1]	Serious inconsistency[3]	no serious indirectness	Very serious[2]	none	122/1066 (11.2%)	23.7%	RE RR 0.72 (0.36 to 1.46)	66 fewer per 1000 (from 152 fewer to 109 more)	⊕OOO VERY LOW	CRITICAL

All cause hospitalisation												
0	No evidence available					none	-	0%	not pooled	not pooled		IMPORTANT
Study drug discontinuation (and control switching)												
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	77/1016 (7.6%)	14.4%	RR 0.53 (0.40 to 0.68)	68 fewer per 1000 (from 46 fewer to 86 fewer)	⊕⊕OO LOW	IMPORTANT
Repeat ablation within one year												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	168/1012 (16.6%)	17.6%	RR 0.94 (0.78 to 1.14)	11 fewer per 1000 (from 39 fewer to 25 more)	⊕⊕OO LOW	IMPORTANT
Any documented atrial arrythmia												
4	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	394/1233 (31.9%)	34.0%	RR 0.94 (0.84 to 1.06)	20 fewer per 1000 (from 54 fewer to 20 more)	⊕⊕OO LOW	IMPORTANT

[1] Risk of bias very serious due to selection and performance bias in studies
[2] If confidence intervals crossed one MID the imprecision was deemed serious. If the confidence intervals crossed two MIDS imprecision was deemed very serious
[3] Inconsistency serious if I2 from 50-74% and very serious if I2 >75%

Table 12: Clinical evidence profile: Amiodarone v usual care [unclear/mixed stratum]

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Amiodarone v usual care [unclear/mixed stratum]**	**Control**	**Relative (95% CI)**	**Absolute**		
Quality of life SF36 Physical (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	107	99	-	MD 0.7 higher (1.57 lower to 2.97 higher)	⊕⊕⊕O MODERATE	CRITICAL

Quality of life SF36 Mental (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	107	99	-	MD 0.5 lower (3.14 lower to 2.14 higher)	⊕⊕⊕O MODERATE	CRITICAL
Mortality												
2	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/151 (0.66%)	1.6%	RR 0.59 (0.08 to 4.34)	7 fewer per 1000 (from 15 fewer to 53 more)	⊕OOO VERY LOW	CRITICAL
Stroke or thromboembolic complications												
2	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/151 (0.66%)	0.5%	RR 0.93 (0.06 to 14.74)	0 fewer per 1000 (from 5 fewer to 69 more)	⊕OOO VERY LOW	CRITICAL
Hospitalisation with a primary diagnosis of atrial arrhythmia												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	-	-	Rate ratio 0.59(0.32 to1.09)	-	⊕⊕OO LOW	CRIYICAL
Cardioversion for AF												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	6/44 (13.6%)	18.6%	RR 0.73 (0.28 to 1.94)	50 fewer per 1000 (from 134 fewer to 175 more)	⊕OOO VERY LOW	CRITICAL
Cardioversion for AF (rate ratio)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	-	-	Rate ratio 0.53(0.30 to 0.94)	-	⊕⊕OO LOW	CRITICAL
All cause hospitalisation												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	4/107 (3.7%)	0%	OR 7.06 (0.98 to 50.9)	40 more per 1000 (from 0 fewer to 80 more)	⊕OOO LOW	IMPORTANT
Study drug discontinuation (and control switching)												

2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	Serious[3]	none	28/150 (18.7%)	28%	RR 0.83 (0.55 to 1.27)	48 fewer per 1000 (from 126 fewer to 76 more)	⊕⊕OO LOW	IMPORTANT
Repeat ablation within one year												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	Serious[3]	none	0/141 (0%)	2.2%	RD -0.03 (-0.06 to 0.00)	30 fewer per 1000 (from 60 fewer to 00 fewer)	⊕⊕OO LOW	IMPORTANT
Any documented atrial arrythmia												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	50/150 (33.3%)	50.4%	RR 0.67 (0.5 to 0.89)	166 fewer per 1000 (from 55 fewer to 252 fewer)	⊕⊕OO LOW	IMPORTANT

[1] Serious risk of bias due to selection bias or performance bias
[2] Very serious risk of bias due to selection bias and attrition bias
[3] Serious imprecision if confidence intervals crossed one MID and very serious if the confidence intervals crossed two MIDS
[4] Serious imprecision because OIS was <0.80

