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Oral Class I and III antiarrhythmic drugs for maintaining sinus rhythm after catheter ablation of atrial fibrillation (Review)

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[Intervention Review]

Oral Class I and III antiarrhythmic drugs for maintaining sinus rhythm after catheter ablation of atrial fibrillation

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ABSTRACT

Background

Recurrence of atrial tachyarrhythmias (ATa) following catheter ablation for atrial fibrillation (AF) is a common problem. Antiarrhythmic drugs have been used shortly after ablation in an attempt to maintain sinus rhythm, particularly Class I and III agents. However, it still needs to be established if the use of Class I or III antiarrhythmic medications, or both, reduce the risk of recurrence of ATa.

Objectives

To assess the effects of oral Class I and III antiarrhythmic drugs versus control (standard medical therapy without Class I or III antiarrhythmics, or placebo) for maintaining sinus rhythm in people undergoing catheter ablation for AF.

Search methods

We systematically searched CENTRAL, MEDLINE, Embase, Web of Science Core Collection, and two clinical trial registers without restrictions on language or date to 5 August 2022.

Selection criteria

We sought published, unpublished, and ongoing parallel-design, randomised controlled trials (RCTs) involving adult participants undergoing ablation for AF, with subsequent comparison of Class I and/or III antiarrhythmic use versus control (standard medical therapy or non-Class I and/or III antiarrhythmic use).

Data collection and analysis

We used standard methodological procedures expected by Cochrane and performed meta-analyses with risk ratios (RR) and Peto odds ratios (Peto OR). Our primary outcomes were recurrence of atrial tachyarrhythmias; adverse events: thromboembolic events; adverse events: myocardial infarction; adverse events: new diagnosis of heart failure; and adverse events: requirement for one or more hospitalisations for atrial tachyarrhythmia. Our secondary outcomes were: all-cause mortality; and requirement for one or more repeat ablations. Where possible, we performed comparison analysis by Class I and/or III antiarrhythmic and divided follow-up periods for our primary outcome. We performed comprehensive assessments of risk of bias and certainty of evidence applying the GRADE methodology.

Main results

We included nine RCTs involving a total of 3269 participants. Participants were on average 59.3 years old; 71.0% were male; and 72.9% and 27.4% had paroxysmal and persistent AF, respectively. Class I and/or III antiarrhythmics may reduce recurrence of ATa at 0 to 3 months postablation (risk ratio (RR) 0.74, 95% confidence interval (CI) 0.59 to 0.94, 8 trials, 3046 participants, low-certainty evidence) and likely reduce recurrence at > 3 to 6 months, our a priori primary time point (RR 0.85, 95% CI 0.78 to 0.93, 5 trials, 2591 participants, moderate-certainty evidence). Beyond six months the evidence is very uncertain, and the benefit of antiarrhythmics may not persist (RR 1.14, 95% CI 0.84 to 1.55, 4 trials, 2244 participants, very low-certainty evidence). The evidence suggests that Class I and/or III antiarrhythmics may not increase the risk of thromboembolic events, myocardial infarction, all-cause mortality, or requirement for repeat ablation, at 0 to 3, > 3 to 6, and > 6 months (where data were available; low- to very low-certainty evidence). The use of Class I and/or III antiarrhythmics postablation likely reduces hospitalisations for ATa by approximately 57% at 0 to 3 months (RR 0.43, 95% CI 0.28 to 0.64, moderate-certainty evidence). No data were available beyond three months. No data were available on new diagnoses of heart failure.

Fewer data were available for Class I and III antiarrhythmics individually. Based on only one and two trials (n = 125 to 309), Class I antiarrhythmics may have little effect on recurrence of ATa at 0 to 3, > 3 to 6, and > 6 months (RR 0.88, 95% CI 0.64 to 1.20, 2 trials, 309 participants; RR 0.54, 95% CI 0.25 to 1.19, 1 trial, 125 participants; RR 0.87, 95% CI 0.57 to 1.32, 1 trial, 125 participants; low-certainty evidence throughout); requirement for hospitalisation for ATa at 0 to 3 months (low-certainty evidence); or requirement for repeat ablation at 0 to 3 months (low-certainty evidence). No data were available for thromboembolic events, myocardial infarction, new diagnosis of heart failure, or all-cause mortality at any time points, or hospitalisation or repeat ablation beyond three months.

Class III antiarrhythmics may have little effect on recurrence of ATa at up to 3 months and at > 3 to 6 months (RR 0.76, 95% CI 0.50 to 1.16, 4 trials, 599 participants, low-certainty evidence; RR 0.82, 95% CI 0.62 to 1.09, 2 trials, 318 participants, low-certainty evidence), and beyond 6 months one trial reported a possible increase in recurrence of ATa (RR 1.95, 95% CI 1.29 to 2.94, 1 trial, 112 participants, low-certainty evidence). Class III antiarrhythmics likely reduce hospitalisations for ATa at 0 to 3 months (RR 0.40, 95% CI 0.26 to 0.63, moderate-certainty evidence), and may have little effect on all-cause mortality (low- to very low-certainty evidence). The effect of Class III antiarrhythmics on thromboembolic events and requirement for repeat ablation was uncertain (very low-certainty evidence for both outcomes). No data were available for myocardial infarction or new diagnosis of heart failure at any time point, outcomes other than recurrence beyond 6 months, or for hospitalisation and repeat ablation > 3 to 6 months.

We assessed the majority of included trials as at low or unclear risk of bias. One trial reported an error in the randomisation process, raising the potential risk of selection bias; most of the included trials were non-blinded; and two trials were at high risk of attrition bias.

Authors' conclusions

We found evidence to suggest that the use of Class I and/or III antiarrhythmics up to 3 months after ablation is associated with a reduced recurrence of ATa 0 to 6 months after ablation, which may not persist beyond 6 months, and an immediate reduction in hospitalisation for ATa 0 to 3 months after ablation. The evidence suggests there is no difference in rates of all-cause mortality, thromboembolic events, or myocardial infarction between Class I and/or III antiarrhythmics versus control.

PLAIN LANGUAGE SUMMARY

Oral Class I and III antiarrhythmic drugs for maintaining sinus rhythm after catheter ablation of atrial fibrillation

Review question

We wanted to find out how effective certain classes of antiarrhythmic drugs (medications used to prevent or treat an irregular heart rhythm) are for maintaining sinus rhythm (normal heart rhythm) in people after catheter ablation (a technique using catheters to create controlled burns in the heart to prevent and treat arrhythmia occurrence) for atrial fibrillation (a common type of irregular heart rhythm), compared to catheter ablation alone.

Background

The most common abnormal heart rhythm, atrial fibrillation can cause the upper two chambers of the heart (atria) to beat very rapidly leading to symptoms such as palpitations, dizziness, and shortness of breath. Treatment of atrial fibrillation typically includes medications to control the heart rate and reduce the risk of stroke. However, in some people, restoring the normal heart rhythm to control symptoms is achieved by creating controlled burns with ablation catheters to eliminate atrial fibrillation. Patients often revert back to atrial fibrillation

despite ablation, and certain antiarrhythmic drugs (of which we were only interested in Class I and III) are given to reduce the risk of recurrence of arrhythmia.

Selection criteria

We performed a thorough search of databases for all trials including atrial fibrillation and all individual Class I and Class III antiarrhythmic drugs including, for example, flecainide, propafenone, amiodarone, dronedarone, and sotalol.

Study characteristics

We conducted the search on 5 August 2022, and identified 4682 citations (papers), out of which nine were eligible randomised controlled trials (a type of study where people are randomly assigned to one of two or more treatment groups). The studies included a total of 3269 participants from six countries, who were assigned to either Class I or III antiarrhythmics (or both) or placebo (sugar pill)/standard treatment. People taking part in the studies were on average 59 years old, and 71% were male. Most people had paroxysmal atrial fibrillation (meaning they were not in atrial fibrillation all the time and alternated with normal rhythms).

Results

We found that the effect of Class I and/or III antiarrhythmic drugs given up to around 3 months after ablation may reduce recurrence of arrhythmia at 0 to 3 months, and likely reduces recurrence at greater than 3 to 6 months, although the benefit does not appear to continue beyond 6 months (the evidence for this last result was very uncertain). We also looked at adverse outcomes (i.e. complications). We found that the use of antiarrhythmics was probably associated with a reduction in hospitalisation at 0 to 3 months. We also found evidence suggesting that antiarrhythmics are not associated with different rates of thromboembolic events (clots in the brain, lungs, or legs), heart attacks, death due to any cause, or requirement for repeat ablation compared with control or standard treatment.

Certainty of the results

Our confidence in the evidence was low for recurrence of arrhythmias at 0 to 3 months, moderate at 3 to 6 months, and very low at greater than 6 months. Our confidence in the evidence for reduction of hospitalisation for arrhythmias was moderate.

SUMMARY OF FINDINGS

Summary of findings 1. Class I and/or III antiarrhythmics versus control for maintaining sinus rhythm after catheter ablation of atrial fibrillation

Class I and/or III antiarrhythmics versus control for maintaining sinus rhythm after catheter ablation of atrial fibrillation

Patients or population: Human trial participants undergoing ablation for atrial fibrillation

Settings: Community and healthcare settings

Intervention: Class I and/or III antiarrhythmics

Comparison: Standard medical therapy or placebo postablation not including Class I or III antiarrhythmics

Outcomes at > 3 to 6 months after ablation	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments NNTB (95% CI)
	Risk with placebo or no treatment	Risk with Class I/III antiarrhythmic drugs				
Recurrence of atrial tachyarrhythmias	453 per 1000	385 per 1000 (353 to 421)	RR 0.85 (0.78 to 0.93)[a]	2591 (5 trials)	⊕⊕⊕◯ MODERATE[1]	NNTB 15 (10 to 32)
Adverse events: thromboembolic events	10 per 1000	10 per 1000 (1 to 155)	Peto OR 0.96 (0.06 to 15.50)[b]	212 (1 trial)	⊕◯◯◯ VERY LOW[2]	
Adverse events: myocardial infarction	No data available at > 3 to 6 months, but available at > 6 months[c]					
Adverse events: new diagnosis of heart failure	No data available at any time point[d]					
Adverse events: requirement for 1 or more hospitalisations for atrial tachyarrhythmia	No data available at > 3 to 6 months, but available at 0 to 3 months[e]					
All-cause mortality	1 per 1000	22 per 1000 (1 to 357)	Peto OR 1.00 (0.06 to 16.24)[f]	90 (1 trial)	⊕⊕◯◯ LOW[3]	
Requirement for 1 or more repeat ablations	No data available at > 3 to 6 months, but available at 0 to 3 months and > 6 months[g]					

*The risk in the intervention group (and its 95% confidence interval) is calculated based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: confidence interval; **NNTB:** number needed to treat for an additional beneficial outcome; **OR:** odds ratio; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Outcomes at time points other than primary time point of interest (> 3 to 6 months)

[a]Recurrence of atrial tachyarrhythmias: 0 to 3 months: RR 0.74 (0.59 to 0.94); > 6 months: RR 1.14 (0.84 to 1.55).
[b]Thromboembolic events: 0 to 3 months: not estimable; > 6 months: Peto OR 2.74 (0.39 to 19.5).
[c]Myocardial infarction: 0 to 3 months: not available; > 6 months: Peto OR 1.01 (0.06 to 16.09).
[d]New diagnosis of heart failure: 0 to 3 months: not available; > 6 months: not available.
[e]Hospitalisations for atrial tachyarrhythmia: 0 to 3 months: RR 0.43 (0.28 to 0.64); > 6 months: not available.
[f]All-cause mortality: 0 to 3 months: Peto OR 0.13 (0.00 to 6.57); > 6 months: Peto OR 1.50 (0.26 to 8.68).
[g]Repeat ablation: 0 to 3 months: RR 1.10 (0.61 to 2.00); > 6 months: RR 0.95 (0.79 to 1.13).

[1]Downgraded one level for risk of bias, regarding exclusion of participants lost to follow-up in Darkner 2014, and randomisation generation and allocation concealment in Kaitani 2016.
[2]Downgraded for imprecision (two levels) (95% CI 0.06 to 15.5, which is consistent with both appreciable benefit and appreciable harm, and low event numbers) and risk of bias, specifically concerning exclusion of participants lost to follow-up in Darkner 2014 (one level).
[3]Downgraded for imprecision (one level) (95% CI 0.06 to 16.2, which is consistent with both appreciable benefit and appreciable harm) and risk of bias, specifically concerning exclusion of participants lost to follow-up in Darkner 2014 (one level).
Outcomes have been downgraded twice for imprecision where there are few events and the 95% CI include both appreciable benefit and harm.

Summary of findings 2. Class I antiarrhythmics versus control for maintaining sinus rhythm after catheter ablation of atrial fibrillation

Class I antiarrhythmics versus control for maintaining sinus rhythm after catheter ablation of atrial fibrillation

Patients or population: Human trial participants undergoing ablation for atrial fibrillation

Settings: Community and healthcare settings

Intervention: Class I antiarrhythmics

Comparison: Standard medical therapy or placebo postablation not including Class I or III antiarrhythmics

Outcomes at > 3 to 6 months after ablation	Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)

	Risk with placebo or no treatment	Risk with Class I antiarrhythmic drugs			
Recurrence of atrial tachyarrhythmias	238 per 1000	129 per 1000 (60 to 283)	RR 0.54 (0.25 to 1.19)[a]	125 (1 trial)	⊕⊕◯◯ LOW[1]
Adverse events: thromboembolic events	No data available[b]				
Adverse events: myocardial infarction	No data available[c]				
Adverse events: new diagnosis of heart failure	No data available[d]				
Adverse events: requirement for 1 or more hospitalisations for atrial tachyarrhythmia	No data available at > 3 to 6 months, but available at 0 to 3 months[e]				
All-cause mortality	No data available[f]				
Requirement for 1 or more repeat ablation	No data available at > 3 to 6 months, but available at 0 to 3 months[g]				

*The risk in the intervention group (and its 95% confidence interval) is calculated based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

Outcomes at time points other than primary time point of interest (> 3 to 6 months)

[a]Recurrence of atrial tachyarrhythmias: 0 to 3 months: RR 0.88 (0.64 to 1.20); > 6 months: RR 0.87 (0.57 to 1.32).
[b]Thromboembolic events: 0 to 3 months: not available; > 6 months: not available.
[c]Myocardial infarction: 0 to 3 months: not available; > 6 months: not available.
[d]New diagnosis of heart failure: 0 to 3 months: not available; > 6 months: not available.
[e]Hospitalisations for atrial tachyarrhythmia: 0 to 3 months: RR 0.34 (0.01 to 8.28); > 6 months: not available.
[f]All-cause mortality: 0 to 3 months: not available; > 6 months: not available.
[g]Repeat ablation: 0 to 3 months: RR 0.88 (0.51 to 1.53); > 6 months: not available.

[1]Downgraded two levels for imprecision (95% CI 0.25 to 1.19, which is consistent with both appreciable benefit and appreciable harm) and not meeting the optimal information size.

Summary of findings 3. Class III antiarrhythmics versus control for maintaining sinus rhythm after catheter ablation of atrial fibrillation

Class III antiarrhythmics versus control for maintaining sinus rhythm after catheter ablation of atrial fibrillation

Patients or population: Human trial participants undergoing ablation for atrial fibrillation

Settings: Community and healthcare settings

Intervention: Class III antiarrhythmics

Comparison: Standard medical therapy or placebo postablation not including Class I or III antiarrhythmics

Outcomes at > 3 to 6 months after ablation	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with placebo or no treatment	Risk with Class III antiarrhythmic drugs			
Recurrence of atrial tachyarrhythmias	413 per 1000	339 per 1000 (256 to 450)	RR 0.82 (0.62 to 1.09)[a]	318 (2 trials)	⨁⨁◯◯ LOW[1]
Adverse events: thromboembolic events	10 per 1000	10 per 1000 (1 to 155)	Peto OR 0.96 (0.06 to 15.50)[b]	212 (1 trial)	⨁◯◯◯ VERY LOW[2]
Adverse events: myocardial infarction	No data available[c]				
Adverse events: new diagnosis of heart failure	No data available[d]				
Adverse events: requirement for 1 or more hospitalisations for atrial tachyarrhythmia	No data available at > 3 to 6 months, but available at 0 to 3 months[e]				
All-cause mortality	10 per 1000	1 per 1000 (0 to 66)	Peto OR 0.13 (0.00 to 6.57)[f]	212 (1 trial)	⨁◯◯◯ VERY LOW[3]
Requirement for 1 or more repeat ablation	No data available at > 3 to 6 months, but available at 0 to 3 months[g]				

*The risk in the intervention group (and its 95% confidence interval) is calculated based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: confidence interval; **OR:** odds ratio; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Outcomes at time points other than primary time point of interest (> 3 to 6 months)

[a]Recurrence of atrial tachyarrhythmias: 0 to 3 months: RR 0.76 (0.50 to 1.16); > 6 months: RR 1.95 (1.29 to 2.94).
[b]Thromboembolic events: 0 to 3 months: not estimable; > 6 months: not available.
[c]Myocardial infarction: 0 to 3 months: not available; > 6 months: not available.
[d]New diagnosis of heart failure: 0 to 3 months: not available; > 6 months: not available.
[e]Hospitalisations for atrial tachyarrhythmia: 0 to 3 months: RR 0.40 (0.26 to 0.63); > 6 months: not available.
[f]All-cause mortality: 0 to 3 months: Peto OR 1.00 (0.06 to 16.24); > 6 months: not available.
[g]Repeat ablation: 0 to 3 months: RR 1.18 (0.66 to 2.11); > 6 months: not available.

[1]Downgraded for imprecision (one level) (95% CI 0.62 to 1.09, which is consistent with both appreciable benefit and appreciable harm) and risk of bias, specifically concerning exclusion of participants lost to follow-up in Darkner 2014 (one level).
[2]Downgraded for imprecision (two levels) (95% CI 0.06 to 15.5, which is consistent with both appreciable benefit and appreciable harm, and low event numbers) and risk of bias concerning exclusion of participants lost to follow-up in Darkner 2014 (one level).
[3]Downgraded for imprecision (two levels) (95% CI 0.00 to 6.57, which is consistent with both appreciable benefit and appreciable harm, and low event numbers) and risk of bias concerning exclusion of participants lost to follow-up in Darkner 2014 (one level).

BACKGROUND

Description of the condition

Atrial fibrillation (AF) is the most commonly occurring abnormal heart rhythm condition. It is associated with increased morbidity and mortality through strokes caused by blood clots and also through association with failure of the left lower chamber (ventricle) of the heart (Markides 2003; Poon 2005). Recent data from the UK demonstrate an increase in the prevalence of AF by 50% from 2000 to 2016, meaning that the condition now affects 3.3% of the general practice population aged 35 years or older (Adderley 2019). The worldwide prevalence of 0.5% (33.5 million individuals) is likely to be underestimated, given the large proportion of asymptomatic and undiagnosed individuals (Patel 2018).

There are multiple risk factors for AF, including, for example, structural heart disease, both inherited and secondary to hypertension, ischaemia or valvular heart disease, hyperthyroidism, and high body mass index (BMI), whilst AF without risk factors is only seen in 15% of AF cases (Markides 2003). Typically the abnormal electrical activity of AF arises from the muscle layer of the pulmonary veins into the left atrium of the heart (Markides 2003). People presenting with new-onset AF can be treated with rate control with or without anticoagulation, depending on their risk for stroke (Kirchhof 2017). Rate control, through the use of beta blockers, calcium channel blockers or digoxin, may be appropriate for people with hypertension, structural heart disease, and permanent AF. However, in some people, such as those with severe symptoms, who do not benefit from rate control therapy, or who prefer to reduce their burden of AF, the AF needs to be eliminated and a normal heart rate (e.g. normal sinus rhythm) restored (Boriani 2018).

Atrial tachyarrhythmias (ATa), including AF, atrial flutter, or atrial tachycardias, can occur after ablation. In atrial flutter or macroreentrant tachycardias, an electrical signal propagates in a circular motion around the atrium, causing the atria to beat much faster than the ventricles. Focal atrial tachycardias originate and propagate from a localised ectopic focus in the atria (Kirchhof 2017).

Description of the intervention

Rhythm control in AF is achieved by chemical cardioversion using antiarrhythmic drugs, electrical cardioversion, or cardiac ablation therapy (Kirchhof 2017). Ablation therapy has emerged as an alternative in symptomatic or drug-resistant patients, and it is well established that catheter ablation is superior to oral antiarrhythmic drugs alone for rhythm control (Haegeli 2014). Catheter ablation uses a catheter to identify the abnormal electrical triggers causing AF, which are then neutralised using radiofrequency impulses or other methods (Haegeli 2014). Consensus guidelines recommend catheter ablation for paroxysmal and persistent AF, class I and IIa recommendations respectively (Calkins 2017; January 2019b). There are multiple modalities for delivering cardiac ablation, with the best evidence supporting radiofrequency ablation and cryoablation (Hindricks 2020). The 2020 European Society of Cardiology (ESC) AF guidelines, based on level A evidence (meaning a strong recommendation for clinicians), recommend catheter ablation of symptomatic paroxysmal AF to improve AF symptoms in people with symptomatic recurrences (Burns 2011; Hindricks 2020; Kirchhof 2017).

The Vaughan-Williams classification divides antiarrhythmic drugs into five classes based on their electrophysiological action (effect on ion channels), as follows.

1. Class I agents interfere with the sodium (Na^+) channel.
2. Class II agents are antisympathetic agents (beta-blockers).
3. Class III agents affect potassium (K^+) efflux.
4. Class IV agents affect calcium channels and the atrioventricular (AV) node.
5. Class V agents work by other or unknown mechanisms.

In addition to having other actions, oral Class I and Class III drugs slow the repolarisation of cardiac myocytes which increases the refractory period, making them effective in rhythm control (Lei 2018). Drugs that belong to other classes are often used in rate control and are less relevant for this review.

How the intervention might work

Prolonged AF causes structural and physiological changes that enable AF to subsist. Failure to maintain normal rhythm after ablation is not uncommon, and thus postprocedural antiarrhythmic medications (generally Class I and III agents) have been thought to prevent recurrence of AF when used after ablation. People with early relapses in the 'blanking period' (a period of approximately three months in which occurrences of ATa - including AF, atrial flutter, or atrial tachycardias - after ablation are possible due to periprocedural inflammation and not considered as a true ablation failure) are thought to be more likely to relapse. These ATa are rhythms that originate from the atrium as a consequence of abnormal electrical activity and may represent a failure of the ablation treatment. Patients can become relapse-free after the inflammation from the ablation subsides (Willems 2016). Antiarrhythmic drugs may play a role in reducing early relapses in the blanking period during electrophysiological reorganisation or in the period immediately after the blanking period (three to six months and long term), and thus reduce recurrences postablation. There are fewer data on intermediate follow-up (i.e. the time between the blanking period and long-term follow-up), which is an area that requires analysis (Willems 2016). AF ablation is associated with a significant reduction in hospitalisation, with Guo and colleagues showing a 56% reduction in hospitalisation in the first year after AF ablation (Guo 2019). Class I and III antiarrhythmic agents can be well-tolerated; however, side effects are a serious concern (Markides 2003). A recent Cochrane Review raised concerns about possible harm by sotalol following cardioversion, with one additional death observed for every 102 participants treated with sotalol for one year (Valembois 2019). Amiodarone in particular causes severe toxicity of the lungs, liver, and eyes, amongst many other adverse effects. Class I drugs are pro-arrhythmic and can also cause toxicity in multiple other body systems (Rehman 2015).

Why it is important to do this review

Previous meta-analyses have disputed whether antiarrhythmic drugs are protective at reducing the rate of recurrence of ATa (Goldenberg 2016; Xu 2015). Goldenberg and colleagues found that short-term antiarrhythmics after pulmonary vein isolation appeared not to reduce recurrence of ATa (Goldenberg 2016), whereas Xu and colleagues in 2015 concluded that antiarrhythmic

drugs reduced the early reoccurrence of AF after catheter ablation by more than 50%, but no significant differences were observed for late reoccurrence (Xu 2015). Neither reviews performed detailed subgroup analysis (Goldenberg 2016; Xu 2015). However, it is still thought that combination therapy (ablation and drugs together) is likely to be more effective than ablation alone. New trials such as Kaitani 2016 have since been conducted, and a new review was required.

A recently updated Cochrane Review focused on the use of antiarrhythmic drugs after electrical cardioversion and concluded that the long-term benefit of antiarrhythmic drugs is unclear (Valembois 2019). Current guidelines from the National Institute for Health and Care Excellence (NICE) emphasise the need for expert opinion to guide the decision for ablation; however, there is no guidance on the use of antiarrythmic drugs with ablation (NICE 2019). The 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) guidelines and its 2019 focused update recommended ablation in people with AF, and that AF ablation is reasonable with symptomatic AF and heart failure in order to lower mortality rate and hospitalisation. However, there is no mention of antiarrhythmic drug use postablation (January 2019b). Given the high cost and risk of complications of a repeat ablation, and the toxicity and dangers of antiarrhythmic drugs, this is an important question to answer.

The 2020 ESC guidelines recommend catheter ablation of AF in symptomatic patients with paroxysmal or persistent AF without major risk factors for recurrence (Class I recommendation with level A evidence) who have tried a Class I or III antiarrhythmic that failed or to which they were intolerant. Additionally, catheter ablation of AF should be considered as first-line therapy in tachycardia-induced cardiomyopathy independent of symptoms (Class I recommendation with level B evidence). The latest ESC guidelines discuss the need for data comparing different antiarrhythmic interventions in people with recurrent AF after catheter ablation, but lay out the need for further evidence (Hindricks 2020; Kirchhof 2017).

OBJECTIVES

To assess the effects of oral Class I and III antiarrhythmic drugs versus control (standard medical therapy without Class I or III antiarrhythmics, or placebo) for maintaining sinus rhythm in people undergoing catheter ablation for atrial fibrillation (AF).

METHODS

Criteria for considering studies for this review

Types of studies

We included all published, unpublished, and ongoing randomised controlled trials (RCTs) that were randomised at the level of the participant. We excluded cluster-RCTs (as this method of randomisation will introduce dependence and thus require further analysis), cross-over trials (due to the short follow-up period and the long-term effect of the drugs being used), and quasi-randomised studies (due to the risk of selection bias).

Types of participants

We included adult participants (aged 18 years or older) of either sex who have had AF of any type or duration and had restoration of sinus rhythm with catheter ablation. For mixed populations, if only a subset met the inclusion criteria, we contacted the trial authors to obtain subgroup data. If we could not obtain the data for the subpopulation of interest, we included the study only if a minimum of 60% of the study population met the inclusion criteria, in which case we explored the impact of this decision in sensitivity analysis. We did not exclude any specific populations.

Types of interventions

1. Combinations of any Class I and/or Class III antiarrhythmics versus control.
2. Single Class I antiarrhythmics (flecainide, propafenone) versus control.
3. Single Class III antiarrhythmics (amiodarone, dofetilide, dronedarone, sotalol) versus control.

We defined control as standard medical therapy postablation not including Class I or III antiarrhythmics, or placebo with standard medical therapy postablation not including Class I or III antiarrhythmics. Non-antiarrhythmic medications other than Class I or III antiarrhythmics were eligible as concomitant medications, provided they applied to all treatment arms.

We defined standard medical therapy as rate-controlling agents such as beta blockers, calcium channel blockers, and digoxin; novel anticoagulant agents and vitamin K antagonists; and other cardiac procedures such as coronary angioplasty, pacemaker implantation, and defibrillator implantation.

Concomitant medications included but were not limited to angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, statins, hypertension agents such as dihydropyridine calcium-channel blockers, alpha blockers, diuretics, vasodilators such as hydralazine and minoxidil and centrally acting agents such as clonidine and methyldopa.

Types of outcome measures

We reported data from eligible studies for our prespecified outcomes, listed below. In cases of duplication, we considered the most relevant publication the primary source of data, and used duplicate publications as supplemental information.

Given the difference in reporting and follow-up of individual studies, and to avoid unit of analysis error, we presented our outcomes at several follow-up periods (0 to 3 months, greater than 3 to 6 months, and greater than 6 months). Where possible, the longest available follow-up was used. Our main follow-up period of interest was greater than 3 to 6 months, given that 3 months is considered to be a 'blanking period' where ATa are not uncommon as the body is recovering from the ablation.

Primary outcomes

1. Participants with recurrence of any ATa (AF, atrial flutter, or atrial tachycardia) lasting greater than 30 seconds.
2. Adverse events, considered separately as the following individual outcomes:
   a. participants with a thromboembolic event (including transient ischaemic attack, ischaemic stroke, deep vein thrombosis, pulmonary embolism, and splanchnic vein thrombosis);
   b. participants with a myocardial infarction;

c. participants with a new diagnosis of heart failure;
d. participants who required hospitalisation one or more times for AF.

Secondary outcomes

1. All-cause mortality.
2. The number of participants who required one or more repeat ablations.

Search methods for identification of studies

Electronic searches

We identified trials through systematic searches of the following bibliographic databases on 5 August 2022:

1. Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (Issue 8, 2022);
2. MEDLINE ALL (Ovid, 1946 to 4 August 2022);
3. Embase (Ovid, 1980 to 2022 week 30);
4. Web of Science Core Collection (Clarivate Analytics, 1900 to 5 August 2022).

We adapted the preliminary search strategy for MEDLINE (Ovid) for use in the other databases in 2020. We then updated these strategies in 2022 to include additional drug terms and a catheter ablation concept. The Cochrane sensitivity and precision maximising RCT filter was applied to MEDLINE (Ovid), and an adaption of this was applied to Web of Science (Lefebvre 2021). For Embase, the Cochrane RCT filter was applied (Glanville 2019).

We also conducted a search of ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (apps.who.int/trialsearch) for ongoing or unpublished trials on 5 August 2022. Our search strategies are shown in Appendix 1.

We searched all databases from their inception to the present, and imposed no restrictions on language of publication or publication status. We did not perform a separate search for adverse effects of interventions used for the treatment of AF (i.e. with Class I and III antiarrhythmics). We considered adverse effects as described in the included studies only.

Searching other resources

We checked reference lists of the included studies and any relevant systematic reviews identified for additional references to trials. We also examined any relevant retraction statements and errata for included studies. We contacted study authors for information on ongoing trials.

Data collection and analysis

Selection of studies

Five review authors (JJHB, MWa, MWh, MA, CP) independently screened abstracts against the inclusion criteria, classifying them as eligible or not eligible. Each title was screened by at least two review authors, working independently, using Covidence software (Covidence). After retrieval of full-text papers, five review authors (JJHB, MWa, MWh, MA, CP) independently screened the full texts and identified studies for inclusion and exclusion, with a minimum of two review authors working independently to screen each full text. Any disagreements were resolved through involvement of a third review author (JJHB, MA). We identified and excluded duplicates and collated multiple reports of the same study so that each study, rather than each report, was the unit of interest in the review. We recorded and reported the reasons for exclusion of full-text reports. We completed a PRISMA flow diagram and 'Characteristics of excluded studies' table (Liberati 2009). We used Google Translate to translate non-English manuscripts (Google Translate). We expanded upon the reasons for exclusion of a small group of 'narrowly excluded trials', a subgroup of trials excluded following full-text review that may have been eligible if not for the specific reasons detailed.

Data extraction and management

We used a data collection form that had been piloted on at least one study in the review. Four review authors (JJHB, MWa, MWh, CP) extracted the following study characteristics from the included studies.

1. Methods: study design, total duration of study, number of study centres and location, study setting, and date of study.
2. Participants: number (n) randomised, n lost to follow-up/ withdrawn, n analysed, mean age, age range, gender, inclusion criteria, and exclusion criteria. In addition, we collected data on left atrial size, percentage of paroxysmal and persistent AF, and presence of comorbidities (detailed in the Background section and Table 1).
3. Interventions: intervention, comparison, number of ablations per participant, concomitant medications, and excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported for primary outcomes.
5. Notes: funding for trial, and notable conflicts of interest of trial authors.

Three of four review authors (JJHB, MWa, MWh, CP) independently extracted outcome data from each included study. Any disagreements were resolved by consensus or by involving a third review author (MA). One review author (JJHB) transferred data into the RevMan Web file (RevMan Web 2022). We double-checked that data had been entered correctly by comparing the data presented in the systematic review with the data extraction form. A second check of extracted data was performed by review authors MA, JJHB, MWa, and CP.

Assessment of risk of bias in included studies

Two of four review authors (JJHB, MWa, MWh, CP) independently assessed risk of bias for each included study using the Cochrane risk of bias tool, as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). Any disagreements were resolved by discussion or by involving another review author (MA). We assessed risk of bias according to the following domains.

1. Random sequence generation
2. Allocation concealment
3. Blinding of participants and personnel
4. Blinding of outcome assessment
5. Incomplete outcome data
6. Selective outcome reporting
7. Other bias

We judged each study to be at low, high, or unclear risk of bias for each of the domains listed, and provided direct quotes from the study report along with justifications for our judgements in the risk of bias table. For a study to be considered at overall low risk of bias, it had to be low risk of bias for all domains, whilst studies were judged to be overall unclear or high risk of bias if they were assessed to be unclear or high risk within at least one domain, respectively. We were interested in quantifying the effect of assignment to the interventions at baseline, regardless of whether the interventions were received as intended (the 'intention-to-treat' effect). When considering treatment effects, we took into account the risk of bias for the studies that contributed to that outcome.

Measures of treatment effect

We used risk ratios to present our analyses of the following outcomes: recurrence of ATa, requirement for one or more repeat ablations, adverse events: myocardial infarction, and adverse events: requirement for one or more hospitalisations. For outcomes with very low event rates, defined as rates below 1%, we used the Peto one-step odds ratio method, as this is considered the most powerful statistical method in this context, per Section 10.4.4.3 of the *Cochrane Handbook* (Deeks 2022).

Unit of analysis issues

In the case of multi-arm trials, we used the data from the study arms for our prespecified comparisons (e.g. individual drugs versus placebo or no treatment) and excluded study arms that were irrelevant to the scope of this review. For studies that included placebo and no treatment as two different controls, we combined the control arms.

For studies that reported more than one follow-up time point, we analysed outcomes at the longest possible time of follow-up as a separate comparison to avoid a unit of analysis error.

Dealing with missing data

We contacted investigators via email where missing data were considered to be a potential problem in order to maximise data inclusion and to verify key study characteristics. We planned to impute any missing data where reasonably possible, making explicit any assumptions used. We would include an assessment of the impact of imputation within our sensitivity analysis.

Assessment of heterogeneity

We inspected forest plots visually to consider the direction and magnitude of effects and the degree of overlap between confidence intervals. We used the I^2 and Tau^2 statistics to measure heterogeneity amongst the trials in each analysis. We acknowledge that there is substantial uncertainty in the I^2 value when there are only a small number of studies. We also considered the P value from the Chi^2 test. We reported the clinical characteristics of the included studies including inclusion and exclusion criteria to help guide our clinical assessment of heterogeneity.

When we identified substantial heterogeneity we reported this. Moreover, we planned to carry out subgroup analyses for all outcomes. We considered heterogeneity as substantial if there was a low P value (less than 0.1) in the Chi^2 test for heterogeneity, or if Tau^2 was greater than zero. As strict thresholds for interpreting I^2 are not recommended, we followed the rough guide outlined in Section 10.10.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2022; Higgins 2017):

1. 0% to 40%: might not be important;
2. 30% to 60%: may represent moderate heterogeneity;
3. 50% to 90%: may represent substantial heterogeneity;
4. 75% to 100%: probable considerable heterogeneity.

We only pooled studies if they were considered similar, without substantial heterogeneity.

Assessment of reporting biases

For analyses that included 10 or more studies, we planned to create a funnel plot to explore potential publication bias and to perform a formal statistical test for asymmetry (Egger 1997). In the case of a small number of included studies, the ability to detect publication bias is largely diminished, and it is difficult to exclude the presence of publication bias.

Data synthesis

We undertook meta-analyses only where this was meaningful, that is where the treatments, participants, and the underlying clinical question were similar enough for pooling to make sense, and in the absence of substantial heterogeneity (> 50%). We carried out statistical analysis using RevMan Web (RevMan Web 2022). Due to clinical heterogeneity across trials with AF ablation, differences in comorbidities, differences in medication dose, and the addition of co-interventions, we used a random-effects model for our meta-analysis. We looked at the random-effects summary as the average range of possible treatment effects. We presented the average treatment effect with a 95% confidence interval. We included all eligible studies regardless of their risk of bias, and carried out sensitivity analysis to determine whether risk of bias could affect our conclusions. Where results were statistically significant within the summary of findings tables, the number needed to treat for an additional beneficial outcome (NNTB) is provided, calculated using the assumed comparator risk (ACR) and the effect estimate, per Section 15.4.4 of the *Cochrane Handbook* (Schünemann 2019).

We reported baseline characteristics as weighted means where possible, with standard deviations (SD) produced from the mean from each relevant study. Where medians were reported, the average is accompanied by an interquartile range (IQR).

Subgroup analysis and investigation of heterogeneity

We planned to carry out subgroup analyses for all outcomes, and the following factors, but only for > 3 to 6 months (our primary time point of interest).

1. Participants undergoing their first ablation versus those who have undergone successive ablations (to explore whether drugs are more or less successful in people who have undergone previous unsuccessful ablations). This subgroup analysis applied to all three planned comparisons.
2. Each individual drug (flecainide, propafenone, amiodarone, dofetilide, dronedarone, and sotalol) versus control. This subgroup analysis only applied to comparisons 1 and 2 (Types of interventions).

Sensitivity analysis

We carried out the following sensitivity analyses on all outcomes where feasible.

1. Only including studies with low overall risk of bias. We considered a study to be at low risk of bias for this analysis if it met the criteria for low risk of bias in the following domains: random sequence generation, allocation concealment, and incomplete outcome data.
2. Only including studies without missing data.

As recommended in the *Cochrane Handbook*, we carried out further sensitivity analysis on i) eligibility criteria, ii) data analysis, and iii) analysis methods, and assessed whether the result could impact our conclusions (Deeks 2011), as follows.

1. Risk of bias (including only studies at low risk of bias, and only studies at low and unclear risk of bias)
2. Removal of surgical ablation as the minority ablation method used (see Table 2).
3. Addition of narrowly excluded trials, defined as a subgroup of trials excluded following full-text review that may have been eligible if not for the specific reasons detailed.
4. Impact of restriction to trials mainly including participants with paroxysmal AF.
5. Effect of using random-effects analysis with odds ratio as opposed to risk ratio.

Summary of findings and assessment of the certainty of the evidence

We created separate summary of findings tables for each of our comparisons, as follows.

1. Combinations of any Class I and/or Class III antiarrhythmics versus control.
2. Single Class I antiarrhythmics (flecainide, propafenone) versus control.
3. Single Class III antiarrhythmics (amiodarone, dofetilide, dronedarone, sotalol) versus control.

The summary of findings tables include the outcomes listed in Types of outcome measures. The summary of findings tables cover all outcomes for the follow-up periods of 0 to 3 months, > 3 to 6 months, and > 6 months. The > 3 to 6 months follow-up period immediately following the blanking period was our primary time point of interest.

We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the certainty of the body of evidence as it relates to the studies which contribute data to the meta-analyses for the prespecified outcomes. We used the methods and recommendations described in Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2017), employing GRADEpro GDT software (GRADEpro GDT). We used the overall risk of bias judgement from the Cochrane risk of bias tool as part of GRADE assessment for each outcome. We justified all decisions to downgrade the certainty of the evidence using footnotes, and added comments to aid the reader's understanding of the review where necessary.

To investigate imprecision, we calculated the optimal information size (OIS) using default type I error probability and power (α 0.05, power 0.80), by comparing proportions of two independent samples, as recommended in the GRADE Handbook (Schünemann 2013).

Two of three review authors (JJHB, MWa, MWh), working independently, judged the certainty of the evidence, with any disagreements resolved by discussion or by involving a third review author (MA). Judgements were justified, documented, and incorporated into the reporting of results for each outcome. We extracted study data, formatted our comparisons in data tables, and prepared summary of findings tables before writing the results and conclusions of our review.

RESULTS

Description of studies

See Characteristics of included studies.

Results of the search

Our search identified 8002 citations; following deduplication, 4682 citations were reduced to 59 potentially relevant articles (Figure 1), from which we identified nine eligible RCTs for inclusion. There were three additional published duplicates or supplementary manuscripts of Darkner 2014 (AMIO-CAT) (Darkner 2015; Darkner 2017; Diederichsen 2016); two of Mohanty 2015 (SPECULATE) (Di Biase 2011; Di Biase 2012) and Tarasov 2017 (Tarasov 2017a; Tarasov 2017b); and one at six-month follow-up of Roux 2009 (5A study) (Leong-Sit 2011). Search strategies are shown in Appendix 1. We identified two eligible trials with a multi-arm design (Lodziński 2014; Tarasov 2017); it was possible to combine the arms of Tarasov 2017 as necessary, whereas one arm of Lodziński 2014 involving participants taking "previous antiarrhythmics" was excluded from analysis.

Figure 1. PRISMA flow diagram.

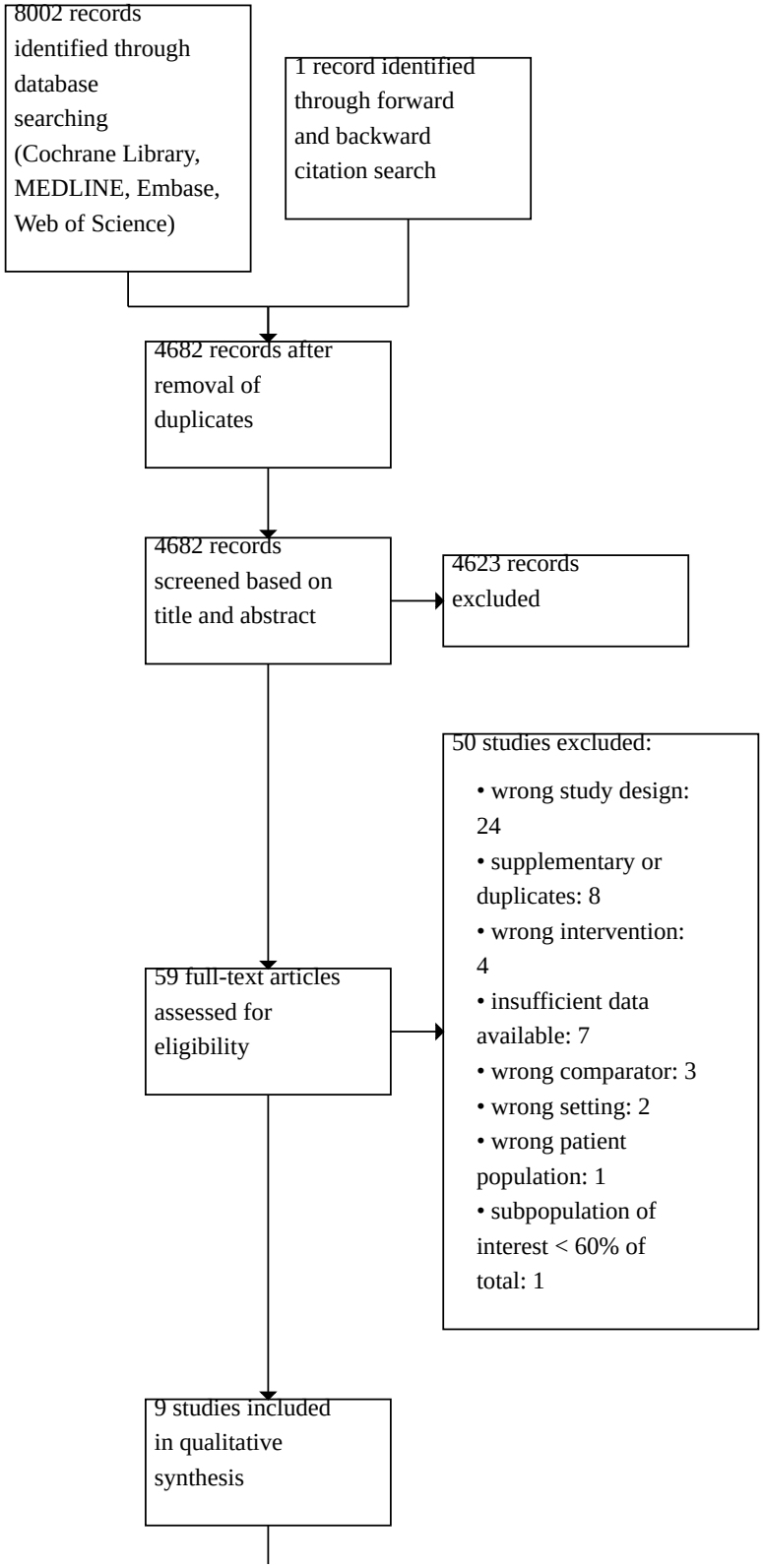
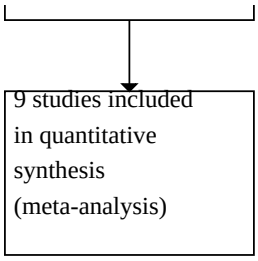


Figure 1. (Continued)



We planned to carry out subgroup analyses for all outcomes, but this was not feasible due to an insufficient number of pooled studies. No missing data were identified.

Included studies

Participants and ablation procedures

Study-level baseline participant characteristics are shown in Table 1.

We included nine RCTs involving a total of 3269 participants randomised to receive either a Class I or III antiarrhythmic (or both) or placebo/standard care after ablation for AF (Ad 2016; Darkner 2014; Hayashi 2014; Kaitani 2016; Lodziński 2014; Mohanty 2015; Roux 2009; Tarasov 2017; Turco 2007). Each included RCT had a reasonable sample size, with a median of 126 ±109 to 232 participants (range 97 to 2044), and follow-up durations of mean 27 ±11.2 months (range 13 to 48 months). Trials recruited from six different countries, with three trials recruiting from the USA (Ad 2016; Mohanty 2015; Roux 2009), one from Italy (Turco 2007), two from Japan (Hayashi 2014; Kaitani 2016), one from Denmark (Darkner 2014), one from Poland (Lodziński 2014), and one from Russia (Tarasov 2017). The mean age of participants was 59.3 ±5.14 years, and 71.0% ±7.12% of participants were male. The proportion of participants with paroxysmal AF and persistent AF was 72.9% ±30.0% and 27.4% ±30.3%, respectively. Two studies only included paroxysmal AF (Roux 2009; Tarasov 2017). Participants in the included trials had a mean AF duration of 53.2 ±25.7 months, ranging from a trial average of 16.5 months to 79.5 months, and the mean left atrial diameter was 4.09 ±0.43 cm (trial mean range 3.8 cm to 5.1 cm). Number of prior antiarrhythmics and previous ablations for AF were generally poorly reported. Three studies reported an average of 1.22 previous antiarrhythmics amongst their included participants (Darkner 2014; Hayashi 2014; Roux 2009), and Kaitani 2016 reported that 59.4% of their participants had been taking at least one ineffective antiarrhythmic before start of the trial. Four studies commented on history of previous AF ablation, with two studies reporting that all of their participants were receiving their first ablation (Ad 2016; Hayashi 2014), and two studies including an average of 27.1% of participants who were receiving a second ablation (Darkner 2014; Roux 2009). Regarding comorbidities, 50.4% ±8.20% of participants had hypertension; 11.8% ±3.42% had diabetes; and the mean left ventricular ejection fraction was 62.9% ±6.31%.