Table 13: Clinical evidence profile: Flecainide v usual care [unclear/mixed stratum]

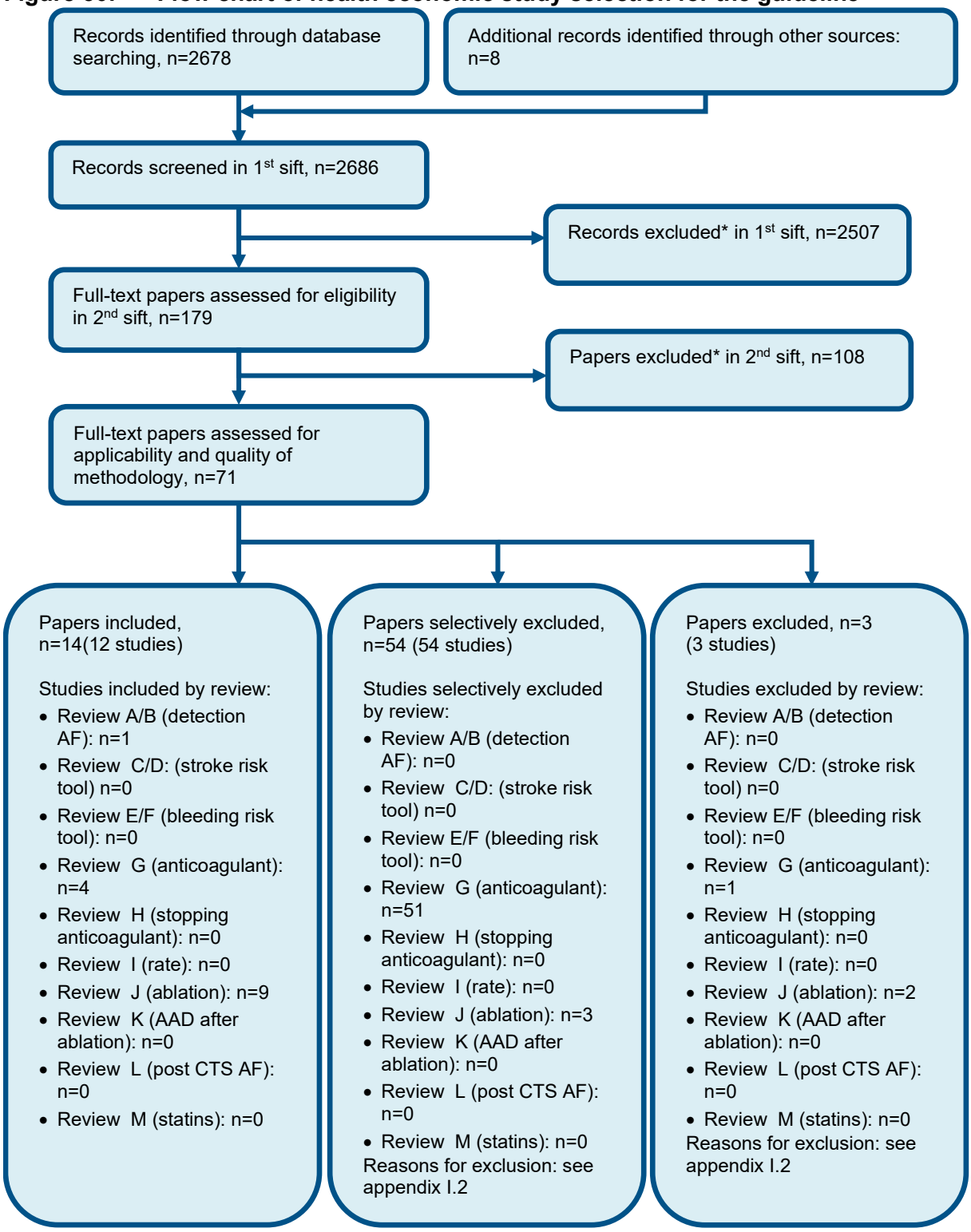
Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Flecainide v usual care [unclear/mixed stratum]**	**Control**	**Relative (95% CI)**	**Absolute**		
Quality of life SF36 Physical (Better indicated by lower values)												
0	No evidence available					none	0	-	-	not pooled		CRITICAL
Mortality												
0	No evidence available					none	-	0%	not pooled	not pooled		CRITICAL
Stroke or thromboembolic complications												