The majority of trials implemented percutaneous catheter ablation (Darkner 2014; Hayashi 2014; Kaitani 2016; Lodziński 2014; Mohanty 2015; Roux 2009; Tarasov 2017; Turco 2007), most of which were radiofrequency ablations (Darkner 2014; Hayashi 2014; Lodziński 2014; Mohanty 2015; Turco 2007). One trial used surgical ablation (Ad 2016). The majority of trials implemented an ablation strategy that involved the pulmonary veins in order to restore sinus rhythm. Specific approaches and strategies of the included trials are summarised in Table 2.

Intervention and comparator

One trial exclusively used Class I antiarrhythmics (flecainide) (Hayashi 2014), and four trials exclusively used Class III antiarrhythmics (Lodziński 2014), of which three used amiodarone (Ad 2016; Darkner 2014; Mohanty 2015). Three trials used a combination of Class I and/or III antiarrhythmics (Kaitani 2016; Roux 2009; Turco 2007), and one trial reported subgroups of both Class I and II antiarrhythmics (Tarasov 2017). Doses of Class I and III antiarrhythmics were clinically appropriate where reported; three trials did not specify antiarrhythmic doses (Ad 2016; Lodziński 2014; Turco 2007). Before the initiation of each trial, a run-in period of median of 3 ±1 to 3 months was used (range 0.25 to 4 months), with Lodziński 2014 using a run-in period of 7 days. Antiarrhythmics were used for a blanking period of median 8 ±5.25 to 12.2 weeks; Darkner 2014 reported having titrated down the dose of amiodarone over the duration of their blanking period. Hayashi 2014 used flecainide throughout the duration of follow-up. Two trials did not specify the duration of postablation antiarrhythmic therapy (Lodziński 2014; Turco 2007). In most included studies, the comparator was ablation alone, without antiarrhythmics (Lodziński 2014; Roux 2009; Turco 2007), no amiodarone (Ad 2016; Mohanty 2015), non-Class I or III antiarrhythmics (Hayashi 2014; Tarasov 2017), or the studies did not specify beyond 'control' (Kaitani 2016; Tarasov 2017).

Outcomes

In nine included trials, data were provided on our primary outcome of ATa recurrence. Data for this outcome came from electrocardiogram (ECG) recordings taken at regular intervals using an ECG event recorder or transtelephonic ECG (Ad 2016; Hayashi 2014; Kaitani 2016; Mohanty 2015; Roux 2009; Tarasov 2017; Turco 2007), ambulatory ECG monitoring (Darkner 2014; Hayashi 2014; Kaitani 2016; Lodziński 2014; Mohanty 2015; Tarasov 2017; Turco 2007), and/or 12-lead ECGs (Darkner 2014; Hayashi 2014; Kaitani 2016; Mohanty 2015; Tarasov 2017; Turco 2007). Most trials did not specify the duration of reported recurrences of ATa (Ad 2016; Lodziński 2014; Tarasov 2017; Turco 2007); those that did reported complete freedom (Mohanty 2015), ATa lasting > 30 s (Darkner 2014; Hayashi 2014; Kaitani 2016), or ATa lasting > 24 h (Roux 2009). Regarding secondary outcomes, three trials reported all-cause

mortality (Ad 2016; Darkner 2014; Kaitani 2016); four trials reported participants requiring one or more repeat ablations (Darkner 2014; Kaitani 2016; Mohanty 2015; Tarasov 2017); and six trials reported adverse events of interest (Ad 2016; Darkner 2014; Hayashi 2014; Kaitani 2016; Roux 2009; Tarasov 2017).

Other characteristics

Five studies reported power calculations with a minimum median size of n = 182 ±124 to 182 (range 124 to 1840) (Ad 2016; Darkner 2014; Hayashi 2014; Kaitani 2016; Roux 2009). Five studies did not report industry funding (Ad 2016; Darkner 2014; Hayashi 2014; Kaitani 2016; Roux 2009); three studies specifically stated that they received no industry funding (Darkner 2014; Hayashi 2014; Kaitani 2016); and one study reported having received industry funding (Tarasov 2017).

Lodziński 2014 had a high attrition rate divided by intervention, thus we included assessment of this factor in sensitivity analysis.

Excluded studies

See Characteristics of excluded studies.

The reason for exclusion of most studies excluded at the full-text stage was wrong design (n = 23 of 44 excluded; see Figure 1).

There are five noteworthy excluded studies that narrowly missed inclusion (Brignole 2002; Duytschaever 2018; Stabile 2006; Wang 2019; Wu 2008). Stabile 2001 was excluded because although it reported freedom from AF and atrial flutter recurrence at 15 months, this subgroup did not represent > 60% of the total study size; instead, this study was included in sensitivity analysis. Wang 2019 provided no data that could be used in any of our primary and secondary outcomes, and was thus excluded; we contacted the authors to enquire about potential unpublished data, but did not receive a response. Duytschaever 2018 included Class I or III antiarrhythmics in both the control and intervention arms. Wu 2008 was excluded because we were unable to confirm if the antiarrhythmics used were Class I or III. We excluded Brignole 2002 because we sought studies that investigated maintenance of sinus rhythm following ablation, and this study used atrioventricular nodal ablation, thus following ablation participants would not be in sinus rhythm.

Ad 2016 describes the potential for cross-over but was principally of parallel design; we included this study and used data taken before any cross-over.

Risk of bias in included studies

See Characteristics of included studies, Figure 2, and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

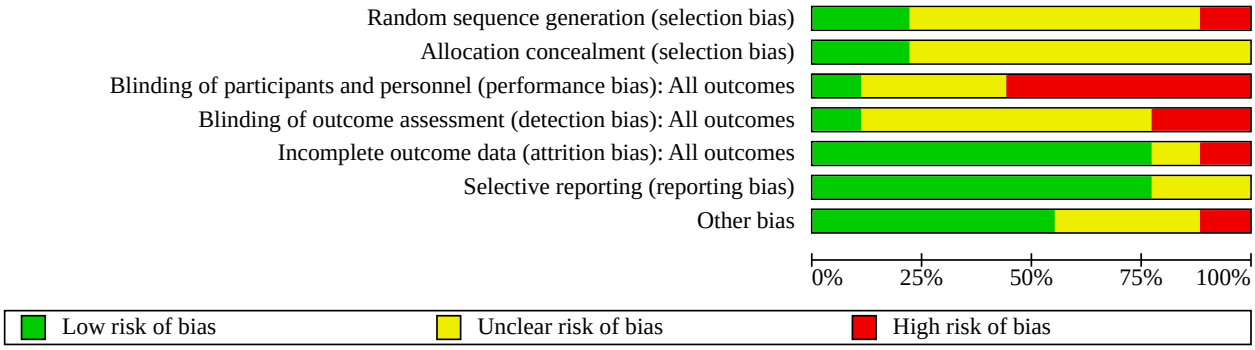
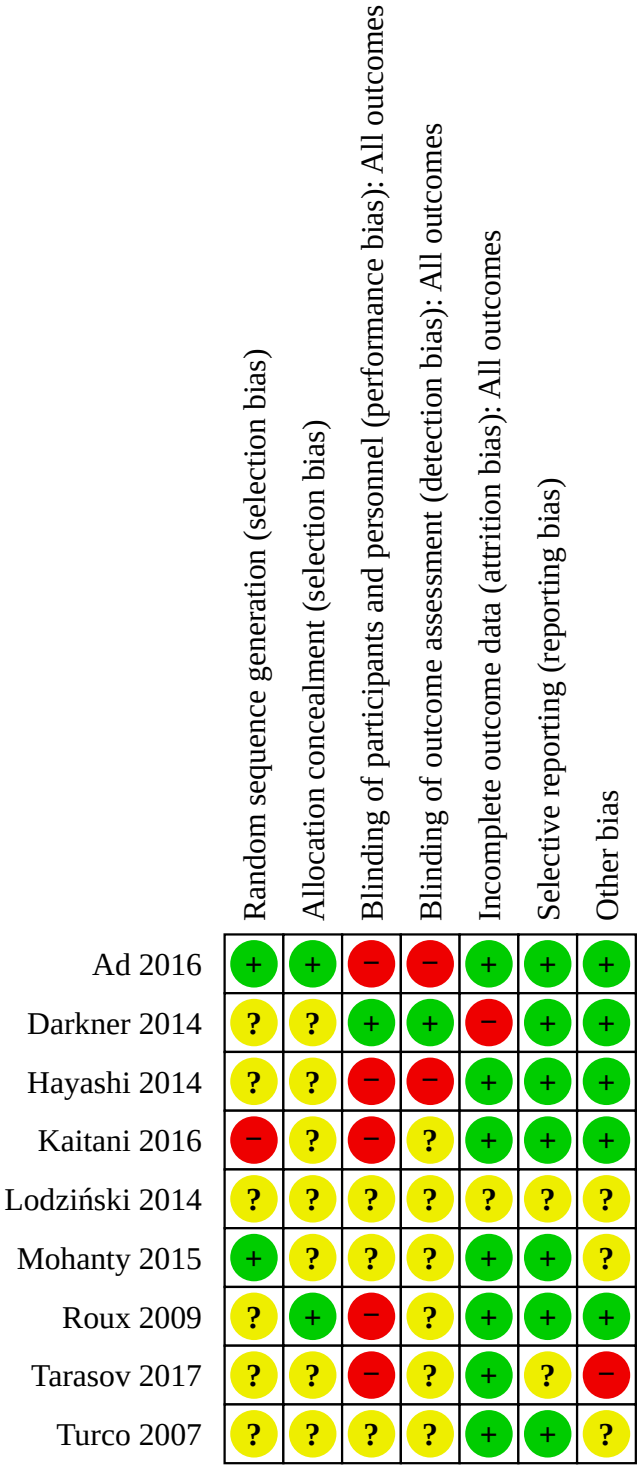


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Five trials explicitly reported adequate random sequence generation (Ad 2016; Hayashi 2014; Kaitani 2016; Mohanty 2015; Turco 2007), and three trials described using randomisation and implied adequate sequence generation (Darkner 2014; Lodziński 2014; Roux 2009; Tarasov 2017). Kaitani 2016 describe an error in their randomisation program, which they attempted to mitigate by re-allocating individuals towards imbalances.

Three studies used adequate allocation concealment (Ad 2016; Roux 2009; Turco 2007), and three studies likely used adequate allocation concealment (Darkner 2014; Hayashi 2014; Kaitani 2016). Insufficient information regarding allocation concealment was provided in three studies, leading to a judgement of unclear risk of bias (Lodziński 2014; Mohanty 2015; Tarasov 2017).

Blinding

We considered Darkner 2014, a double-blind, placebo-controlled trial, to be at low risk of performance bias. For three trials, information was insufficient to assess whether participants and personnel could have been aware of the allocation; we assessed these studies as at unclear risk performance bias (Lodziński 2014; Mohanty 2015; Turco 2007). Five trials were clearly non-blinded and were therefore assessed as at high risk of performance bias due to the possibility that this may have introduced differences between randomised groups other than the intervention being evaluated (Ad 2016; Hayashi 2014; Kaitani 2016; Roux 2009; Tarasov 2017).

We also considered Darkner 2014 to be at low risk for detection bias, as the assessors in this trial were blinded. Most included trials provided insufficient information to judge blinding of outcome assessment and were thus considered to be at unclear risk of detection bias (Kaitani 2016; Lodziński 2014; Mohanty 2015; Roux 2009; Tarasov 2017; Turco 2007). Ad 2016 and Hayashi 2014 did not blind outcome assessors and were thus considered to be at high risk of detection bias, as the lack of blinding could have led to changes to recorded outcomes.

Incomplete outcome data

All trials but one had low rates of loss to follow-up (median 0.64% ±0.86% (range 0% to 2.36%)), without differential group loss (Ad 2016; Darkner 2014; Hayashi 2014; Kaitani 2016; Mohanty 2015; Roux 2009; Tarasov 2017; Turco 2007).

Darkner 2014 implemented a per-protocol analysis by excluding participants who were lost to follow-up from analysis, and was thus considered at high risk of attrition bias.

Lodziński 2014 had a loss to follow-up rate of 18.6% at 2-month follow-up and 34.8% at a mean of 55-month follow-up. It was not possible to ascertain whether there was differential loss between groups, and no sensitivity analyses were reported. We therefore judged this study to be at unclear risk of attrition bias.

Selective reporting

In all included trials, the method of measuring the outcomes of interest was appropriate, and measurement of each outcome did not differ between groups. However, as previously stated, outcome assessors were aware of the intervention in most included trials (Ad 2016; Hayashi 2014; Kaitani 2016; Lodziński 2014; Mohanty 2015; Roux 2009; Tarasov 2017); this was not mentioned in one trial (Turco 2007); and outcome assessors were presumably blinded in the remaining trial, which was described as "double-blind" but not further specified (Darkner 2014). Due to this, all included studies were judged to be low risk of bias in measurement of the outcomes of interest.

Five trials analysed results in accordance with a prespecified plan (Ad 2016; Darkner 2014; Kaitani 2016; Mohanty 2015; Roux 2009), reporting results in the final published manuscript as set out in a prespecified protocol (a priori on ClinicalTrials.gov). Three trials likely used a prespecified plan (Hayashi 2014; Tarasov 2017; Turco 2007), and one trial described deviating from protocol in recording of their results (Lodziński 2014). Lodziński 2014 describes how most of the centres that recruited participants used differing protocols to record results, and therefore results were “divided into groups” "to make them comparable”. It is thus implied that these results were analysed using a plan produced after collection of results. The included studies do not appear to have selected from multiple outcome measurements. Tarasov 2017 appeared to have potentially performed several analyses of the data to produce three similar presentations of the data, although these duplicates were all comparable. We therefore considered eight trials to be at low risk of reporting bias (Ad 2016; Darkner 2014; Hayashi 2014; Kaitani 2016; Mohanty 2015; Roux 2009; Tarasov 2017; Turco 2007), and Lodziński 2014 to be at unclear risk of reporting bias.

Other potential sources of bias

All trials but two provided baseline characteristics evidence supporting the adequacy of their randomisation procedures. Lodziński 2014 provided neither information nor comment that would enable the comparison of characteristics between intervention arms, and was thus considered to be unclear risk of other bias. As mentioned above, Kaitani 2016 attempted to mitigate an error in their randomisation program by re-allocating individuals towards imbalances. However, there were residual significant differences in age, sex, body weight, some comorbidities, and aspects of the ablation procedure that would not be consistent with chance given the large participant number; we thus judged Kaitani 2016 to be at high risk of other bias.

It is also worth noting that Lodziński 2014 had a particularly short run-in of seven days. If participants had been taking Class I or III antiarrhythmics with long half-lives, such as amiodarone, then this could have affected the results, especially as there is no mention of whether participants were on antiarrhythmics before study inclusion.

Effects of interventions

See: **Summary of findings 1** Class I and/or III antiarrhythmics versus control for maintaining sinus rhythm after catheter ablation of atrial fibrillation; **Summary of findings 2** Class I antiarrhythmics versus control for maintaining sinus rhythm after catheter ablation of atrial fibrillation; **Summary of findings 3** Class III antiarrhythmics versus control for maintaining sinus rhythm after catheter ablation of atrial fibrillation

The vast majority of available data were eligible for inclusion in our meta-analyses (see analyses below).

Class I and/or III versus control

See Summary of findings 1.

Recurrence of atrial tachyarrhythmias

Nine included trials provided data on recurrence of ATa (3269 participants) (Ad 2016; Darkner 2014; Hayashi 2014; Kaitani 2016; Lodziński 2014; Mohanty 2015; Roux 2009; Tarasov 2017; Turco 2007). Overall in combined analysis (Class I and/or III) of data from eight trials, low-certainty evidence suggests that Class I and/or III antiarrhythmics may reduce the risk of recurrence of ATa during the first three months following ablation for AF (risk ratio (RR) 0.74, 95% confidence interval (CI) 0.59 to 0.94, 8 trials, 3046 participants, low-certainty evidence) (Analysis 1.1) (Ad 2016; Darkner 2014; Hayashi 2014; Kaitani 2016; Lodziński 2014; Roux 2009; Tarasov 2017; Turco 2007). There was evidence of significant heterogeneity (I^2 = 65%, P = 0.006, Tau^2 = 0.06) that was not explained by subgroup analysis by antiarrhythmic class.

Aggregated data from five trials provided evidence that Class I and/or III antiarrhythmics likely reduce the risk of recurrence of ATa at > 3 to 6 months after ablation (RR 0.85, 95% CI 0.78 to 0.93, 5 trials, 2591 participants, moderate-certainty evidence) (Analysis 1.2) (Darkner 2014; Hayashi 2014; Kaitani 2016; Mohanty 2015; Roux 2009). Heterogeneity was non-significant (I^2 = 0%, P > 0.1, Tau^2 = 0), with the directionality of all included trials being in favour of antiarrhythmics. This included the individual analysis of two trials examining either Class I or III antiarrhythmics (excluding trials that examined Class I or III individually), which included the large trial by Kaitani 2016, and demonstrated that Class I or III antiarrhythmics probably reduce risk of recurrence (RR 0.86, 95% CI 0.78 to 0.94, 2148 participants, 2 trials, moderate-certainty evidence) (Kaitani 2016; Roux 2009).

However, evidence based on aggregated data from four trials suggests that this effect is uncertain beyond six months (RR 1.14, 95% CI 0.84 to 1.55, 4 trials, 2244 participants, very low-certainty evidence) (Analysis 1.3) (Hayashi 2014; Kaitani 2016; Mohanty 2015; Turco 2007). There was significant heterogeneity (I^2 = 68%, P = 0.03, Tau^2 = 0.06), predominantly because a single study in the Class III antiarrhythmics group suggested an effect estimate in favour of control (RR 1.95, 95% CI 1.29 to 2.94, 1 trial, 112 participants, moderate-certainty evidence) (Mohanty 2015).

Sensitivity analysis

In our protocol, we stated that we would perform sensitivity analysis by removing trials at 'high' or 'unclear' risk of bias for the following risk of bias domains: random sequence generation, allocation concealment, or incomplete outcome data. This resulted in all trials being removed for our primary outcome for this comparison at > 3 to 6 months and > 6 months time points. However, for the 0 to 3 month time point, Ad 2016 remained in the analysis and alone showed that antiarrhythmics reduce recurrence of ATa (RR 0.38, 95% CI 0.20 to 0.71, 1 trial, 90 participants, high-certainty evidence). Removal of trials at high risk of bias for domains other than blinding widened the effect estimates of the primary outcome such that it is uncertain whether antiarrhythmics reduce recurrence of ATa at 0 to 3 months and > 3 to 6 months (0 to 3 months: RR 0.67, 95% CI 0.44 to 1.02, I^2 = 73%, P = 0.002, Tau^2 = 0.18, 6 trials, 792 participants, very low-certainty evidence; Ad 2016; Hayashi 2014; Lodziński 2014; Roux 2009; Tarasov 2017; Turco 2007; > 3 to 6 months: RR 0.79, 95% CI 0.55 to 1.15, I^2 = 0%, P > 0.1, Tau^2 = 0, 3 trials, 347 participants, low-certainty evidence; Hayashi 2014; Mohanty 2015; Roux 2009). Lodziński 2014 was the only trial from which we did not use 100% of the participants in our analysis. Removal in sensitivity analysis did not markedly affect the effect estimate for ATa recurrence at 0 to 3 months (RR 0.69, 95% CI 0.54 to 0.88, I^2 = 64%, P = 0.01, Tau^2 = 0.06, 7 trials, 2936 participants, low-certainty evidence) (Ad 2016; Darkner 2014; Hayashi 2014; Kaitani 2016; Roux 2009; Tarasov 2017; Turco 2007). Removal of Ad 2016, as the only trial investigating use of antiarrhythmics following surgical ablation, did not change the effect estimate for recurrence of ATa at 0 to 3 months from being in favour of antiarrhythmics (RR 0.80, 95% CI 0.65 to 0.99, 7 trials, 2956 participants, moderate-certainty evidence) and heterogeneous (I^2 = 57%, P = 0.03, Tau^2 = 0.04). Addition of Stabile 2001, a narrowly excluded study, did not markedly change our estimate at > 6 months, although this estimate is of unclear significance due to the very low certainty of the evidence (RR 0.96, 95% CI 0.66 to 1.40, I^2 = 81%, P = 0.04, Tau^2 = 0.14, 5 trials, 2292 participants, very low-certainty evidence) (Hayashi 2014; Kaitani 2016; Lodziński 2014; Mohanty 2015; Stabile 2001; Turco 2007). Removal of Darkner 2014, as the only trial including mainly permanent AF, did not alter our conclusions (0 to 3 months: RR 0.75, 95% CI 0.58 to 0.99, I^2 = 66%, P = 0.007, Tau^2 = 0.07, 7 trials, 2834 participants, low-certainty evidence; > 3 to 6 months: RR 0.85, 0.78 to 0.94, I^2 = 0%, P > 0.1, Tau^2 = 0, 4 trials, 1198 participants, moderate-certainty evidence) (Ad 2016; Hayashi 2014; Kaitani 2016; Lodziński 2014; Mohanty 2015; Roux 2009; Tarasov 2017; Turco 2007). Analysis using odds ratios (OR) resulted in more pronounced effect estimates of Class I and/or III antiarrhythmic drugs at 0 to 3 months (OR 0.59, 95% CI 0.41 to 0.86, I^2 = 64%, P = 0.006, Tau^2 = 0.15, 8 trials, 3046 participants, low-certainty evidence) (Ad 2016; Darkner 2014; Hayashi 2014; Kaitani 2016; Lodziński 2014; Roux 2009; Tarasov 2017; Turco 2007); and at > 3 to 6 months (OR 0.75, 95% CI 0.64 to 0.87, I^2 = 0%, P > 0.1, Tau^2 = 0, 5 trials, 2591 participants, moderate-certainty evidence) (Darkner 2014; Hayashi 2014; Kaitani 2016; Mohanty 2015; Roux 2009).

The only report of follow-up data from participants who had undergone a repeat ablation and were then compared according to antiarrhythmics versus control was from a duplicate abstract from Tarasov 2017 (Tarasov 2017a). They reported equal "effectiveness" of antiarrhythmic drugs versus no antiarrhythmic drugs (88.6% versus 88.3%, respectively). However, it is likely that the intervention group of antiarrhythmic drugs also included the non-Class I and/or III antiarrhythmic verapamil, in addition to propafenone and sotalol. Consequently, we did not include these data in meta-analysis.

Adverse events: thromboembolic events

Three trials (2340 participants, 6 cases) provided low- to very low-certainty evidence suggesting no difference in thromboembolic events between antiarrhythmics and control at 0 to 3 months (0 events, 1 trial, 90 participants, low-certainty evidence) (Analysis 1.4) (Ad 2016); > 3 to 6 months (Peto OR 0.96, 95% CI 0.06 to 15.50, 1 trial, 212 participants, very low-certainty evidence) (Analysis 1.5) (Darkner 2014); and > 6 months (Peto OR 2.74, 95% CI 0.39 to 19.47, 1 trial, 2038 participants, very low-certainty evidence) (Analysis 1.6) (Kaitani 2016). Combining these time points produced consistent results (Peto OR 1.93, 95% CI 0.39 to 9.60, I^2 = 0%, P > 0.1, 3 trials, 2340 participants, very low-certainty evidence) (Ad 2016; Darkner 2014; Kaitani 2016).

Sensitivity analysis

Sensitivity analysis at > 3 to 6 months including only studies at low risk of bias or those without missing data was not possible.

Adverse events: myocardial infarction

Only one trial (2038 participants, 2 cases) (Analysis 1.7) provided data on rates of myocardial infarction in both Class I and/or III antiarrhythmic and control groups, and suggested no distinguishable difference (Peto OR 1.01, 95% CI 0.06 to 16.1, 1 trial, 2038 participants, very low-certainty evidence) (Kaitani 2016).

Sensitivity analysis

Sensitivity analysis at > 3 to 6 months including only studies at low risk of bias or those without missing data was not possible.

Adverse events: new diagnosis of heart failure

No data were available for this outcome.

Adverse events: requirement for one or more hospitalisations for atrial tachyarrhythmias

In meta-analysis of three trials (448 participants) at 0 to 3 months after ablation, there was moderate-certainty evidence of a large reduction in rates of hospitalisation with Class I and/or III antiarrhythmics versus control (RR 0.43, 95% CI 0.28 to 0.64, 3 trials, 448 participants, moderate-certainty evidence) (Analysis 1.8) (Darkner 2014; Hayashi 2014; Roux 2009). There was no evidence of heterogeneity (I^2 = 0%, P > 0.1, Tau^2 = 0). This estimate equates to a number needed to treat for an additional beneficial outcome (NNTB) of 7 (95% CI 5 to 10). It was not possible to stratify individual studies by time of follow-up beyond three months (mean 2.5 ±0.87 months, range 1.5 to 3 months) (Darkner 2014; Hayashi 2014; Roux 2009). Moreover, Tarasov 2017 reported mean ±SD "hospitalisations for arrhythmia" at three-month follow-up that were consistent with our findings (propafenone: 0.45 and sotalol: 0.59 versus verapamil: 0.68 and no antiarrhythmics: 0.89).

Sensitivity analysis

In sensitivity analysis, as stated a priori, we removed trials that were 'high' or 'unclear' risk of bias for the following risk of bias domains: random sequence generation, allocation concealment, and incomplete outcome data. As for our primary outcome of recurrence of ATa, this resulted in all trials being removed for this outcome. Removal of trials at high risk of bias for domains other than blinding widened the effect estimate for requirement for one or more hospitalisations for ATa at 0 to 3 months (RR 0.57, 95% CI 0.21 to 1.51, I^2 = 0%, P > 0.1, Tau^2 = 0, 2 trials, 236 participants, moderate-certainty evidence) (Hayashi 2014; Roux 2009). Ad 2016 did not specify whether their "readmission" rate was for reasons related to ATa. Similarly, Kaitani 2016 did not report hospitalisation secondary to ATa, but did provide data on cardioversion at < 90 days and ≥ 90 days, which produced opposing results. Furthermore, sensitivity analysis examining all-cause hospitalisation (follow-up range 3 months to median 387 days) showed that antiarrhythmics likely lead to fewer hospitalisations (RR 0.47, 95% CI 0.32 to 0.68, I^2 = 0%, P > 0.1, Tau^2 = 0, 5 trials, 2576 participants, moderate-certainty evidence) (Ad 2016; Darkner 2014; Hayashi 2014; Kaitani 2016; Roux 2009). Furthermore, meta-analysis of all-cause hospitalisation or cardioversion at up to six months remained in favour of antiarrhythmics reducing hospitalisations with minimal, insignificant heterogeneity (RR 0.59, 95% CI 0.39 to 0.90, I^2 = 47%, P > 0.1, Tau^2 = 0.09, 5 trials, 2576 participants, low-certainty evidence) (Ad 2016; Darkner 2014; Hayashi 2014; Kaitani 2016; Roux 2009), although Kaitani 2016 provided data on requirement of cardioversion at > 3 months suggesting that this effect does not persist long term (RR 2.17, 95% CI 1.13 to 4.16, 1 trial, 2038 participants, moderate-certainty evidence). This is consistent with data from Darkner 2014 which provided a rate ratio of hospitalisation for ATa for the entire duration of the study that was non-significant in comparison to their data from the blanking period used in the above analysis (RR 0.59, 95% CI 0.32 to 1.06, P > 0.05, 1 trial, 212 participants). Sensitivity analysis at > 3 to 6 months including only studies at low risk of bias or those without missing data was not possible.

All-cause mortality

Based on low- to moderate-certainty evidence from three trials (2340 participants, 8 cases), there did not appear to be any effect of Class I and/or III antiarrhythmics use after ablation on all-cause mortality at 0 to 3 months (Peto OR 0.13, 95% CI 0.00 to 6.57, 1 trial, 212 participants, moderate-certainty evidence) (Analysis 1.9) (Ad 2016); > 3 to 6 months (Peto OR 1.00, 95% CI 0.06 to 16.24, 1 trial, 90 participants, low-certainty evidence) (Analysis 1.10) (Darkner 2014); and > 6 months (Peto OR 1.50, 95% CI 0.26 to 8.68, 1 trial, 2038 participants, low-certainty evidence) (Analysis 1.11) (Kaitani 2016). Combining all three time points also supported this assertion (Peto OR 1.00, 95% CI 0.25 to 4.01, I^2 = 0%, P > 0.1, 3 trials, 2340 participants, low-certainty evidence) (Ad 2016; Darkner 2014; Kaitani 2016).

Sensitivity analysis

Sensitivity analysis at > 3 to 6 months including only studies at low risk of bias or those without missing data was not possible.

Requirement for one or more repeat ablation

Based on data from four trials, it was unclear if Class I and/or III antiarrhythmics have any effect on repeat ablation at 0 to 3 months after ablation versus control (RR 1.10, 95% CI 0.61 to 2.00, I^2 = 53%, P > 0.1, Tau^2 = 0.13, 3 trials, 567 participants, very low-certainty evidence) (Analysis 1.12) (Darkner 2014; Mohanty 2015; Tarasov 2017). At > 3 to 6 months after ablation, the evidence suggests that Class I and/or III antiarrhythmics may not affect the requirement for repeat ablation (RR 0.95, 95% CI 0.79 to 1.13, 1 trial, 1365 participants, low-certainty evidence) (Analysis 1.13) (Kaitani 2016). Combining these time points also produced unclear results (RR 1.02, 95% CI 0.80 to 1.30, 4 trials, 1932 participants, very low-certainty evidence), with evidence of heterogeneity (I^2 = 27%, P > 0.1, Tau^2 = 0.02) (Darkner 2014; Kaitani 2016; Mohanty 2015; Tarasov 2017).

Sensitivity analysis

Sensitivity analysis at > 3 to 6 months including only studies at low risk of bias or those without missing data was not possible.

Class I antiarrhythmics versus control

See Summary of findings 2.

Recurrence of atrial tachyarrhythmias

Analysis based on data from one to two trials showed that Class I antiarrhythmics do not appear to reduce recurrence of ATa at 0 to 3, > 3 to 6, and > 6 months (0 to 3 months: RR 0.88, 95% CI

0.64 to 1.20, I^2 = 0%, P > 0.1, Tau^2 = 0, 2 trials, 309 participants, low-certainty evidence; > 3 to 6 months: RR 0.54, 95% CI 0.25 to 1.19, 1 trial, 125 participants, low-certainty evidence; > 6 months: RR 0.87, 95% CI 0.57 to 1.32, 1 trial, 125 participants, low-certainty evidence) (Analysis 2.1; Analysis 2.2; Analysis 2.3) (Hayashi 2014; Tarasov 2017).

Sensitivity analysis

Sensitivity analysis including only studies at low risk of bias or those without missing data was not possible.

Adverse events: thromboembolic events

No data were available for this outcome.

Adverse events: myocardial infarction

No data were available for this outcome.

Adverse events: new diagnosis of heart failure

No data were available for this outcome.

Adverse events: requirement for one or more hospitalisations for atrial tachyarrhythmias

Only one trial reported Class I data on postablation hospitalisation for ATa, showing that Class I antiarrhythmics may have little effect on reducing hospitalisation (RR 0.34, 95% CI 0.01 to 8.28, 1 trial, 126 participants, low-certainty evidence) (Analysis 2.4) (Hayashi 2014).

Sensitivity analysis

Sensitivity analysis including only studies at low risk of bias or those without missing data was not possible.

All-cause mortality

No data were available for this outcome.

Requirement for one or more repeat ablation

Evidence from only one trial showed that Class I antiarrhythmics may have little effect in reducing repeat ablations (RR 0.88, 95% CI 0.51 to 1.53, 1 trial, 183 participants, low-certainty evidence) (Analysis 2.5) (Tarasov 2017).

Sensitivity analysis

Sensitivity analysis including only studies at low risk of bias or those without missing data was not possible.

Class III antiarrhythmics versus control

See Summary of findings 3.

Recurrence of atrial tachyarrhythmias

Based on pooled data from four trials, Class III antiarrhythmics alone may have little effect on recurrence of ATa at 0 to 3 months (RR 0.76, 95% CI 0.50 to 1.16, I^2 = 75%, P < 0.01, Tau^2 = 0.13, low-certainty evidence) (Analysis 3.1) (Ad 2016; Darkner 2014; Lodziński 2014; Tarasov 2017). Class III antiarrhythmics may also have little effect on recurrence at > 3 to 6 months (RR 0.82, 95% CI 0.62 to 1.09, I^2 = 0%, P > 0.1, Tau^2 = 0.00, low-certainty evidence) (Analysis 3.2) (Darkner 2014; Mohanty 2015). Mohanty 2015 was the only trial to investigate a Class III antiarrhythmic (amiodarone) after six months, reporting a possible higher ATa recurrence (RR 1.95, 95% CI 1.29 to 2.94, 1 trial, 112 participants, low-certainty evidence) (Analysis 3.3). However, this was not consistent with findings from trials that investigated Class I and III antiarrhythmics (Kaitani 2016; Turco 2007).

Sensitivity analysis

Removal of trials that were 'high' or 'unclear' risk of bias for the risk of bias domains random sequence generation, allocation concealment, and incomplete outcome data showed that Class III antiarrhythmics reduce recurrence of ATa at 0 to 3 months (RR 0.38, 95% CI 0.20 to 0.71, 1 trial, 90 participants, high-certainty evidence) (Ad 2016). Sensitivity analysis for missing data was not necessary. We utilised data from a subgroup of Lodziński 2014; following exclusion of these data, the evidence for recurrence of ATa with Class III antiarrhythmics at 0 to 3 months remained unclear (RR 0.66, 95% CI 0.41 to 1.05, I^2 = 70%, P < 0.1, Tau^2 = 0.12, 3 trials, 483 participants, very low-certainty evidence) (Ad 2016; Darkner 2014; Tarasov 2017). Despite the removal of Ad 2016 as the only included trial investigating use of antiarrhythmics following surgical ablation, the estimate for Class III antiarrhythmics at 0 to 3 months remained similar (RR 0.90, 95% CI 0.62 to 1.29, I^2 = 66%, P < 0.1, Tau^2 = 0.07, 3 trials, 509 participants, very low-certainty evidence). The addition of Stabile 2001, a narrowly excluded study, suggested that Class III antiarrhythmics may have little effect on recurrence at > 6 months (RR 0.64, 95% CI 0.34 to 1.21, I^2 = 75%, P < 0.1, Tau^2 = 0.16, 2 trials, 160 participants, low-certainty evidence) (Ad 2016; Stabile 2001). Darkner 2014 was the only trial to include mainly permanent AF; removal of this study did not change our conclusions for Class III antiarrhythmics at 0 to 3 months and > 3 to 6 months (RR 0.80, 95% CI 0.45 to 1.43, 3 trials, 387 participants, low-certainty evidence; RR 0.88, 95% CI 0.47 to 1.62, 1 trial, 112 participants, low-certainty evidence, respectively) (Ad 2016; Lodziński 2014; Mohanty 2015; Tarasov 2017).

Adverse events: thromboembolic events

Based on very low-certainty evidence, it is unclear whether Class III antiarrhythmics have any effect on thromboembolic events following ablation at 0 to 3 months (not estimatable due to no events, 1 trial, 90 participants) (Analysis 3.4) (Ad 2016); or > 3 to 6 months (Peto OR 0.96, 95% CI 0.06 to 15.5, 1 trial, 212 participants, very low-certainty evidence) (Analysis 3.5) (Darkner 2014).

Sensitivity analysis

Sensitivity analysis including only studies at low risk of bias at 0 to 3 months was consistent with the estimate above, and was not possible at > 3 to 6 months. Sensitivity analysis on the basis of missing data was not necessary.

Adverse events: myocardial infarction

No data were available for this outcome.

Adverse events: new diagnosis of heart failure

No data were available for this outcome.

Adverse events: requirement for one or more hospitalisations for atrial tachyarrhythmias

One trial reported that Class III antiarrhythmics likely reduce hospitalisations for ATa substantially at 0 to 3 months (RR 0.40, 95% CI 0.26 to 0.63, 1 trial, 212 participants, moderate-certainty evidence) (Analysis 3.6) (Darkner 2014).

Sensitivity analysis

Sensitivity analysis including only studies at low risk of bias or those without missing data was not possible.

All-cause mortality

At 0 to 3 months, evidence from Ad 2016 suggests that Class III antiarrhythmics do not affect all-cause mortality (Peto OR 1.00, 95% CI 0.06 to 16.24, 1 trial, 90 participants, low-certainty evidence) (Analysis 3.7) (Ad 2016). At > 3 to 6 months, it is unclear whether Class III antiarrhythmics affect all-cause mortality (Peto OR 0.13, 95% CI 0.00 to 6.57, 1 trial, 212 participants, very low-certainty evidence) (Analysis 3.8) (Darkner 2014).

Sensitivity analysis

Sensitivity analysis including only studies at low risk of bias at 0 to 3 months was consistent with the estimate above, and was not possible at > 3 to 6 months. Sensitivity analysis on the basis of missing data was not necessary.

Requirement for one or more repeat ablation

Based on the analysis of three trials, it is unclear whether Class III antiarrhythmics affect requirement for repeat ablation 0 to 3 months after ablation (RR 1.18, 95% CI 0.66 to 2.11, I^2 = 46%, P > 0.05, Tau^2 = 0.11, 3 trials, 505 participants, very low-certainty evidence) (Analysis 3.9) (Darkner 2014; Mohanty 2015; Tarasov 2017). Mohanty 2015 did not specify the timing of re-ablation.

Sensitivity analysis

Sensitivity analysis at > 3 to 6 months including only studies at low risk of bias or those without missing data was not possible.

DISCUSSION

Summary of main results

This review examined the effect of oral Class I and/or III antiarrhythmics versus no antiarrhythmics in the maintenance of sinus rhythm following catheter ablation for AF. We identified and included 9 parallel-group RCTs involving 3269 participants. For our first primary outcome, recurrence of ATa, the evidence showed a possible benefit of Class I and/or III antiarrhythmics (overall group) in reducing rates of ATa recurrence during the blanking phase (0 to 3 months) (RR 0.74, 95% CI 0.59 to 0.94, 8 trials, 3046 participants, low-certainty evidence), and a likely benefit in reducing rates at > 3 to 6 months (RR 0.85, 95% CI 0.78 to 0.93, 5 trials, 2591 participants, moderate-certainty evidence). This benefit of antiarrhythmics did not appear to last beyond six months (RR 1.14, 95% CI 0.84 to 1.55, 4 trials, 2244 participants, very low-certainty evidence). In addition to a reduction of ATa up to six months after the blanking period, hospitalisations for ATa were reduced with the use of antiarrhythmics up to three months after ablation (RR 0.43, 95% CI 0.28 to 0.64, 3 trials, 448 participants, moderate-certainty evidence). Furthermore, sensitivity analysis supported these results for all-cause hospitalisations (0 to > 6 month follow-up: RR 0.47, 95% CI 0.32 to 0.68, I^2 = 0%, P > 0.1, Tau^2 = 0, 5 trials, 2576 participants, moderate-certainty evidence) and hospitalisations/cardioversions (0 to > 6 month follow-up: RR 0.59, 95% CI 0.39 to 0.90, I^2 = 47%, P > 0.1, Tau^2 = 0.09, 5 trials, 2576 participants, low-certainty evidence). We found no evidence suggesting a beneficial or detrimental effect of antiarrhythmics or lack of antiarrhythmics for the other adverse events or other outcomes of interest for which sufficient data were available: all-cause mortality, requirement for one or more repeat ablation, thromboembolic events, and myocardial infarction. Regarding the three outcomes for which there were very low event rates (all-cause mortality, thromboembolic events, and myocardial infarction), when considering number needed to treat for one additional harmful outcome (NNTH), none of the outcomes NNTH exceeded 100, thus assuming patients are willing to accept an absolute risk of ≤ 1%, we can conclude the risk of these adverse events to be equal between antiarrhythmics and control. It is important to bear in mind that the studies included in this review only prescribed antiarrhythmics up to three months.

Overall completeness and applicability of evidence

This review constitutes the most up-to-date, complete appraisal of evidence regarding the benefits of short-term Class I and/or III antiarrhythmic therapy (up to three months) in maintaining sinus rhythm following ablation for AF. The search was comprehensive and was performed in the CENTRAL, MEDLINE, Embase, Web of Science Core Collection databases and in clinical trials registries. We identified one trial registry protocol that is likely eligible and appears to be in progress (NCT02913014).

All included trials reported recurrence of ATa, at various follow-up periods after ablation; for five trials this was their primary outcome, or at least part of it (Ad 2016; Darkner 2014; Hayashi 2014; Kaitani 2016; Roux 2009). Our seven outcomes of interest covered the vast majority of data reported in the included studies, except for cardioversion; requirement for electrical cardioversion was reported in seven included trials (Ad 2016; Darkner 2014; Hayashi 2014; Kaitani 2016; Roux 2009; Tarasov 2017; Turco 2007). That being said, for many of our included trials these data will overlap with the data reported on hospitalisations for ATa, and in one case was confirmed to do so (Roux 2009).

It is worth noting that one trial reported data on recurrence of ATa to > 24 hours, thus it is possible that this study missed shorter episodes of recurrence. However, as Roux 2009 made up 2% and 2.5% of the weighting for the 0 to 3 month and > 3 to 6 month primary outcome analyses, it is unlikely to have had a substantial effect on our conclusions.

Of note, none of the included studies continued to prescribe Class I and/or III antiarrhythmics beyond three months following ablation. Most included participants had paroxysmal AF (72.8%), whilst the remainder mainly had persistent AF (27.4%). The characteristics of included studies would be applicable to clinical practice; the use of antiarrhythmics in all cases was within the clinically appropriate dosage; and outcomes were all relevant to clinical practice.

Due to an insufficient number of pooled studies, it was not feasible to perform subgroup analysis by individual antiarrhythmic drug or by first versus successive ablations. This will be reviewed in future iterations.

Quality of the evidence

We assessed the certainty of the evidence according to the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a), using the GRADE approach (Schünemann 2013). An inclusion criterion of our review was that all studies had to be RCTs. Based on the risk of bias domains

random sequence generation, allocation concealment, incomplete outcome data, selective reporting, and other bias, we considered one trial to be at low risk of bias (Ad 2016), six trials as at unclear risk of bias (Hayashi 2014; Lodziński 2014; Mohanty 2015; Roux 2009; Tarasov 2017; Turco 2007), and two trials as at high risk of bias (Darkner 2014; Kaitani 2016).

In assessing the limitations of studies, only Kaitani 2016 reported limitations sufficient to merit a judgement of high risk of bias for random sequence generation, due to a randomisation programming error. Darkner 2014 excluded participants that were lost to follow-up, and so was considered to be at high risk of bias for incomplete outcome data. Hayashi 2014 reported an extensive ablation strategy that is likely to be more intensive than routine practice; however, the participants from this trial were the minority of all participants included in the outcomes to which the trial provided data, thus not meriting downgrading of the certainty of evidence for these outcomes. Four trials highlighted the potential risk of missing recurrence events due to the lack of loop recorders (Ad 2016; Darkner 2014; Hayashi 2014; Lodziński 2014); however, this did not merit a judgement of low risk of bias because the data represented a reliable measurement of incidence that is equal across control and intervention arms. Roux 2009 described the exclusion of persistent AF as a limitation; this did not merit a judgement of low risk of bias, as overall the proportions of paroxysmal and persistent AF in the studies included in meta-analysis were relevant to clinical practice. Kaitani 2016 and Hayashi 2014 considered that the doses of antiarrhythmics they used may have been lower or different than those routinely used in Western countries, but they were applicable to the countries where the studies were conducted, thereby improving the generalisability of this review.

We downgraded the certainty of the evidence for imprecision for the following outcomes: recurrence of ATa at 0 to 3, > 3 to 6, and > 6 months with Class I antiarrhythmics, and at > 6 months with Class III antiarrhythmics; 'requirement for one or more hospitalisations for ATa' at 0 to 3 months with Class III antiarrhythmics and 0 to 3 months with Class I antiarrhythmics; and requirement for one or more repeat ablation at 0 to 3 months with Class I antiarrhythmics, as the optimal information size was higher than the total participant numbers in the analysis. Further details of imprecision leading to downgrading of the certainty of the evidence for our main time point of interest are provided in the footnotes of the summary of findings tables.

We did not consider indirectness to be an issue given our stringent inclusion criteria. We were not able to investigate for publication bias, as we did not include > 10 studies (Egger 1997).

Of note, it is possible that the reassuringly low mortality data may well reflect the fact that ablation is performed in a less comorbid population selected for the procedure, thus introducing a risk of selection bias. Nonetheless, this is an internally consistent feature of this review, and so conclusions are therefore limited to the detailed demographic (see Table 1).

Potential biases in the review process

This systematic review was undertaken in accordance with the standards detailed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). We employed a comprehensive search of the most relevant databases. We performed backward citation searches on the included studies. The flow of studies through the review has been transparently outlined in full (Figure 1). We applied no language or date restrictions. At least two review authors (CP, JJHB, MA, MWa, MWh, or RB) assessed studies for inclusion; two review authors (JJHB and CP, MWa, MWh, or RB) independently collected data and information on risk of bias; data collection was checked by MA, CP, MWa, and JJHB; and analyses were performed by JJHB and checked by another review author (JJHB and CP, MWa, MWh, or RB). Any disagreements were resolved through discussion and consensus. Reasons for exclusion of the excluded studies have been provided. Where information was not available, we contacted the study authors, but have received no response.

Our conclusion for the outcome 'requirement for one or more hospitalisations for ATa' is based on a minority of included studies (Darkner 2014; Hayashi 2014; Roux 2009), and thus may not be as generalisable as, for example, our first primary outcome, recurrence of ATa. As part of our sensitivity analysis of whether antiarrhythmics do indeed reduce hospitalisation, we broadened the inclusion criteria to also include 'all-cause hospitalisation' and 'cardioversion' (as cardioversion is most likely to take place during a hospital admission), and found consistent results in favour of antiarrhythmics reducing all of these events by approximately 40% (Ad 2016; Darkner 2014; Hayashi 2014; Kaitani 2016; Roux 2009). Due to a lack of data, it was not possible to divide secondary outcomes by time points. As previously mentioned, we were not able to assess for publication bias.

Agreements and disagreements with other studies or reviews

Our results both agree with and differ from two previous systematic reviews (Goldenberg 2016; Xu 2015). Similar to our findings, Xu 2015 concluded that antiarrhythmic drugs reduce the early reoccurrence of AF after catheter ablation, but not long-term reoccurrence. However, that review diverges from our meta-analysis in finding early reoccurrence to be twice as likely without the use of antiarrhythmics (our estimates were 24% less at 0 to 3 months and 15% less at > 3 to 6 months). Goldenberg 2016 found consistent trends in "overall effect" of antiarrhythmics and in their sensitivity analysis that were not significant. Both Goldenberg 2016 and Xu 2015 included fewer studies than our review: Goldenberg 2016 included 8 studies (2952 participants) and Xu 2015 included 6 studies (814 participants), whereas our review included 9 studies (3269 participants). It should also be noted that Xu 2015 only evaluated participants in two groups: 0 to 3 months and 3 months onwards, and Goldenberg 2016 did not subgroup by follow-up time.