0	No evidence available					none	-	0%	not pooled	not pooled		CRITICAL
Hospitalisation with a primary diagnosis of atrial arrythmia												
0	No evidence available					none	-	0%	not pooled	not pooled		CRITICAL
Cardioversion for AF												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/62 (6.5%)	1.6%	RR 4.06 (0.47 to 35.35)	49 more per 1000 (from 8 fewer to 550 more)	⊕OOO VERY LOW	CRITICAL
All cause hospitalisation												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/62 (0%)	1.6%	OR 0.14 (0 to 6.93)	14 fewer per 1000 (from 16 fewer to 85 more)	⊕OOO VERY LOW	IMPORTANT
Study drug discontinuation (and control switching)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	12/62 (19.4%)	27%	RR 0.72 (0.37 to 1.37)	76 fewer per 1000 (from 170 fewer to 100 more)	⊕OOO VERY LOW	IMPORTANT
Repeat ablation within one year												
0	No evidence available					none	-	0%	not pooled	not pooled		IMPORTANT
Any documented atrial arrythmia												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	16/62 (25.8%)	28.6%	RR 0.9 (0.51 to 1.61)	29 fewer per 1000 (from 140 fewer to 174 more)	⊕OOO VERY LOW	IMPORTANT

[1] Very serious risk of bias due to selection and performance bias
[2] Imprecision serious if confidence intervals crossed one MID and very serious if confidence intervals crossed two MIDS

Appendix G: Health economic evidence selection

Figure 30: Flow chart of health economic study selection for the guideline



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

Appendix H: Health economic evidence tables

None.

Appendix I: Excluded studies

I.1 Excluded clinical studies

Table 14: Studies excluded from the clinical review

Study	Exclusion reason
Al-Khatib 2013[2]	Systematic review (references checked)
Ali 2004[3]	Abstract only
Aliot 2015[4]	protocol
Brignole 2002[7]	opinion paper. After AV node ablation and pace strategy
Brignole 2003[6]	opinion paper
Chakravarty 2012[8]	Systematic review: study designs inappropriate
Chen 2016[9]	Systematic review (references checked)
Clarnette 2018[10]	Systematic review is not relevant to review question or unclear PICO
Duytschaever 2018[13]	Only patients free of AF after 3 month blanking period were randomised
Goldenberg 2016[14]	Systematic review (references checked)
Gu 2012[15]	Inappropriate comparison
Hou 2011[17]	Non randomised; not comparing study interventions
Huang 2017[18]	Application of a single application of amiodarone during ablation, not following ablation
Ishigaki 2015[19]	Non-protocol intervention - beta blocker
Kirchhof 2013[21]	Protocol
Kuck 2014[22]	Editorial
Kumagai 2013[23]	AAD given pre-ablation
Li 2015[25]	Systematic review (references checked)
Mohanty 2015[28]	Peri-procedural administration including during ablation
Mohanty 2015[27]	Erratum

Murgatroyd 2002[29]	Study design - literature review
Oral 2002[31]	Population limited to those experiencing immediate AF recurrence after ablation
Polymeropoulos 2011[32]	AAD given during ablation for immediate cardioversion. AAD given during ablation for immediate cardioversion .Not guideline condition. Not review population. Inappropriate comparison. Incorrect interventions
Schwartzman 2015[34]	Incorrect comparisons - comparing whether control or no control of AF at discharge following ablation and CRT affected outcomes
Stabile 2001[35]	population only those with a positive response to flecainide (conversion to atrial flutter)
Stabile 2013[36]	Systematic review (references checked)
Vroomen 2016[39]	Systematic review (references checked)
Wang 2017[41]	AAD given during procedure intravenously
Xu 2015[43]	Systematic review (references checked)
Xu 2016[42]	Systematic review (references checked)
Zhao 2016[45]	Systematic review (references checked)
Tian, 2019[37]	Candesartan NOT PROTOCOL TREATMENT
Wang, 2019[40]	No protocol outcomes
Yin, 2019[44]	amiodarone + acupuncture v amiodarone; thus effects of AAD cancel leaving just effects of acupuncture - not a protocol treatment

I.2 Excluded health economic studies

Table 15: Studies excluded from the health economic review

Reference	Reason for exclusion
None	