Our review included studies that prescribed Class I and/or III antiarrhythmics up to three months after ablation. In a moderately sized, multicentre RCT performed by Duytschaever 2018, participants who had had catheter ablation undertaken for AF and who had received an extended period of antiarrhythmics (1 year) had markedly lower rates of ATa recurrence at 12-month follow-up compared with control, who had received antiarrhythmics for the first 3 months (21.9% versus 2.7%, respectively). Consequently, stopping antiarrhythmics at three months may explain our findings that any benefit of antiarrhythmics appears to wane after six months. Our findings are also similar to Wu 2008, a narrowly excluded study that found significant differences in AF recurrence following antiarrhythmics for 3 months at 3-month follow-up, but not at 12-month follow-up. The same is true when comparing

our results with Gu 2012, who compared single versus extensive antiarrhythmic use up to 2 months after ablation with 2- and 12-month follow-up. They, too, found reduced ATa recurrence (non-significant versus extensive) in the early term that did not persist into long-term follow-up.

AUTHORS' CONCLUSIONS

Implications for practice

Catheter ablation is a costly procedure with the risks associated with invasive procedures. Trying to maintain sinus rhythm after ablation through antiarrhythmics has thus been a strategy that has been used clinically. In practice, this is limited by the selection, duration, and dosing of medications. Our review shows that the effects of antiarrhythmics, despite only being used for three months in the analysed studies, persisted beyond three months but not beyond six months. The fact that rehospitalisations are also reduced in the first three months with antiarrhythmics adds to the evidence for their usage.

Our review may add to the evidence for Class I and III antiarrhythmic usage for people postablation; nonetheless, this needs to be a decision tailored clinically to each patient due to limitations in our understanding of complications such as thromboembolism, myocardial infarction, and new diagnosis of heart failure. There is also less evidence for the effects of these drugs beyond six months, although this may be due to the fact that they were stopped at three months in the included studies.

It is clear that people undergoing atrial fibrillation (AF) ablation have improved quality of life postablation and have a significant reduction in AF burden (Blomstrom-Lundqvist 2019). This is why the European Society of Cardiology (ESC) has changed its recommendations from antiarrhythmics as first-line therapy, and if failing this then undergoing ablation in symptomatic paroxysmal AF, to "AF catheter ablation should be considered before a trial of [antiarrhythmics] in patients with paroxysmal AF episodes (Class IIa), or maybe considered in patients with persistent AF without risk factors for recurrence (Class IIb)". This has clinical implications, as patients referred for ablation will not necessarily be on antiarrhythmics before ablation. Our meta-analysis suggests that due to effects outside of the blanking period (i.e. the initial three months) and the reduction in hospitalisation in the first three months, these patients may still be considered for antiarrhythmics if they are undergoing ablation for maintenance of sinus rhythm.

The ESC also states that: "a. Continuing [antiarrhythmic] treatment for 6 weeks to 3 months may reduce early AF recurrences, rehospitalizations and cardioversions during this period. Clinical practice regarding routine [antiarrhythmic] treatment after ablation varies and there is no convincing evidence that such treatment is routinely needed" (Hindricks 2020).

The latest American Heart Association (AHA) guidance does not provide a recommendation on this question (January 2019a).

This review provides low- to moderate-certainty evidence that Class I and/or III antiarrhythmics during the blanking period reduce the recurrence of atrial tachyarrhythmias up to six months after the ablation. It is increasingly clear that Class I and/or III antiarrhythmics are probably beneficial when given during the blanking period.

Hospitalisation post-AF has also been a major problem, with one study in the USA involving 811 participants reporting that 9.7% were hospitalised within 30 days of ablation and 19.1% had a visit to Accident and Emergency (Freeman 2018). At one year, 28.9% of participants were readmitted and 44.5% were seen in Accident and Emergency (Freeman 2018). Guo and colleagues have already shown that AF ablation results in a 56% reduction in hospitalisation postablation (Guo 2019). Another study by Aurora and colleagues reported that 16.5% of ablation patients were readmitted within 90 days (Arora 2018). Since one of the main benefits of AF ablation is reduction in hospitalisation, the fact that this meta-analysis shows some benefit in reduction in hospitalisation provides further evidence for Class I and/or III antiarrhythmic usage.

Implications for research

The available evidence is limited by the lack of systematic assessment in the majority of studies of important clinical outcomes such as all-cause mortality, thromboembolic events, and myocardial infarction. Future trials investigating antiarrhythmics (Class I and III) should measure their effects on such clinical outcomes. Given the moderate heterogeneity in ablation strategies utilised between included studies, further work should endeavour to standardise ablation strategies to assess antiarrhythmic efficacy as well as matching for demographic factors.

We believe a large, multicentre trial is needed to further clarify this question. Firstly, the vast majority of included randomised controlled trials were not blinded, and secondly there was variability in the results of the included studies. Due to these limitations, additional data from a large, multicentre randomised study is required with important clinical outcomes such as myocardial infraction, all-cause mortality, and thromboembolic events. This study should also compare different periods of antiarrhythmics usage, such as less than three months to up to a year.

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The following people conducted the editorial process for this article.

1. Sign-off Editor (final editorial decision): Mike Brown, Michigan State University College of Human Medicine, USA
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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ad 2016

Study characteristics	
Methods	**Design:** randomised controlled trial **Group:** parallel group **Blinding:** non-blinded **Date of enrolment:** 1 January 2011 to 1 December 2012 **Number of study centres:** single-centre **Study duration:** 3 years
Participants	**Inclusion criteria:** age ≥ 18 years, 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 > 1 year **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 to 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 **Group differences:** no significant differences were found between the 2 groups **Number randomised:** 97 **Number analysed:** 90 **Number lost to follow-up:** 1 lost to follow up, 2 deaths **Paroxysmal and persistent AF proportions:** 38.9% persistent AF, 61.1% paroxysmal AF ***Baseline characteristics*** **Mean age (years):** intervention: 63.8, control: 63.4 **Age range (years):** N/a **Mean sex (% male):** intervention: 73%, control: 71% **Mean left atrial diameter (cm):** intervention: 5, control: 5.1 **Mean AF duration (months):** intervention: 23, control: 20 **Mean number of prior antiarrhythmic drugs (n):** N/a **History of previous AF ablation (%):** N/a **Mean left ventricular ejection fraction (%):** intervention: 55.2%, control: 54.4% **Hypertension (%):** intervention: 60%, control: 67%

Ad 2016 *(Continued)*

	Chronic obstructive pulmonary disease (%): intervention: 20%, control: 24% **Diabetes mellitus (%):** intervention: 18%, control: 7% **Pre-existing antiarrhythmic drugs at randomisation (%):** N/a
Interventions	2 comparison arms: 1) amiodarone versus 2) no amiodarone
Outcomes	**Primary outcome:** 1. 60-day, freedom from atrial arrhythmia recurrence **Collection method for primary outcome:** 6 and 12 months, 48 to 72 hour event monitor **Secondary outcomes:** 1. 30-day, operative mortality 2. 3-month, stroke/ transient ischaemic attack (TIA) 3. 30-day, readmission
Notes	**Setting, country:** Inova Heart and Vascular Institute Cardiac Surgery, USA **Author contact details:** Niv.Ad@inova.org Inova Heart and Vascular Institute, 3300 Gallows Rd, Ste 3100, Falls Church, VA 22042 **Sponsorship source:** none reported **Optimal sample size estimate**: 186 **Clinical trial registry record:** NCT01416935

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The random-allocation sequence was generated by the study statistician." "The random-allocation sequence was created with computer-generated random numbers, and blocked randomization of 10 patients in each block, to ensure balance in the treatment groups in case the study needed to be stopped early."
Allocation concealment (selection bias)	Low risk	"Sequentially numbered opaque envelopes containing the treatment allocation were utilized to conceal the sequence."
Blinding of participants and personnel (performance bias) All outcomes	High risk	"patients were enrolled and assigned to treatment groups by the research coordinator." Non-blinded study. This may have introduced differences between randomised groups other than the intervention being evaluated.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding used in this study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Most participants at 6 weeks (88%) and 12 weeks (84%) had rhythm status determined by long-term monitoring (CardioNet or pacemaker interrogation). In 3 participants who were randomised, no follow-up for rhythm status was obtained, including 2 participants who died before 6 weeks, and 1 participant who was lost to follow-up.

Ad 2016 *(Continued)*

Selective reporting (reporting bias)	Low risk	Adverse outcomes reported except cause of death. Cause of hospitalisation not reported.
Other bias	Low risk	No industry funding reported. Optimal sample size estimate: 186

Darkner 2014

Study characteristics	
Methods	**Design:** randomised controlled trial **Group:** parallel group **Blinding:** double-blind **Date of enrolment:** February 2009 at Rigshospitalet/January 2011 at Gentofte Hospital **Number of study centres:** double-centre **Setting:** tertiary hospital **Study duration:** 6 months
Participants	**Inclusion criteria:** patients with paroxysmal or persistent AF undergoing first-time or repeat ablation were eligible for inclusion **Exclusion criteria:** 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 (NYHA class III, IV, or LVEF < 35%), significant heart valve disease, previous participation in the study, thyroid disease, severe pulmonary or liver disease, and woman with child-bearing potential **Group differences:** no significant difference **Number randomised:** 212 **Number analysed:** 206 **Number lost to follow-up:** 5 lost to follow-up, 1 died **Paroxysmal and persistent AF proportions:** paroxysmal 50.5%, persistent 49.5% ***Baseline characteristics*** **Mean age (years):** intervention: 62, control: 61 **Age range (years):** 53 to 66 **Mean sex (% male):** intervention: 81%, control: 86% **Mean left atrial diameter (cm):** intervention: 4.4, control: 4.4 **Mean AF duration (months):** intervention: 78, control: 76 **Mean number of prior antiarrhythmic drugs (n):** intervention: 1.2, control: 1.1 **History of previous AF ablation (%):** intervention: 30%, control: 28% **Mean left ventricular ejection fraction (%):** intervention: 51%, control: 50%

Darkner 2014 *(Continued)*

Hypertension (%): intervention: 37%, control: 42%

Hyperlipidaemia (%): intervention: 32%, control: 28%

History of right atrial flutter (%): intervention: 12%, control: 15%

Coronary artery disease (%): intervention: 6%, control: 8%

Sleep apnoea (%): intervention: 2%, control: 2%

Diabetes mellitus (%): intervention: 9%, control: 8%

Pre-existing antiarrhythmic drugs at randomisation (%):

Intervention:

1. beta-blocker 58%
2. calcium channel blocker 15%
3. digoxin 15%
4. flecainide/propafenone 21%
5. sotalol 1%
6. dronedarone 13%

Control:

1. beta-blocker 62%
2. CCB 10%
3. digoxin 12%
4. flecainide/propafenone 24%
5. sotalol 2%
6. dronedarone 12%

Interventions	2 comparison arms: 1) amiodarone versus 2) placebo
Outcomes	**Primary outcome:** 1. 3-month, freedom from atrial tachyarrhythmia 2. 6-month, freedom from atrial tachyarrhythmia **Collection method for primary outcome:** 12-lead ECG at 1, 3, and 6 months, and 3-day Holter monitoring at 6 to 8 weeks and at 6-month follow-up **Secondary outcomes:** 1. 6-month, mortality 2. blanking period, re-ablation due to recurrent, refractory atrial tachyarrhythmias 3. 6-month, stroke/TIA 4. blanking period, atrial tachyarrhythmia-related hospitalisations*
Notes	**Setting, country:** Rigshospitalet og Gentofte Hospital, Copenhagen University, Denmark **Author contact details:** stine.darkner.01@regionh.dk **Sponsorship source:** this work was supported by the Danish Heart Foundation and The Heart Centre Research Committee at Rigshospitalet, Copenhagen **Optimal sample size:** 182 (calculated based on 50% reduction rate) **Clinical trial registry record:**NCT00826826
Risk of bias	

Darkner 2014 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Refers to "The randomization code" but does not clarify beyond that about how the code was generated
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind trial, placebo controlled
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All cardiac rhythm recordings concerning the primary outcome were evaluated by an adjudication committee before unblinding the trial."
Incomplete outcome data (attrition bias) All outcomes	High risk	Participants who were lost to follow-up or who died before completing the 6-month follow-up visit were excluded from the analysis of the primary endpoint. These participants were excluded from final analysis.
Selective reporting (reporting bias)	Low risk	The trial was registered at ClinicalTrials.gov prior to study start (NCT00826826), and was monitored by the regional Good Clinical Practice unit. Study was registered and all outcomes have been addressed.
Other bias	Low risk	No industry funding Calculated based on 50% reduction rate: 182

Hayashi 2014

Study characteristics	
Methods	**Design:** randomised controlled trial **Group:** parallel group **Blinding:** non-blinded **Date of enrolment:** 1 November 2010 to 28 February 2013 **Number of study centres:** single-centre **Setting:** tertiary teaching hospital **Study duration:** 28 months
Participants	**Inclusion criteria:** all patients referred to the Nippon Medical School Teaching Hospital for ablation of AF were screened **Exclusion criteria:** < 18 years, a history of radiofrequency catheter ablation or surgery for AF amiodarone therapy within 3 months, bepridil therapy within 1 month, congestive heart failure, hypertrophic cardiomyopathy, ischaemic heart disease, left ventricular ejection fraction of < 0.50, sick sinus syndrome, undergoing haemodialysis, patient refusal, living too far from the study site to be followed, enrolment in another clinical trial, failure to complete pulmonary vein isolation **Group differences:** not significantly different

Hayashi 2014 *(Continued)*

	Number randomised: 126 **Number analysed:** 125 **Number lost to follow-up:** 1 **Paroxysmal and persistent AF proportions:** 71.4% paroxysmal AF, 28.6% persistent AF ***Baseline characteristics*** **Mean age (years):** intervention: 62, control: 64 **Age range (years):** N/a **Mean sex (% male):** intervention: 77%, control: 77% **Mean left atrial diameter (cm):** intervention: 38%, control: 38% **Mean AF duration (months):** intervention: 14%, control: 19% **Mean number of prior antiarrhythmic drugs (n):** intervention: 1, control: 1 **History of previous AF ablation (%):** intervention: 0, control: 0 **Mean left ventricular ejection fraction (%):** intervention: 69%, control: 68% **Hypertension (%):** intervention: 65%, control: 61% **Sleep apnoea (%):** intervention: 8%, control: 5% **Chronic obstructive pulmonary disease (%):** intervention: 0%, control: 2% **Diabetes mellitus (%):** intervention: 5%, control: 9% **Pre-existing antiarrhythmic drugs at randomisation (%):** N/a
Interventions	2 comparison arms: 1) flecainide versus 2) control (no Class I or III antiarrhythmics)
Outcomes	**Primary outcome:** 1. 3-month, freedom from ATa > 30 s 2. 6-month, maintenance of sinus rhythm (with medications stopped at 3 months) 3. 12-month, maintenance of sinus rhythm (with medications stopped at 3 months) **Collection method for primary outcome:** telemetry until discharge, then an event recorder for 4 months, including 12-lead ECG at 2 weeks, 1, 2, 3, 4, 5, 6, 7, 8, 10, and 12 months **Secondary outcomes:** 1. 3-month, hospitalisation
Notes	**Setting, country:** Nippon Medical School Teaching Hospital, Japan **Author contact details:** m-h4510@nms.ac.jp, Department of Cardiovascular Medicine, Nippon Medical School, 1-1-5 Sendagi, Bunkyo-ku, Tokyo 113-8603, Japan **Sponsorship source:** Japanese national grant named MEXTKAKENHI Grant Number 22790735 **Optimal sample size estimate:** 124, assuming recurrence rate of 50% **Clinical trial registry record:** none reported
Risk of bias	

Hayashi 2014 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided on sequence generation.
Allocation concealment (selection bias)	Unclear risk	No information provided on allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	"The present study was designed as a prospective randomized non-blinded trial." High risk of bias due to inadequate or absent blinding of personnel. This may have introduced differences between randomised groups other than the intervention being evaluated.
Blinding of outcome assessment (detection bias) All outcomes	High risk	High risk of bias due to inadequate or absent blinding of outcome assessor
Incomplete outcome data (attrition bias) All outcomes	Low risk	No issues with study participants withdrawing from the study
Selective reporting (reporting bias)	Low risk	No trial registration mentioned. It appears that all outcomes have been addressed.
Other bias	Low risk	No industry funding Optimal sample size estimate: 124, assuming recurrence rate of 50%

Kaitani 2016

Study characteristics	
Methods	**Design:** randomised controlled trial **Group:** parallel group **Blinding:** non-blinded **Date of enrolment:** 1 November 2011 to 1 March 2014 **Number of study centres:** multicentre **Setting:** tertiary hospitals, cardiovascular centres **Study duration:** 12 months
Participants	**Inclusion criteria:** patients who were 21 to 79 years old undergoing first-time radio frequency 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), NYHA class IV heart failure, LVEF < 40%, left atrial 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 who the attending physician considered inappropriate to enrol in the study

Kaitani 2016 *(Continued)*

Group differences: there were significant differences in age, gender, and age-related participant characteristics between groups. Also, participants in the control group had more often received ATP-guided pulmonary vein isolation.

Number randomised: 2044

Number analysed: 2027

Number lost to follow-up: 6 lost to follow-up, 5 died

Paroxysmal and persistent AF proportions: 67.5% paroxysmal AF; 22.6% persistent AF and 9.9% long-lasting AF

Baseline characteristics

Mean age (years): intervention: 65.9, control: 60.7

Age range (years): 21 to 79

Mean sex (% male): intervention: 72.9%, control: 77.2%

Mean left atrial diameter (cm): intervention: 3.89, control: 3.90

Mean AF duration (months): N/a

Mean number of prior antiarrhythmic drugs (n): intervention: 58.5%, control: 60.2%

History of previous AF ablation (%): N/a

Mean left ventricular ejection fraction (%): intervention: 64.5%, control: 64.2%

Hypertension (%): intervention: 55.2%, control: 51.5%

Diabetes mellitus (%): intervention: 15.2%, control: 11.5%

Pre-existing antiarrhythmic drugs at randomisation (%): N/a

Interventions	2 comparison arms: 1) Class I or III antiarrhythmics (pilsicainide, flecainide, cibenzoline, propafenone, disopyramide aprindine, bepridil, amiodarone, or sotalol) versus 2) control (no antiarrhythmics)
Outcomes	**Primary outcome:** 1. 60-day, event-free survival from atrial tachyarrhythmia 2. 90-day, event-free survival from atrial tachyarrhythmia 3. 365-day, event-free survival from atrial tachyarrhythmia** **Collection method for primary outcome:** single-lead ECG for 2 weeks, twice daily and when the participant has symptoms. An ambulatory ECG at hospital discharge, 6 and 12 months. Also, a 12-lead ECG at 3, 6, and 12 months **Secondary outcomes:** 1. 1-year, mortality 2. 365-day freedom from repeat ablation** 3. 90-day, stroke/ transient ischaemic attack (TIA) 4. 90-day, myocardial infarction (MI) 5. 90-day, hospitalisation for heart failure (HF)
Notes	**Setting, country:** Kansai region, Japan **Author contact details:** shizuta@kuhp.kyoto-u.ac.jp **Sponsorship source:** this study was supported by Research Institute for Production Development in Kyoto, Japan. No conflicts of interest declared.

Kaitani 2016 *(Continued)*

Optimal sample size estimate: 1840

Clinical trial registry record:NCT01477983

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	A computer program was used for random sequence generation. There were significant differences in age, gender, and age-related participant characteristics between groups. "Because of the programming error in the randomization system to minimize the imbalance of allocation in each dichotomized age stratum, patients were oppositely allocated to the treatment group towards imbalance, which affected the distribution of other stratification variables and age-related baseline patient characteristics (Table 1)."
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	"For safety reason, the actual choice and dosage of the AADs were left to the discretion of the attending physician." "Ambulatory electrocardiograms were read by cardiologists at the core laboratory who were unaware of the treatment assignments." No mention of placebo use
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Ambulatory electrocardiograms were read by cardiologists at the core laboratory who were unaware of the treatment assignments." "All the clinical data were imputed by clinical research coordinators, clinicians, and/or attending physicians at the local centre." Some evidence of blinding, but unclear about the majority of outcome data
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participant adverse outcomes were reported. 6 lost to follow-up (0.2935%), and 5 died.
Selective reporting (reporting bias)	Low risk	All outcomes were reported.
Other bias	Low risk	No industry funding Optimal sample size estimate: 1840

Lodziński 2014

Study characteristics

Methods	**Design:** randomised controlled trial **Group:** parallel group **Blinding:** non-blinded **Date of enrolment:** 1 January 2003 to 1 January 2007

Lodziński 2014 *(Continued)*

	Number of study centres: single-centre **Setting:** tertiary university teaching hospital **Study duration:** 55 months
Participants	**Inclusion criteria:** first pulmonary vein isolation due to AF; age above 18 years; and sinus rhythm during the first 24 h after PVI **Exclusion criteria:** reversible cause of AF; bradycardia of 50 bpm or less, atrioventricular or intraventricular blocks; contraindications to antiarrhythmic agents used during study (in case of contraindication to amiodarone, sotalol was used); and PVI procedure with heart tamponade complication **Group differences:** not statistically different at 2 months, statistically different for sex, age, and left atrial diameter at 55 months **Number randomised:** 210 **Number analysed:** 171 at 2 months; 137 at 55 months **Number lost to follow-up:** 39 at 2 months; 73 at 55 months **Paroxysmal and persistent AF proportions:** 80.2% paroxysmal AF, 19.8% persistent AF ***Baseline characteristics*** **Mean age (years):** intervention: 50.8, control: 47.6 **Age range (years):** N/a **Mean sex (% male):** intervention: 71%, control: 71.9% **Mean left atrial diameter (cm):** intervention: 4.3, control: 4.1 **Mean AF duration (months):** intervention: 80.2, control: 76.0 **Mean number of prior antiarrhythmic drugs (n):** N/a **History of previous AF ablation (%):** N/a **Chronic heart failure (%):** intervention: 1.6%, control: 1.8% **Hypertension (%):** intervention: 49%, control: 39% **Hyperlipidaemia (%):** intervention: 19%, control: 12% **Coronary artery disease (%):** intervention: 12%, control: 8.8% **Diabetes mellitus (%):** intervention: 6.8%, control: 3.5% **Pre-existing antiarrhythmic drugs at randomisation (%):** N/a
Interventions	3 comparison arms: 1) no antiarrhythmics versus 2) amiodarone or sotalol versus 3) last ineffective antiarrhythmic We used comparison arms 1) versus 2) in our analysis.
Outcomes	**Primary outcome:** 1. 2-month, without AF lasting at least 30 s **Collection method for primary outcome:** 2, 24 h Holters
Notes	**Setting, country:** Medical University of Warsaw, Poland **Authors contact details:** piotr.lodzinski@me.com

Lodziński 2014 *(Continued)*

Sponsorship source: none reported

Optimal sample size: no sample size calculation reported

Clinical trial registry record: none reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The groups were randomised, although it is unclear how this was done.
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information regarding blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Does not report if there was blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Significant loss to follow-up by 2 months (18.6%). It is possible that this loss to follow-up could be related to the intervention, therefore we have assessed this domain as unclear risk.
Selective reporting (reporting bias)	Unclear risk	Trial not analysed in accordance with prespecified plan. “Due to different protocols on result description among different centres, the medical data gathered during follow-up were inconsistent. To make them comparable, the results were divided into groups” It is thus implied that the results were analysed according to a post-protocol plan.
Other bias	Unclear risk	No industry funding reported. No sample size calculation reported.

Mohanty 2015

Study characteristics

Methods

Design: randomised controlled trial

Group: parallel group

Blinding: non-blinded

Date of enrolment: 1 July 2010 to 1 June 2012

Number of study centres: multicentre

Setting: unclear

Study duration: 32 months

Mohanty 2015 *(Continued)*

Participants	**Inclusion criteria:** N/a **Exclusion criteria:** patients with chronic hepatic disease, concomitant treatment with other Class I or III antiarrhythmic drugs, severe pulmonary disease, or systemic heart failure (NYHA class III or IV) were excluded from the study **Group differences:** no significant differences **Number randomised:** 112 **Number analysed:** 112 **Number lost to follow-up:** 0 **Paroxysmal and persistent AF proportions:** 100% long-standing persistent AF ***Baseline characteristics*** **Mean age (years):** intervention: 60, control: 62 **Age range (years):** N/a **Mean sex (% male):** intervention: 75%, control: 68% **Mean left atrial diameter (cm):** intervention: 4.8, control: 4.7 **Mean AF duration (months):** intervention: 81, control: 78 **Mean number of prior antiarrhythmic drugs (n):** N/a **History of previous AF ablation (%):** N/a **Mean left ventricular ejection fraction (%):** intervention: 55%, control: 54% **Hypertension (%):** intervention: 48%, control: 46% **Coronary artery disease (%):** intervention: 21%, control: 25% **Diabetes mellitus (%):** intervention: 16%, control: 11% **Pre-existing antiarrhythmic drugs at randomisation (%):** N/a
Interventions	2 comparison arms: 1) amiodarone versus 2) no amiodarone
Outcomes	**Primary outcome:** 1. 6-month, freedom from AF/atrial tachyarrhythmia for at least 30 seconds 2. mean 32-month, freedom from AF/atrial tachyarrhythmia for at least 30 seconds **Collection method for primary outcome:** 12-lead ECG and 7-day Holter at 3, 6, 9, and 12 months, in addition to an event recorder for 5 months after ablation **Secondary outcomes:** 1. re-ablation
Notes	**Setting, country:** unclear, USA **Author contact details:** dr.natale@gmail.com **Sponsorship source:** none reported **Optimal sample size:** no sample size calculation reported

Mohanty 2015 *(Continued)*

Errata: following publication of the original manuscript of Mohanty 2015, an amendment was made such that "the headers in Table 1 were reversed". We have considered this minor amendment, and it does not impact the conclusions of our review (Mohanty 2015).

Clinical trial registry record: NCT01173809

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A computer algorithm written in SAS (SAS Institute, Cary, NC) was used for performing block randomization."
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information
Incomplete outcome data (attrition bias) All outcomes	Low risk	It appears that all data were addressed.
Selective reporting (reporting bias)	Low risk	Complications reported, all outcomes commented on.
Other bias	Unclear risk	No industry funding reported. No sample size calculation reported.

Roux 2009

Study characteristics

Methods	**Design:** randomised controlled trial **Group:** parallel group **Blinding:** non-blinded **Date of enrolment:** 1 December 2006 to 1 March 2008 **Number of study centres:** single-centre **Setting:** tertiary university teaching hospital **Study duration:** 6 months
Participants	**Inclusion criteria:** patients with paroxysmal AF undergoing pulmonary vein ablation. Paroxysmal AF was defined as typical episodes lasting > 30 seconds and spontaneously returning to sinus rhythm within 7 days.

Roux 2009 *(Continued)*

Exclusion criteria: inability to tolerate any AAD, amiodarone therapy within 3 months of the ablation procedure; participation in another clinical trial

Group differences: no formal statistical comparison, but baseline characteristics appear to be similar

Number randomised: 110

Number analysed: 110

Number lost to follow-up: 0

Paroxysmal and persistent AF proportions: 100% paroxysmal AF

Baseline characteristics

Mean age (years): intervention: 56, control: 55

Age range (years): N/a

Mean sex (% male): intervention: 70, control: 72

Mean left atrial diameter (cm): intervention: 4.3, control: 4.1

Mean AF duration (months): intervention: 71, control: 81

Mean number of prior antiarrhythmic drugs (n): intervention: 1.7, control: 1.5

History of previous AF ablation (%): intervention: 25%, control: 25%

Mean left ventricular ejection fraction (%): intervention: 61%, control: 62%

Hypertension (%): intervention: 47%, control: 53%

Hyperlipidaemia (%): intervention: 43%, control: 53%

History of right atrial flutter (%): intervention: 34%, control: 33%

Coronary artery disease (%): intervention: 13%, control: 12%

Sleep apnoea (%): intervention: 13%, control: 12%

Chronic obstructive pulmonary disease (%): intervention: 4%, control: 2%

Diabetes mellitus (%): intervention: 8%, control: 4%

Pre-existing antiarrhythmic drugs at randomisation (%): N/a

Interventions	2 comparison arms: 1) antiarrhythmics (propafenone, flecainide, sotalol, or dofetilide) versus 2) no antiarrhythmics
Outcomes	**Primary outcome:** 1. 6-week, arrhythmia lasting 24 h or requiring AAD initiation/change 2. 6-month, arrhythmia lasting 24 h or requiring AAD imitation/change We considered this trial to be eligible for inclusion because although it will only reflect longer episodes of recurrence, these significant periods of recurrence can be compared between the use of antiarrhythmics and control. **Collection method for primary outcome:** 30-day transtelephonic loop recorders at the start of the trial and at 6 months **Secondary outcomes:** 1. 6-week, cardioversion/hospitalisation for arrhythmia***

Roux 2009 *(Continued)*

Notes	**Setting, country:** University of Pennsylvania, USA **Author contact details:** N/a **Sponsorship source:** none reported **Optimal sample size estimate:** 160 **Clinical trial registry record:**NCT00408200

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"We also thank Anthony Killian, RN, for performing the study randomization." "Eligible patients provided consent before their ablation procedure and were randomized in a 1:1 fashion after ablation to either the AAD or no-AAD group using sealed envelopes." Unclear how randomisation sequence was generated
Allocation concealment (selection bias)	Low risk	"Eligible patients provided consent before their ablation procedure and were randomized in a 1:1 fashion after ablation to either the AAD or no-AAD group using sealed envelopes."
Blinding of participants and personnel (performance bias) All outcomes	High risk	"nonblinded" "The antiarrhythmic agent and dose was chosen to provide a therapeutic benefit and uniformity among our large group of prescribing physicians."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information available.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants (100%) received the assigned treatment and completed the 6-week follow-up.
Selective reporting (reporting bias)	Low risk	All outcomes were reported.
Other bias	Low risk	No industry funding reported. Optimal sample size estimate: 160

Tarasov 2017

Study characteristics

Methods	**Design:** randomised controlled trial **Group:** parallel group **Blinding:** non-blinded **Date of enrolment:** 1 November 2012 to 1 October 2015 **Number of study centres:** single-centre

Tarasov 2017 *(Continued)*

	Setting: unclear **Study duration:** 3 years
Participants	**Inclusion criteria:** men and women aged ≥ 25 years; symptomatic paroxysmal AF without organic pathology; taking at least 1 antiarrhythmic; successful catheter ablation of the pulmonary vein orifices **Exclusion criteria:** previous myocardial infarction or other reported organic pathology of the heart; previous ablation of pulmonary vein orifices outside of the protocol; intolerance to the medications used in the protocol **Group differences:** no formal statistical comparison, but visually appear to be comparable **Number randomised:** 251 **Number analysed:** 243 **Number lost to follow-up:** 8 (3 withdrawal of consent, 5 loss to follow-up) **Paroxysmal and persistent AF proportions:** 100% symptomatic paroxysmal AF ***Baseline characteristics*** **Mean age (years):** propafenone: 56.3, sotalol: 55.6, verapamil and control: 56.2 **Age range (years):** N/a **Mean sex (% male):** propafenone: 56.5%, sotalol: 58.3%, verapamil and control: 59.5% **Mean left atrial diameter (cm):** propafenone: 4.17, sotalol: 4.13, verapamil and control: 4.16 **Mean AF duration (months):** propafenone: 52.6%, sotalol: 52.3%, verapamil and control: 54.5% **Mean number of prior antiarrhythmic drugs (n):** N/a **History of previous AF ablation (%):** N/a **Mean left ventricular ejection fraction (%):** N/a **Hypertension (%):** propafenone: 51%, sotalol: 49%, verapamil and control: 49% **Diabetes mellitus (%):** propafenone: 9%, sotalol: 8%, verapamil and control: 7% **Pre-existing antiarrhythmic drugs at randomisation (%):** N/a
Interventions	4 comparison arms: 1) group 1, verapamil; 2) group 2, propafenone; 3) group 3, sotalol; 4) group 4, control (no antiarrhythmics) We utilised all 4 groups in our analysis by combining groups 1) and 3) into an 'antiarrhythmics group', and groups 2) and 4) into a 'control/standard therapy' group.
Outcomes	**Primary outcome:** 1. 3-month, effectiveness after first procedure, defined as recurrent AF requiring antiarrhythmic withdrawal, continuation or repeat ablation **Collection method for primary outcome:** 24 h Holter at 1, 2, 3, 6, and 12 months. 12-lead ECGs and subcutaneous heart rate monitor **Secondary outcomes:** 1. 3-month, participants requiring second ablation 2. 3-month, hospitalisation for arrhythmia

Tarasov 2017 *(Continued)*

Notes	**Setting, country:** National Research Center for Preventive Medicine of the Ministry of Health, Moscow, Russia **Author contact details:** AV Tarasov Institution: National Research Center for Preventive Medicine of the Ministry of Health, Moscow, Russia Email: a730tv@yandex.ru Phone: +7 (903) 799-18-33 **Sponsorship source:** help to publish this article was provided by PRO.MED.CS Praha (pharmaceutical company in Prague) **Optimal sample size:** no sample size calculation reported **Clinical trial registry record:** none reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised, although the trial does not specify how the sequence was generated
Allocation concealment (selection bias)	Unclear risk	Randomisation was concealed for 251 participants using envelopes. "251 patients were randomized by envelopes after screening taking into account inclusion and exclusion criteria"
Blinding of participants and personnel (performance bias) All outcomes	High risk	"open-label" Based on translations from duplicate publications: Tarasov 2017a: "this is a prospective open, randomized study" Tarasov 2017b: "Our prospective open, randomized study"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	"5 did not respect the visits and research methods, therefore, were excluded from the protocol."
Selective reporting (reporting bias)	Unclear risk	Data reported as continuous outcomes, and there is 96.8% availability of data (8/251 loss to follow-up). It appears that multiple analyses were performed, as evidenced in several duplicate publications.
Other bias	High risk	Industry funding: supported by PRO.MED.CS Praha (pharmaceutical company in Prague) No sample size calculation reported.

Turco 2007

Study characteristics

Methods	**Design:** randomised controlled trial

Turco 2007 *(Continued)*

	Group: parallel group **Blinding:** non-blinded **Date of enrolment:** 1 February 2004 **Number of study centres:** single-centre **Setting:** tertiary hospital **Study duration:** 12 months
Participants	**Inclusion criteria:** paroxysmal or persistent AF patients with intolerance to antiarrhythmic drugs, or in whom 2 or more antiarrhythmic drugs had been unsuccessful **Exclusion criteria:** age < 18 or > 75 years; permanent AF (AF was the only recorded rhythm in the last 12 months); AF secondary to a transient or correctable abnormality; persistence of AF episodes triggered by another atrial tachyarrhythmia (i.e. atrial flutter or atrial tachycardia) despite the previous ablation of supraventricular tachycardia; Wolff-Parkinson-White syndrome; NYHA functional class III or IV heart failure or left ventricular ejection fraction ≤ 35%; implanted pacemaker or cardioverter-defibrillator; left atrial diameter > 60 mm **Group differences:** no significant differences **Number randomised:** 107 **Number analysed:** 107 **Number lost to follow-up:** N/a **Paroxysmal and persistent AF proportions:** 60% paroxysmal; 40% permanent ***Baseline characteristics*** **Mean age (years):** intervention: 54, control: 53 **Age range (years):** 47 to 67 **Mean sex (% male):** total: 64.5% **Mean left atrial diameter (cm):** total: 4.8 **Mean AF duration (months):** total: 54 **Mean number of prior antiarrhythmic drugs (n):** N/a **History of previous AF ablation (%):** N/a **Mean left ventricular ejection fraction (%):** total: 57% **Hypertension (%):** total: 57% **Coronary artery disease (%):** total: 5% **Pre-existing antiarrhythmic drugs at randomisation (%):** N/a
Interventions	2 comparison arms: 1) group A, control (ablation alone) versus 2) group B, antiarrhythmics (amiodarone or other Class IC antiarrhythmic)
Outcomes	**Primary outcome:** 1. 1-month, recurrence of atrial arrhythmia 2. 12-month, recurrence of atrial arrhythmia

Turco 2007 *(Continued)*

	Collection method for primary outcome: transtelephonic ECG recorder (Sorin Life Watch) and a weekly 30-second ECG for 12 months in addition to an ECG with palpitations and a standard ECG and ambulatory ECG with visits at 1, 4, 7, 10, and 13 months
Notes	**Setting, country:** electrophysiology lab centres, Naples, Italy **Author contact details:** Michele Brignole, Department of Cardiology and Arrhythmologic Centre, Ospedali Riuniti, Via don Bobbio, 16032 Lavagna, Italy **Sponsorship source:** none reported **Optimal sample size:** no sample size calculation reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients enrolled were randomized to receive one of three different therapeutic approaches:" No information provided on sequence generation.
Allocation concealment (selection bias)	Unclear risk	"Patients enrolled were randomized to receive" No information provided on allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear risk of bias, as no description given of blinding of personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear risk of bias, as no description given of blinding of outcome assessor
Incomplete outcome data (attrition bias) All outcomes	Low risk	It appears that all study outcomes have been addressed. No loss to follow-up
Selective reporting (reporting bias)	Low risk	All outcomes planned and addressed as described. No information about study trial registration
Other bias	Unclear risk	No industry funding reported. No sample size calculation reported.

Abbreviations: AAD: antiarrhythmic drug; AF: atrial fibrillation; ATP: adenosine triphosphate; bpm: beats per minute; ECG: electrocardiogram; HF: heart failure; HRS: Heart Rhythm Society; LVEF: left ventricular ejection fraction; MI: myocardial infarction; N/a: not available; NYHA: New York Heart Association; TIA: transient ischaemic attack

Footnotes:

*Darkner 2014 reports a risk ratio for “AF/AT-related hospitalizations” for “Total study: all patients” during the blanking period and the total number of participants with hospitalisations during the blanking period, from which we calculated event rates.

**Kaitani 2016 reports data on "freedom from atrial tachyarrhythmia" and “freedom from repeat ablation” up to 450 days after the blanking period; however, given their median follow-up period of 387 days, at this follow-up period only a minority of participants have data available. We have therefore taken data from the 365-day follow-up time point.

***Roux 2009 reports a combined outcome of hospitalisation and cardioversion. As we expect the vast majority of the 14 participants involved to have required hospitalisation for cardioversion, we have used these data in our 'adverse events: participants who required hospitalisation one or more times for ATa' outcome.

Note - Google Translate was used to extract information from Tarasov 2017.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Brignole 2002	AV nodal ablation used not with the intention of restoring normal sinus rhythm.
Duytschaever 2018	Class I or III antiarrhythmics in both control and intervention arms
Farkowski 2010	Wrong study design
Goldenberg 2016	Meta-analysis, not original data - wrong study design
Gu 2012	Class Ic and II vs Class IC OR Class II (only) - wrong intervention
Hummel 2014	Only randomised to ablation OR medical management - wrong study design
Huynh 2014	Review on AMIO-CAT trial. No original data - wrong study design
Jais 2008	Ablation vs AAD, then cross-over - wrong study design
Kettering 2018	Non-randomised - wrong study design
Kondo 2016	Non-randomised - wrong study design
Liakishev 2008	APAF trial published in J Am Coll Cardiol 2006 by Pappone et al: ablation vs AAD, then cross-over - wrong study design
Mont 2014	Ablation vs AAD - wrong study design
NCT00000556	No ablation before randomisation. AFFIRM compared ablation vs AAD - wrong study design
NCT00408200	Excluded as duplicate pre-publication trials abstract of Roux 2009 (5A study) - no data available
NCT00826826	Excluded as duplicate pre-publication trials abstract of Darkner 2014 (AMIO-CAT) - no data available
NCT01416935	Suitable for inclusion (amiodarone vs no amiodarone postsurgical ablation), but no longer recruiting - no data available
NCT01775891	Pilsicainide (Class IC) vs other Class IC, e.g. flecainide/propafenone - wrong study design
NCT02132767	Inclusion criteria: cardiac surgery (CABG, aortic valve or ascending aortic root replacement or a combination of both), no ablation - wrong setting
NCT02509754	Ablation vs rate control - wrong study design
NCT02913014	Unpublished
Packer 2019	Ablation vs AAD - wrong study design
Park 2014	Pilsicainide (Class IC) vs propafenone/flecainide (Class IC) - wrong comparator
Patten 2004	No prior ablation. Only symptomatic PAF 1 month prior to inclusion - wrong intervention
Plewan 1997	Sotalol or bisoprolol after cardioversion - wrong study design
Podzolkov 2013	No use of ablation in full text - wrong patient population

Study	Reason for exclusion
Podzolkov 2014	Text in Russian. Google Translate from methods: "In all patients, sinus rhythm (SR) was restored within the first days from the moment of hospitalization, to stop the AF paroxysm, 42 (89%) patients were prescribed intravenous infusion of amiodarone, in 2 (11%) patients with SR, self-resolved." Pharmacological conversion, NOT ablation - wrong setting
Pokushalov 2013	After the initial blanking period, thus only including subgroup of participants that failed the initial ablation, then comparing AAD vs re-ablation - wrong comparator
Potpara 2016	Non-randomised survey - wrong study design
Reiffel 2015	Wrong comparator
Roy 1997	No ablation. Comparison amiodarone vs sotalol/propafenone - wrong study design
Sarzaeem 2013	Only CABG patients - wrong study design
Soucier 2001	After CABG/valve surgery only - wrong study design
Stabile 2001	Subpopulation of interest < 60% of total; excluded as group A and D (56% of included participants) have not received ablation, therefore even though group B and C could be used, they do not constitute > 60% study population
Stabile 2006	Ablation + AAD vs AAD - wrong study design
Tang 2016	Ablation vs AAD (2:1) - wrong study design
Tarasov 2016	Profafenone (Class 1C) vs sotalol (Class III) - wrong study design
Vamos 2020	Post hoc analysis, so non-randomised, and dronedarone vs placebo in addition to rate control - wrong study design
van Breugel 2014	Observational, retrospective study - wrong intervention
Wang 2019	No data - not possible to obtain the number of individuals with recurrence of ATa > 30 s or secondary outcomes
Wilber 2010	As it stands, there are no data that can be directly used in our outcomes. We believe that even if subgroup data were obtainable, this information would not be valid to incorporate because the participants would not have been randomised to AAD or control, therefore this subgroup would effectively represent an observational cohort - wrong study design.
Won 2013	Non-randomised, and medications started after AAD runs - wrong intervention
Wu 2008	Insufficient data available, specifically to confirm whether antiarrhythmics used were Class I and/or III

AAD: antiarrhythmic drug
AF: atrial fibrillation
AFFIRM: Atrial Fibrillation Follow-Up Investigation of Rhythm Management
AMIO-CAT: Amiodarone After Catheter Ablation for Atrial Fibrillation
APAF: Ablation for Paroxysmal Atrial Fibrillation
ATa: atrial tachyarrhythmias
AV: atrioventricular
CABG: coronary artery bypass graft surgery
PAF: paroxysmal atrial fibrillation

DATA AND ANALYSES

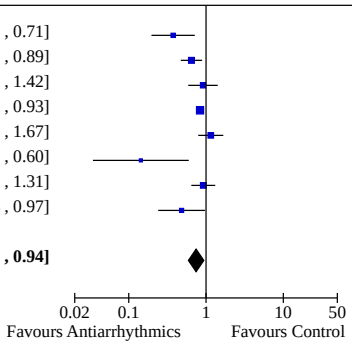
Comparison 1. Class I and/or III antiarrhythmics versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Class I and/or III - Recurrence of atrial tachyarrhythmias - 0 to 3 months after ablation	8	3046	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.59, 0.94]
1.2 Class I and/or III - Recurrence of atrial tachyarrhythmias - > 3 to 6 months after ablation	5	2591	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.78, 0.93]
1.3 Class I and/or III - Recurrence of atrial tachyarrhythmias - > 6 months after ablation	4	2244	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.84, 1.55]
1.4 Class I and/or III - Adverse events: Thromboembolic events - 0 to 3 months after ablation	1	90	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
1.5 Class I and/or III - Adverse events: Thromboembolic events - > 3 to 6 months after ablation	1	212	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.96 [0.06, 15.50]
1.6 Class I and/or III - Adverse events: Thromboembolic events - > 6 months after ablation	1	2038	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.74 [0.39, 19.47]
1.7 Class I and/or III - Adverse events: Myocardial infarction - > 6 months after ablation	1	2038	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.01 [0.06, 16.09]
1.8 Class I and/or III - Adverse events: Requirement for 1 or more hospitalisations for atrial tachyarrhythmia - 0 to 3 months after ablation	3	448	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.28, 0.64]
1.9 Class I and/or III - All-cause mortality - 0 to 3 months after ablation	1	212	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.13 [0.00, 6.57]
1.10 Class I and/or III - All-cause mortality - > 3 to 6 months after ablation	1	90	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.00 [0.06, 16.24]
1.11 Class I and/or III - All-cause mortality - > 6 months after ablation	1	2038	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.50 [0.26, 8.68]
1.12 Class I and/or III - Requirement for 1 or more repeat ablation - 0 to 3 months after ablation	3	567	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.61, 2.00]
1.13 Class I and/or III - Requirement for 1 or more repeat ablation - > 6 months after ablation	1	1365	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.79, 1.13]

Analysis 1.1. Comparison 1: Class I and/or III antiarrhythmics versus control, Outcome 1: Class I and/or III - Recurrence of atrial tachyarrhythmias - 0 to 3 months after ablation

Study or Subgroup	Antiarrhythmics Events	Antiarrhythmics Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Ad 2016 (1)	9	45	24	45	8.3%	0.38 [0.20 , 0.71]
Darkner 2014 (2)	37	108	55	104	16.4%	0.65 [0.47 , 0.89]
Hayashi 2014 (3)	23	62	26	64	12.8%	0.91 [0.59 , 1.42]
Kaitani 2016 (4)	395	1018	475	1024	22.9%	0.84 [0.76 , 0.93]
Lodziński 2014 (5)	31	59	26	57	14.7%	1.15 [0.79 , 1.67]
Roux 2009 (6)	2	53	15	57	2.3%	0.14 [0.03 , 0.60]
Tarasov 2017 (7)	39	122	42	121	15.2%	0.92 [0.65 , 1.31]
Turco 2007 (8)	9	53	19	54	7.5%	0.48 [0.24 , 0.97]
Total (95% CI)		**1520**		**1526**	**100.0%**	**0.74 [0.59 , 0.94]**
Total events:	545		682			

Heterogeneity: Tau² = 0.06; Chi² = 19.93, df = 7 (P = 0.006); I² = 65%
Test for overall effect: Z = 2.53 (P = 0.01)
Test for subgroup differences: Not applicable



Footnotes

(1) Amiodarone versus Control
(2) Amiodarone versus Placebo
(3) Flecainide versus Control
(4) Pilsicainide, Flecainide, Cibenzoline, Propafenone, Disopyramide, Aprindine, Bepridil, Amiodarone, Sotalol versus Control
(5) Amiodarone or Sotalol versus no antiarrhythmics
(6) Propafenone, Flecainide, Sotalol, Dofetilide versus no antiarrhythmics
(7) Propafenone or Sotalol versus Control or Verapamil
(8) Amiodarone or other Class IC antiarrhythmic versus no antiarrhythmics

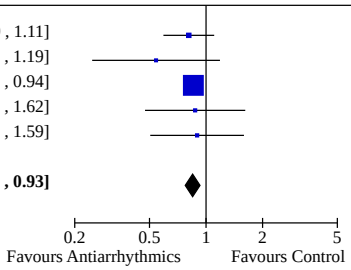
Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.2. Comparison 1: Class I and/or III antiarrhythmics versus control, Outcome 2: Class I and/or III - Recurrence of atrial tachyarrhythmias - > 3 to 6 months after ablation

Study or Subgroup	Antiarrhythmics Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
Darkner 2014 (1)	42	107	48	99	8.4%	0.81 [0.59 , 1.11]	? ? + + − + +
Hayashi 2014 (2)	8	62	15	63	1.3%	0.54 [0.25 , 1.19]	? ? − − + + +
Kaitani 2016 (3)	417	1016	490	1022	85.6%	0.86 [0.78 , 0.94]	− ? − ? + + +
Mohanty 2015 (4)	14	56	16	56	2.2%	0.88 [0.47 , 1.62]	+ ? ? ? + + ?
Roux 2009 (5)	15	53	18	57	2.5%	0.90 [0.50 , 1.59]	? + − ? + + +
Total (95% CI)		**1294**		**1297**	**100.0%**	**0.85 [0.78 , 0.93]**	
Total events:	496		587				

Heterogeneity: Tau² = 0.00; Chi² = 1.43, df = 4 (P = 0.84); I² = 0%
Test for overall effect: Z = 3.57 (P = 0.0004)
Test for subgroup differences: Not applicable



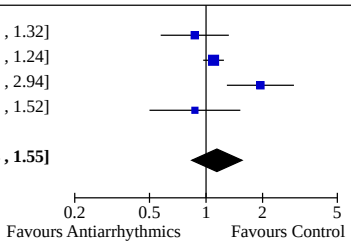
Footnotes
(1) Amiodarone versus Placebo
(2) Flecainide versus Control
(3) Pilsicainide, Flecainide, Cibenzoline, Propafenone, Disopyramide, Aprindine, Bepridil, Amiodarone, Sotalol versus Control
(4) Amiodarone versus Control
(5) Propafenone, Flecainide, Sotalol, Dofetilide versus no antiarrhythmics

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.3. Comparison 1: Class I and/or III antiarrhythmics versus control, Outcome 3: Class I and/or III - Recurrence of atrial tachyarrhythmias - > 6 months after ablation

Study or Subgroup	Antiarrhythmics Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
Hayashi 2014 (1)	24	62	28	63	22.8%	0.87 [0.57 , 1.32]	? ? − − + + +
Kaitani 2016 (2)	308	878	327	1022	36.9%	1.10 [0.97 , 1.24]	− ? − ? + + +
Mohanty 2015 (3)	37	56	19	56	23.1%	1.95 [1.29 , 2.94]	+ ? ? ? + + ?
Turco 2007 (4)	16	54	18	53	17.2%	0.87 [0.50 , 1.52]	? ? ? ? + + ?
Total (95% CI)		**1050**		**1194**	**100.0%**	**1.14 [0.84 , 1.55]**	
Total events:	385		392				

Heterogeneity: Tau² = 0.06; Chi² = 9.24, df = 3 (P = 0.03); I² = 68%
Test for overall effect: Z = 0.85 (P = 0.40)
Test for subgroup differences: Not applicable



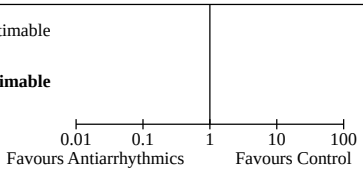
Footnotes
(1) Flecainide versus Control
(2) Pilsicainide, Flecainide, Cibenzoline, Propafenone, Disopyramide, Aprindine, Bepridil, Amiodarone, Sotalol versus Control
(3) Amiodarone versus Control
(4) Amiodarone or other Class IC antiarrhythmic versus no antiarrhythmics

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.4. Comparison 1: Class I and/or III antiarrhythmics versus control, Outcome 4: Class I and/or III - Adverse events: Thromboembolic events - 0 to 3 months after ablation

Study or Subgroup	Antiarrhythmics Events	Antiarrhythmics Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI	Risk of Bias A B C D E F G
Ad 2016 (1)	0	45	0	45		Not estimable		+ + − − + + +
Total (95% CI)		**45**		**45**		**Not estimable**		
Total events:	0		0					

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



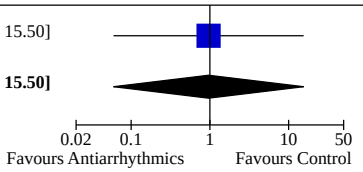
Footnotes
(1) Amiodarone versus Control.

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.5. Comparison 1: Class I and/or III antiarrhythmics versus control, Outcome 5: Class I and/or III - Adverse events: Thromboembolic events - > 3 to 6 months after ablation

Study or Subgroup	Antiarrhythmics Events	Antiarrhythmics Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI	Risk of Bias A B C D E F G
Darkner 2014 (1)	1	108	1	104	100.0%	0.96 [0.06 , 15.50]		? ? + + − + +
Total (95% CI)		**108**		**104**	**100.0%**	**0.96 [0.06 , 15.50]**		
Total events:	1		1					

Heterogeneity: Not applicable
Test for overall effect: Z = 0.03 (P = 0.98)
Test for subgroup differences: Not applicable

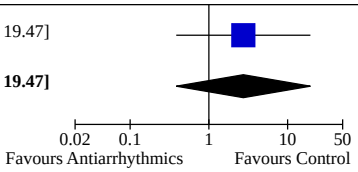


Footnotes
(1) Amiodarone versus Placebo.

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.6. Comparison 1: Class I and/or III antiarrhythmics versus control, Outcome 6: Class I and/or III - Adverse events: Thromboembolic events - > 6 months after ablation

Study or Subgroup	Antiarrhythmics Events	Antiarrhythmics Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI	Risk of Bias A B C D E F G
Kaitani 2016 (1)	3	1016	1	1022	100.0%	2.74 [0.39 , 19.47]		
Total (95% CI)		**1016**		**1022**	**100.0%**	**2.74 [0.39 , 19.47]**		
Total events:	3		1					



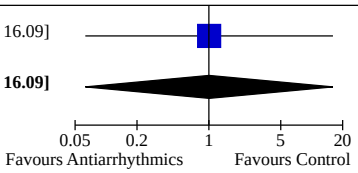
Heterogeneity: Not applicable
Test for overall effect: Z = 1.01 (P = 0.31)
Test for subgroup differences: Not applicable

Footnotes
(1) Pilsicainide, Flecainide, Cibenzoline, Propafenone, Disopyramide, Aprindine, Bepridil, Amiodarone, Sotalol versus Control.

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.7. Comparison 1: Class I and/or III antiarrhythmics versus control, Outcome 7: Class I and/or III - Adverse events: Myocardial infarction - > 6 months after ablation

Study or Subgroup	Antiarrhythmics Events	Antiarrhythmics Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI	Risk of Bias A B C D E F G
Kaitani 2016 (1)	1	1016	1	1022	100.0%	1.01 [0.06 , 16.09]		
Total (95% CI)		**1016**		**1022**	**100.0%**	**1.01 [0.06 , 16.09]**		
Total events:	1		1					

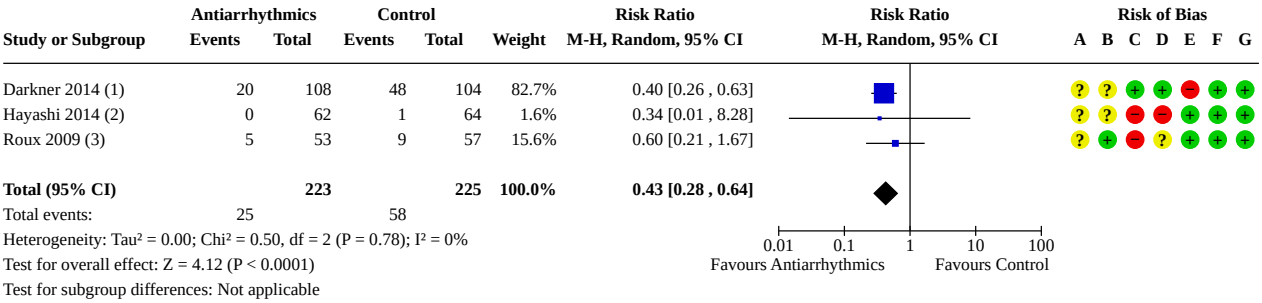


Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)
Test for subgroup differences: Not applicable

Footnotes
(1) Pilsicainide, Flecainide, Cibenzoline, Propafenone, Disopyramide, Aprindine, Bepridil, Amiodarone, Sotalol versus Control.

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.8. Comparison 1: Class I and/or III antiarrhythmics versus control, Outcome 8: Class I and/or III - Adverse events: Requirement for 1 or more hospitalisations for atrial tachyarrhythmia - 0 to 3 months after ablation



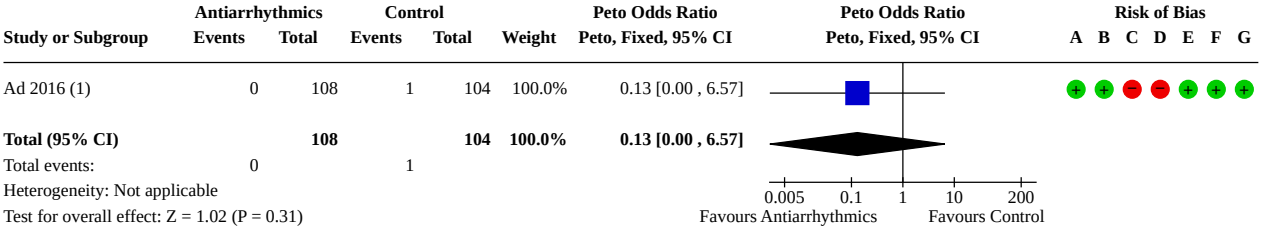
Footnotes

(1) Amiodarone versus Placebo.
(2) Flecainide versus Control.
(3) Propafenone, Flecainide, Sotalol, Dofetilide versus no antiarrhythmics.

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.9. Comparison 1: Class I and/or III antiarrhythmics versus control, Outcome 9: Class I and/or III - All-cause mortality - 0 to 3 months after ablation



Footnotes

(1) Amiodarone versus Control.

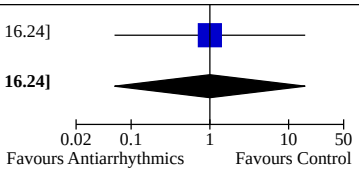
Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.10. Comparison 1: Class I and/or III antiarrhythmics versus control, Outcome 10: Class I and/or III - All-cause mortality - > 3 to 6 months after ablation

Study or Subgroup	Antiarrhythmics Events	Antiarrhythmics Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Risk of Bias A B C D E F G
Darkner 2014 (1)	1	45	1	45	100.0%	1.00 [0.06 , 16.24]	? ? + + − + +
Total (95% CI)		**45**		**45**	**100.0%**	**1.00 [0.06 , 16.24]**	
Total events:	1		1				

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



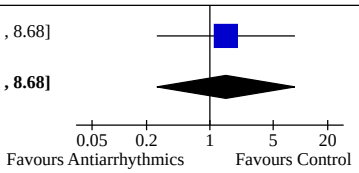
Footnotes
(1) Amiodarone versus Placebo.

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.11. Comparison 1: Class I and/or III antiarrhythmics versus control, Outcome 11: Class I and/or III - All-cause mortality - > 6 months after ablation

Study or Subgroup	Antiarrhythmics Events	Antiarrhythmics Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Risk of Bias A B C D E F G
Kaitani 2016 (1)	3	1016	2	1022	100.0%	1.50 [0.26 , 8.68]	− ? − ? + + +
Total (95% CI)		**1016**		**1022**	**100.0%**	**1.50 [0.26 , 8.68]**	
Total events:	3		2				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.45 (P = 0.65)
Test for subgroup differences: Not applicable



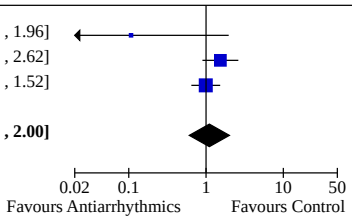
Footnotes
(1) Pilsicainide, Flecainide, Cibenzoline, Propafenone, Disopyramide, Aprindine, Bepridil, Amiodarone, Sotalol versus Control.

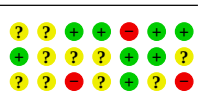
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.12. Comparison 1: Class I and/or III antiarrhythmics versus control, Outcome 12: Class I and/or III - Requirement for 1 or more repeat ablation - 0 to 3 months after ablation

Study or Subgroup	Antiarrhythmics Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Darkner 2014 (1)	0	108	4	104	4.0%	0.11 [0.01 , 1.96]
Mohanty 2015 (2)	23	56	15	56	44.8%	1.53 [0.90 , 2.62]
Tarasov 2017 (3)	31	122	31	121	51.3%	0.99 [0.65 , 1.52]
Total (95% CI)		**286**		**281**	**100.0%**	**1.10 [0.61 , 2.00]**
Total events:	54		50			

Heterogeneity: Tau² = 0.13; Chi² = 4.26, df = 2 (P = 0.12); I² = 53%
Test for overall effect: Z = 0.32 (P = 0.75)
Test for subgroup differences: Not applicable





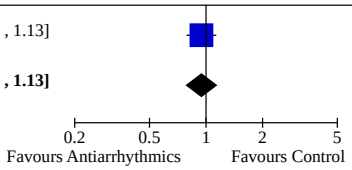
Footnotes
(1) Amiodarone versus Placebo.
(2) Amiodarone versus Control; unclear timing of outcome.
(3) Propafenone or Sotalol versus Control or Verapamil.

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.13. Comparison 1: Class I and/or III antiarrhythmics versus control, Outcome 13: Class I and/or III - Requirement for 1 or more repeat ablation - > 6 months after ablation

Study or Subgroup	Antiarrhythmics Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Kaitani 2016 (1)	167	680	178	685	100.0%	0.95 [0.79 , 1.13]
Total (95% CI)		**680**		**685**	**100.0%**	**0.95 [0.79 , 1.13]**
Total events:	167		178			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.61 (P = 0.54)
Test for subgroup differences: Not applicable



Footnotes
(1) Pilsicainide, Flecainide, Cibenzoline, Propafenone, Disopyramide, Aprindine, Bepridil, Amiodarone, Sotalol versus Control.

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 2. Class I antiarrhythmics versus control

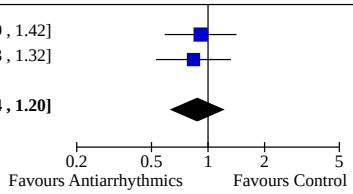
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Class I - Recurrence of atrial tachyarrhythmias - 0 to 3 months after ablation	2	309	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.64, 1.20]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2 Class I - Recurrence of atrial tachyarrhythmias - > 3 to 6 months after ablation	1	125	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.25, 1.19]
2.3 Class I - Recurrence of atrial tachyarrhythmias - > 6 months after ablation	1	125	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.57, 1.32]
2.4 Class I - Adverse events: Requirement for 1 or more hospitalisations for atrial tachyarrhythmia - 0 to 3 months after ablation	1	126	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.01, 8.28]
2.5 Class I - Requirement for 1 or more repeat ablation - 0 to 3 months after ablation	1	183	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.51, 1.53]

Analysis 2.1. Comparison 2: Class I antiarrhythmics versus control, Outcome 1: Class I - Recurrence of atrial tachyarrhythmias - 0 to 3 months after ablation

Study or Subgroup	Antiarrhythmics Events	Antiarrhythmics Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Hayashi 2014 (1)	23	62	26	64	52.3%	0.91 [0.59 , 1.42]
Tarasov 2017 (2)	18	62	42	121	47.7%	0.84 [0.53 , 1.32]
Total (95% CI)		**124**		**185**	**100.0%**	**0.88 [0.64 , 1.20]**
Total events:	41		68			

Heterogeneity: Tau² = 0.00; Chi² = 0.07, df = 1 (P = 0.79); I² = 0%
Test for overall effect: Z = 0.82 (P = 0.41)
Test for subgroup differences: Not applicable



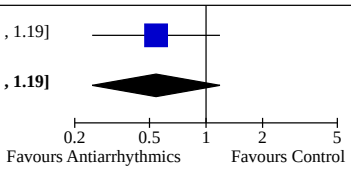
Footnotes
(1) Flecainide versus Control.
(2) Propafenone versus Control or Verapamil.

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.2. Comparison 2: Class I antiarrhythmics versus control, Outcome 2: Class I - Recurrence of atrial tachyarrhythmias - > 3 to 6 months after ablation

Study or Subgroup	Antiarrhythmics Events	Antiarrhythmics Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F	G
Hayashi 2014 (1)	8	62	15	63	100.0%	0.54 [0.25 , 1.19]	?	?	−	−	+	+	+
Total (95% CI)		**62**		**63**	**100.0%**	**0.54 [0.25 , 1.19]**							
Total events:	8		15										

Heterogeneity: Not applicable
Test for overall effect: Z = 1.53 (P = 0.13)
Test for subgroup differences: Not applicable



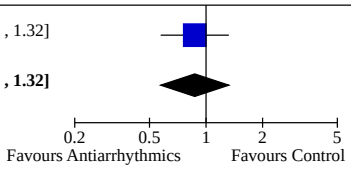
Footnotes
(1) Flecainide versus Control.

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.3. Comparison 2: Class I antiarrhythmics versus control, Outcome 3: Class I - Recurrence of atrial tachyarrhythmias - > 6 months after ablation

Study or Subgroup	Antiarrhythmics Events	Antiarrhythmics Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F	G
Hayashi 2014 (1)	24	62	28	63	100.0%	0.87 [0.57 , 1.32]	?	?	−	−	+	+	+
Total (95% CI)		**62**		**63**	**100.0%**	**0.87 [0.57 , 1.32]**							
Total events:	24		28										

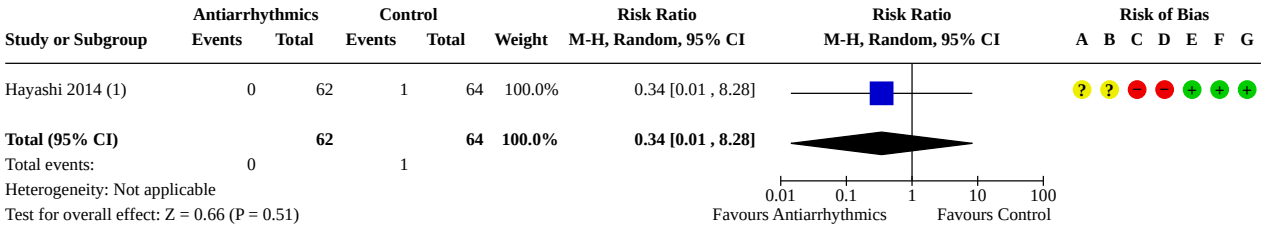
Heterogeneity: Not applicable
Test for overall effect: Z = 0.65 (P = 0.52)
Test for subgroup differences: Not applicable



Footnotes
(1) Amiodarone versus Control.

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

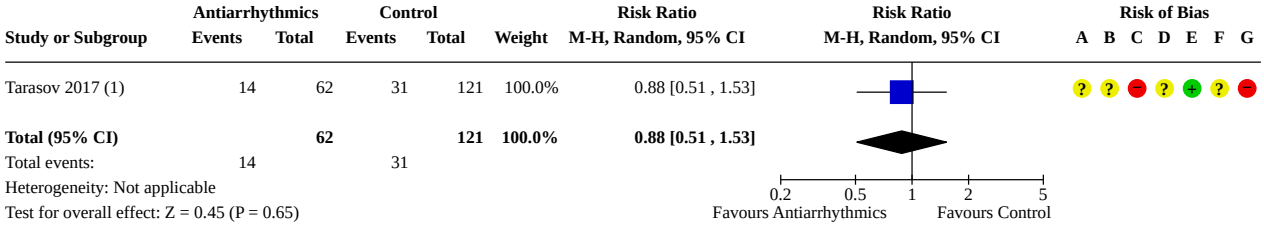
Analysis 2.4. Comparison 2: Class I antiarrhythmics versus control, Outcome 4: Class I - Adverse events: Requirement for 1 or more hospitalisations for atrial tachyarrhythmia - 0 to 3 months after ablation



Footnotes
(1) Flecainide versus Control.

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.5. Comparison 2: Class I antiarrhythmics versus control, Outcome 5: Class I - Requirement for 1 or more repeat ablation - 0 to 3 months after ablation



Footnotes
(1) Propafenone versus Control or Verapamil.

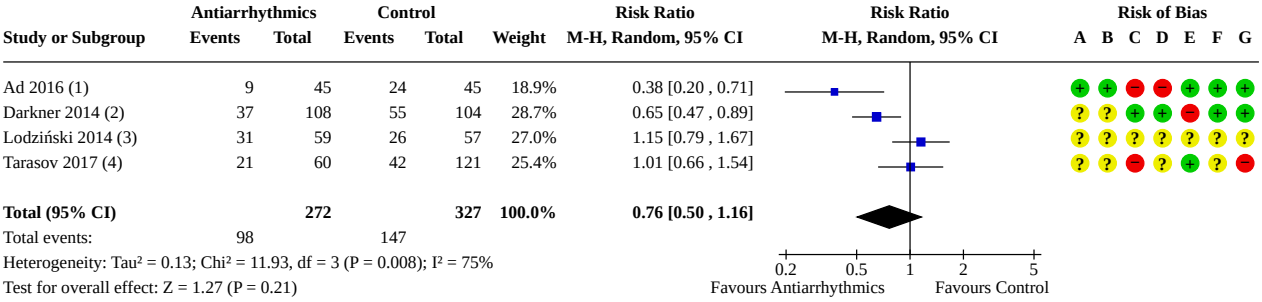
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 3. Class III antiarrhythmics versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Class III - Recurrence of atrial tachyarrhythmias - 0 to 3 months after ablation	4	599	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.50, 1.16]
3.2 Class III - Recurrence of atrial tachyarrhythmias - > 3 to 6 months after ablation	2	318	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.62, 1.09]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.3 Class III - Recurrence of atrial tachyarrhythmias - > 6 months after ablation	1	112	Risk Ratio (M-H, Random, 95% CI)	1.95 [1.29, 2.94]
3.4 Class III - Adverse events: Thromboembolic events - 0 to 3 months after ablation	1	90	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
3.5 Class III - Adverse events: Thromboembolic events - > 3 to 6 months after ablation	1	212	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.96 [0.06, 15.50]
3.6 Class III - Adverse events: Requirement for 1 or more hospitalisations for atrial tachyarrhythmia - 0 to 3 months after ablation	1	212	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.26, 0.63]
3.7 Class III - All-cause mortality - 0 to 3 months after ablation	1	90	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.00 [0.06, 16.24]
3.8 Class III - All-cause mortality - > 3 to 6 months after ablation	1	212	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.13 [0.00, 6.57]
3.9 Class III - Requirement for 1 or more repeat ablation - 0 to 3 months after ablation	3	505	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.66, 2.11]

Analysis 3.1. Comparison 3: Class III antiarrhythmics versus control, Outcome 1: Class III - Recurrence of atrial tachyarrhythmias - 0 to 3 months after ablation



Footnotes

(1) Amiodarone versus Control.
(2) Amiodarone versus Placebo.
(3) Amiodarone or Sotalol versus no antiarrhythmics.
(4) Sotalol versus Control or Verapamil.

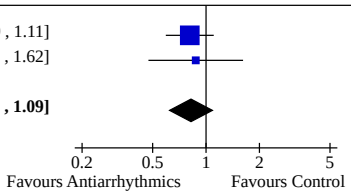
Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 3.2. Comparison 3: Class III antiarrhythmics versus control, Outcome 2: Class III - Recurrence of atrial tachyarrhythmias - > 3 to 6 months after ablation

Study or Subgroup	Antiarrhythmics Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
Darkner 2014 (1)	42	107	48	99	79.6%	0.81 [0.59 , 1.11]	? ? + + − + +
Mohanty 2015 (2)	14	56	16	56	20.4%	0.88 [0.47 , 1.62]	+ ? ? ? + + ?
Total (95% CI)		**163**		**155**	**100.0%**	**0.82 [0.62 , 1.09]**	
Total events:	56		64				

Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.82); I² = 0%
Test for overall effect: Z = 1.38 (P = 0.17)
Test for subgroup differences: Not applicable



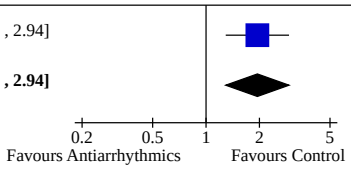
Footnotes
(1) Amiodarone versus Placebo.
(2) Amiodarone versus Control.

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 3.3. Comparison 3: Class III antiarrhythmics versus control, Outcome 3: Class III - Recurrence of atrial tachyarrhythmias - > 6 months after ablation

Study or Subgroup	Antiarrhythmics Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
Mohanty 2015 (1)	37	56	19	56	100.0%	1.95 [1.29 , 2.94]	+ ? ? ? + + ?
Total (95% CI)		**56**		**56**	**100.0%**	**1.95 [1.29 , 2.94]**	
Total events:	37		19				

Heterogeneity: Not applicable
Test for overall effect: Z = 3.18 (P = 0.001)
Test for subgroup differences: Not applicable



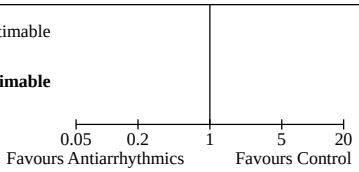
Footnotes
(1) Amiodarone versus Control.

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 3.4. Comparison 3: Class III antiarrhythmics versus control, Outcome 4: Class III - Adverse events: Thromboembolic events - 0 to 3 months after ablation

Study or Subgroup	Antiarrhythmics Events	Antiarrhythmics Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Risk of Bias A B C D E F G
Ad 2016 (1)	0	45	0	45		Not estimable	+ + − − + + +
Total (95% CI)		**45**		**45**		**Not estimable**	
Total events:	0		0				

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



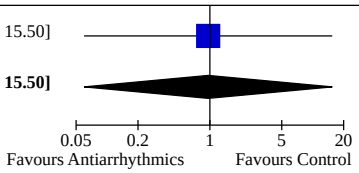
Footnotes
(1) Amiodarone versus Control.

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 3.5. Comparison 3: Class III antiarrhythmics versus control, Outcome 5: Class III - Adverse events: Thromboembolic events - > 3 to 6 months after ablation

Study or Subgroup	Antiarrhythmics Events	Antiarrhythmics Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Risk of Bias A B C D E F G
Darkner 2014 (1)	1	108	1	104	100.0%	0.96 [0.06 , 15.50]	? ? + + − + +
Total (95% CI)		**108**		**104**	**100.0%**	**0.96 [0.06 , 15.50]**	
Total events:	1		1				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.03 (P = 0.98)
Test for subgroup differences: Not applicable



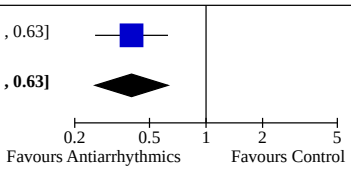
Footnotes
(1) Amiodarone versus Placebo.

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 3.6. Comparison 3: Class III antiarrhythmics versus control, Outcome 6: Class III - Adverse events: Requirement for 1 or more hospitalisations for atrial tachyarrhythmia - 0 to 3 months after ablation

Study or Subgroup	Antiarrhythmics Events	Antiarrhythmics Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Darkner 2014 (1)	20	108	48	104	100.0%	0.40 [0.26 , 0.63]
Total (95% CI)		**108**		**104**	**100.0%**	**0.40 [0.26 , 0.63]**
Total events:	20		48			

Heterogeneity: Not applicable
Test for overall effect: Z = 4.01 (P < 0.0001)
Test for subgroup differences: Not applicable



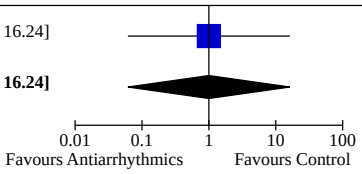
Footnotes
(1) Amiodarone versus Placebo.

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 3.7. Comparison 3: Class III antiarrhythmics versus control, Outcome 7: Class III - All-cause mortality - 0 to 3 months after ablation

Study or Subgroup	Antiarrhythmics Events	Antiarrhythmics Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Ad 2016 (1)	1	45	1	45	100.0%	1.00 [0.06 , 16.24]
Total (95% CI)		**45**		**45**	**100.0%**	**1.00 [0.06 , 16.24]**
Total events:	1		1			

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

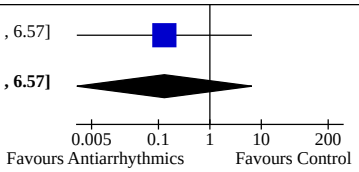


Footnotes
(1) Amiodarone versus Control.

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 3.8. Comparison 3: Class III antiarrhythmics versus control, Outcome 8: Class III - All-cause mortality - > 3 to 6 months after ablation

Study or Subgroup	Antiarrhythmics Events	Antiarrhythmics Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Risk of Bias A B C D E F G
Darkner 2014 (1)	0	108	1	104	100.0%	0.13 [0.00 , 6.57]	? ? + + − + +
Total (95% CI)		**108**		**104**	**100.0%**	**0.13 [0.00 , 6.57]**	
Total events:	0		1				



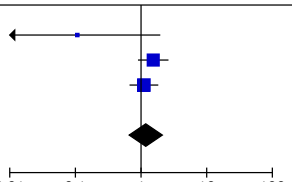
Heterogeneity: Not applicable
Test for overall effect: Z = 1.02 (P = 0.31)
Test for subgroup differences: Not applicable

Footnotes
(1) Amiodarone versus Placebo.

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 3.9. Comparison 3: Class III antiarrhythmics versus control, Outcome 9: Class III - Requirement for 1 or more repeat ablation - 0 to 3 months after ablation

Study or Subgroup	Antiarrhythmics Events	Antiarrhythmics Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
Darkner 2014 (1)	0	108	4	104	3.8%	0.11 [0.01 , 1.96]	? ? + + − + +
Mohanty 2015 (2)	23	56	15	56	47.0%	1.53 [0.90 , 2.62]	+ ? ? ? + + ?
Tarasov 2017 (3)	17	60	31	121	49.2%	1.11 [0.67 , 1.83]	? ? − ? + ? −
Total (95% CI)		**224**		**281**	**100.0%**	**1.18 [0.66 , 2.11]**	
Total events:	40		50				



Heterogeneity: Tau² = 0.11; Chi² = 3.69, df = 2 (P = 0.16); I² = 46%
Test for overall effect: Z = 0.56 (P = 0.58)
Test for subgroup differences: Not applicable

Footnotes
(1) Amiodarone versus Placebo
(2) Amiodarone versus Control; unclear about outcome timing.
(3) Sotalol versus Control or Verapamil.

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

ADDITIONAL TABLES

Table 1. Participant characteristics[a]

Study	Age (years)	Sex (% male)	Mean AF duration (months)	Mean left atrial diameter (cm)	Number of prior antiarrhythmics (mean ±SD)	Previous AF ablations (%)	Hypertension (%)	Diabetes (%)	Mean LVEF (%)
Turco 2007	53.5	64.5	54.0	4.80	-	-	57.0	-	57.0
Roux 2009	55.5	71.0	76.2	4.20	1.60 ±1.0	25	50.1	5.9	61.5
Darkner 2014	61.5	83.5	77.0	4.40	1.15 ±0.8	29	39.5	8.5	50.5
Hayashi 2014	63.0	77.0	16.5	3.80	1.00 ±1.0	0	63.0	7.0	68.5
Lodziński 2014	49.2	71.5	78.1	4.20	-	-	43.9	5.1	-
Mohanty 2015	61.0	71.5	79.5	4.75	-	-	47.0	13.5	54.5
Ad 2016	63.6	72.0	21.5	5.05	-	0	53.3	12.5	54.8
Kaitani 2016	63.3	75.1	-	3.90	-	-	49.3	13.3	64.3
Tarasov 2017	56.1	58.4	53.4	4.16	-	-	51.3	6.0	-

(-) = not reported
Abbreviations: AF: atrial fibrillation; LVEF: left ventricular ejection fraction; SD: standard deviation
[a]Abstracted or calculated total average from all relevant subgroups.

Table 2. Ablation approach and strategy

Trial	Approach	Ablation strategy
Ad 2016	Surgical ablation	Cox maze III/IV lesion set, utilised in all but 1 participant
Darkner 2014	Percutaneous ablation	Pulmonary vein isolation/wide antral circumferential ablation
Hayashi 2014	Percutaneous ablation	Pulmonary vein isolation
Kaitani 2016	Percutaneous ablation	Pulmonary vein isolation/wide antral circumferential ablation
Lodziński 2014	Percutaneous ablation	Pulmonary vein isolation
Mohanty 2015	Percutaneous ablation	Pulmonary vein antral isolation + posterior wall isolation + defragmentation + extra pulmonary vein triggers
Roux 2009	Percutaneous ablation	Pulmonary vein isolation + extra pulmonary vein triggers
Tarasov 2017	Percutaneous ablation	Pulmonary vein ostial isolation
Turco 2007	Percutaneous ablation	Pulmonary vein isolation + mitral isthmus + cavo-tricuspid isthmus

APPENDICES

Appendix 1. Search strategies

Search strategies 2020

CENTRAL

#1 MeSH descriptor: [Atrial Fibrillation] this term only

#2 atrial fibrillat*

#3 atrium fibrillat*

#4 auricular fibrillat*

#5 {OR #1-#4}

#6 MeSH descriptor: [Flecainide] this term only

#7 flecainide*

#8 MeSH descriptor: [Propafenone] this term only

#9 propafenone

#10 MeSH descriptor: [Amiodarone] this term only

#11 Amiodarone

#12 Dofetilide

#13 MeSH descriptor: [Dronedarone] this term only

#14 Dronedarone

#15 MeSH descriptor: [Sotalol] this term only

#16 Sotalol

#17 {OR #6-#16}

#18 #5 AND #17

MEDLINE

1 Atrial Fibrillation/

2 atrial fibrillat*.tw.

3 atrium fibrillat*.tw.

4 auricular fibrillat*.tw.

5 1 or 2 or 3 or 4

6 Flecainide/

7 flecainide*.tw.

8 Propafenone/

9 propafenone.tw.

10 Amiodarone/

11 Amiodarone.tw.

12 Dofetilide.tw.

13 Dronedarone/

14 Dronedarone.tw.

15 Sotalol/

16 Sotalol.tw.

17 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16

18 5 and 17

19 randomized controlled trial.pt.

20 controlled clinical trial.pt.

21 randomized.ab.

22 placebo.ab.

23 clinical trials as topic.sh.

24 randomly.ab.

25 trial.ti.

26 19 or 20 or 21 or 22 or 23 or 24 or 25

27 exp animals/ not humans.sh.

28 26 not 27

29 18 and 28

Embase

1 atrial fibrillation/

2 atrial fibrillat*.tw.

3 atrium fibrillat*.tw.

4 auricular fibrillat*.tw.

5 1 or 2 or 3 or 4

6 flecainide/

7 flecainide*.tw.

8 propafenone/

9 propafenone.tw.

10 amiodarone/

11 Amiodarone.tw.

12 Dofetilide.tw.

13 dronedarone/

14 Dronedarone.tw.

15 sotalol/

16 Sotalol.tw.

17 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16

18 5 and 17

19 random$.tw.

20 factorial$.tw.

21 crossover$.tw.

22 cross over$.tw.

23 cross-over$.tw.

24 placebo$.tw.

25 (doubl$ adj blind$).tw.

26 (singl$ adj blind$).tw.

27 assign$.tw.

28 allocat$.tw.

29 volunteer$.tw.

30 crossover procedure/

31 double blind procedure/

32 randomized controlled trial/

33 single blind procedure/

34 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33

35 (animal/ or nonhuman/) not human/

36 34 not 35

37 18 and 36

38 limit 37 to embase

Web of Science

14 #13 AND #12

13 TS=(random* or blind* or allocat* or assign* or trial* or placebo* or crossover* or cross-over*)

12 #11 AND #4

11 #10 OR #9 OR #8 OR #7 OR #6 OR #5

10 TS=Sotalol

9 TS=Dronedarone

8 TS=Dofetilide

7 TS=Amiodarone

6 TS=propafenone

5 TS=flecainide*

4 #3 OR #2 OR #1

3 TS=auricular fibrillat*

2 TS=atrium fibrillat*

1 TS=atrial fibrillat*

ClinicalTrials.gov

Condition or disease: Atrial Fibrillation

Study type: Interventional Studies (Clinical Trials)

Intervention/treatment: Sotalol or Dronedarone or Dofetilide or Amiodarone or propafenone or flecainide

Search strategies 2022

CENTRAL

#1 MeSH descriptor: [Atrial Fibrillation] this term only

#2 atrial fibrillat*

#3 atrium fibrillat*

#4 auricular fibrillat*

#5 {OR #1-#4}

#6 MeSH descriptor: [Catheter Ablation] this term only

#7 catheter ablat*

#8 (percutaneous NEAR/3 catheter*)

#9 (transcatheter NEAR/3 ablat*)

#10 {OR #6-#9}

#11 MeSH descriptor: [Anti-Arrhythmia Agents] explode all trees

#12 anti-arrhythmi*

#13 MeSH descriptor: [Flecainide] this term only

#14 flecainide*

#15 (Tambocor or apocard or flecadura)

#16 MeSH descriptor: [Propafenone] this term only

#17 propafenone

#18 (arythmol or baxarytmon or cuxafenon or fenoprain or jutanorm or nistaken or norfenon or pintoform or prolecofen or propamerck or rythmol or rytmo-puren or rytmogenat or rytmonorm)

#19 MeSH descriptor: [Amiodarone] this term only

#20 Amiodarone

#21 (Pacerone or amiobeta or amiodarex or amiodarona or amiodarone or amiohexal or aratac or braxan or corbionax or cordarex or cordarone or kordaron or ortacrone or rytmarone or tachydaron or trangorex)

#22 Dofetilide

#23 Tikosyn

#24 MeSH descriptor: [Dronedarone] this term only

#25 Dronedarone

#26 multaq

#27 MeSH descriptor: [Sotalol] this term only

#28 Sotalol

#29 (betapace or darob)

#30 {OR #11-#29}

#31 #5 AND #10 AND #30

MEDLINE

1 Atrial Fibrillation/

2 atrial fibrillat*.tw.

3 atrium fibrillat*.tw.

4 auricular fibrillat*.tw.

5 1 or 2 or 3 or 4

6 Catheter Ablation/

7 catheter ablat*.tw.

8 (percutaneous adj3 catheter*).tw.

9 (transcatheter adj3 ablat*).tw.

10 6 or 7 or 8 or 9

11 exp Anti-Arrhythmia Agents/

12 anti-arrhythmi*.tw.

13 Flecainide/

14 flecainide*.tw.

15 (Tambocor or apocard or flecadura).tw.

16 Propafenone/

17 Propafenone.tw.

18 (arythmol or baxarytmon or cuxafenon or fenoprain or jutanorm or nistaken or norfenon or pintoform or prolecofen or propamerck or rythmol or rytmo-puren or rytmogenat or rytmonorm).tw.

19 Amiodarone/

20 Amiodarone.tw.

21 (Pacerone or amiobeta or amiodarex or amiodarona or amiodarone or amiohexal or aratac or braxan or corbionax or cordarex or cordarone or kordaron or ortacrone or rytmarone or tachydaron or trangorex).tw.

22 Dofetilide.tw.

23 Tikosyn.tw.

24 Dronedarone/

25 Dronedarone.tw.

26 multaq.tw.

27 Sotalol/

28 Sotalol.tw.

29 (betapace or darob).tw.

30 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29

31 5 and 10 and 30

32 randomized controlled trial.pt.

33 controlled clinical trial.pt.

34 randomized.ab.

35 placebo.ab.

36 clinical trials as topic.sh.

37 randomly.ab.

38 trial.ti.

39 32 or 33 or 34 or 35 or 36 or 37 or 38

40 exp animals/ not humans.sh.

41 39 not 40

42 31 and 41

Embase

1 atrial fibrillation/

2 atrial fibrillat*.tw.

3 atrium fibrillat*.tw.

4 auricular fibrillat*.tw.

5 1 or 2 or 3 or 4

6 catheter ablation/

7 catheter ablat*.tw.

8 (percutaneous adj3 catheter*).tw.

9 (transcatheter adj3 ablat*).tw.

10 6 or 7 or 8 or 9

11 exp antiarrhythmic agent/

12 anti-arrhythmi*.tw.

13 flecainide/

14 flecainide*.tw.

15 (Tambocor or apocard or flecadura).tw.

16 propafenone/

17 Propafenone.tw.

18 (arythmol or baxarytmon or cuxafenon or fenoprain or jutanorm or nistaken or norfenon or pintoform or prolecofen or propamerck or rythmol or rytmo-puren or rytmogenat or rytmonorm).tw.

19 amiodarone/

20 Amiodarone.tw.

21 (Pacerone or amiobeta or amiodarex or amiodarona or amiodarone or amiohexal or aratac or braxan or corbionax or cordarex or cordarone or kordaron or ortacrone or rytmarone or tachydaron or trangorex).tw.

22 dofetilide/

23 Dofetilide.tw.

24 Tikosyn.tw.

25 dronedarone/

26 Dronedarone.tw.

27 multaq.tw.

28 sotalol/

29 Sotalol.tw.

30 (betapace or darob).tw.

31 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30

32 5 and 10 and 31

33 Randomized controlled trial/ or Controlled clinical study/ or randomization/ or intermethod comparison/ or double blind procedure/ or human experiment/ or (random$ or placebo or (open adj label) or ((double or single or doubly or singly) adj (blind or blinded or blindly)) or parallel group$1 or crossover or cross over or ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention $1 or patient$1 or subject$1 or participant$1)) or assigned or allocated or (controlled adj7 (study or design or trial)) or volunteer or volunteers).ti,ab. or (compare or compared or comparison or trial).ti. or ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab.

34 (random$ adj sampl$ adj7 ("cross section$" or questionnaire$1 or survey$ or database$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.)

35 Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or (randomi?ed controlled or control group$1).ti,ab.)

36 (((case adj control$) and random$) not randomi?ed controlled).ti,ab.

37 (Systematic review not (trial or study)).ti.

38 (nonrandom$ not random$).ti,ab.

39 ("Random field$" or (random cluster adj3 sampl$)).ti,ab.

40 (review.ab. and review.pt.) not trial.ti.

41 "we searched".ab. and (review.ti. or review.pt.)

42 ("update review" or (databases adj4 searched)).ab.

43 (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/

44 Animal experiment/ not (human experiment/ or human/)

45 or/34-44

46 33 not 45

47 32 and 46

Web of Science

1: TS=(atrial fibrillat*)

2: TS=(atrium fibrillat*)

3: TS=(auricular fibrillat*)

4: #3 OR #2 OR #1

5: TS=(catheter ablat*)

6: TS=((percutaneous NEAR/3 catheter*))

7: TS=((transcatheter NEAR/3 ablat*))

8: #7 OR #6 OR #5

9: TS=(anti-arrhythmi*)

10: TS=((flecainide* or Tambocor or apocard or flecadura))

11: TS=((Propafenone or arythmol or baxarytmon or cuxafenon or fenoprain or jutanorm or nistaken or norfenon or pintoform or prolecofen or propamerck or rythmol or rytmo-puren or rytmogenat or rytmonorm))

12: TS=((Amiodarone or Pacerone or amiobeta or amiodarex or amiodarona or amiodarone or amiohexal or aratac or braxan or corbionax or cordarex or cordarone or kordaron or ortacrone or rytmarone or tachydaron or trangorex))

13: TS=((Dofetilide or Tikosyn))

14: TS=((Dronedarone or multaq))

15: TS=((Sotalol or betapace or darob))

16: #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15

17: #16 AND #8 AND #4

18: TS=((random* or blind* or allocat* or assign* or trial* or placebo* or crossover* or cross-over*))

19: #18 AND #17

ClinicalTrials.gov

Condition or disease: Atrial Fibrillation

Other terms: Catheter ablation

Study type: Interventional Studies (Clinical Trials)

Intervention/treatment: Antiarrhythmic Agent

WHO ICTRP

Condition: Atrial fibrillation

Intervention: Antiarrhythmic

Recruitment status: All

HISTORY

Protocol first published: Issue 10, 2020

CONTRIBUTIONS OF AUTHORS

JJHB assessed studies for inclusion, collected data and information on risk of bias, extracted data, analysed the data, wrote the Results and Discussion sections, addressed peer-review queries, and was responsible for project administration.

MWa wrote the first draft of the protocol, assessed studies for inclusion, collected data and information on risk of bias, extracted data, amended the Background and Methods from the protocol, and helped address peer-review queries.

MWh assessed studies for inclusion, collected data and information on risk of bias, wrote the Authors' conclusions section, and helped address peer-review queries.

CP edited and provided advice on the protocol, assessed studies for inclusion, collected data and information on risk of bias, and extracted data.

RB edited and provided advice on the protocol, assessed studies for inclusion, and collected data and information on risk of bias.

MA assessed studies for inclusion, collected data and information on risk of bias, checked data extraction, wrote the Authors' conclusions section, and helped address peer-review queries.

SS edited and provided advice on the manuscript.

GRA edited and provided advice on the manuscript.

AK edited and provided advice on the manuscript.

MSS edited and provided advice on the manuscript.

AM edited and provided advice on the manuscript.

JT edited and provided advice on the manuscript.

PL edited and provided advice on the manuscript.

GC edited and provided advice on the manuscript.

AB edited and provided advice on the manuscript.

RP acted as the lead senior author and edited and provided advice on the manuscript.

DECLARATIONS OF INTEREST

JJHB: none reported.

MWa: none reported.

MWh: none reported.

CP: none reported.

RB: none reported.

MA: none reported.

SS: none reported.

GRA: none reported.

AK: none reported.

MSS: none reported.

AM: none reported.

JT: the author reports that he or his department has received grants/sponsorship from Medtronic, Abbott, Microport, and Bayer in the last three years. No grants or fees were received for this work. The author has also received speaker fees from Bayer (which manufactures Xarelto).

PL: receives speaker fees and educational grant funding from Boston Scientific, and educational grant funding from Medtronic for work unrelated to the content of this Cochrane Review.

GC: none reported.

AB: none reported.

RP: the author is a member of the Cochrane Heart Editorial team but was not involved in the editorial process or decision-making for this review.

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- None, Other

  None

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Although the protocol had not stipulated a threshold for subgroup analysis, we decided not to carry out subgroup analyses due to the insufficient number of studies. Instead, where individual drugs were used, they are written into the footnotes of the forest plots, except for one outcome where there no data were available on either Class I or III antiarrhythmics (participants with a new diagnosis of heart failure). There were very few data on follow-up of participants who underwent repeat ablation, thus analysis specific to this could not be undertaken.

Because data were available, we have used risk ratios as opposed to odds ratios to present our analyses of the following outcomes: recurrence of atrial tachyarrhythmias, requirement for one or more repeat ablation, adverse events: myocardial infarction, and adverse events: requirement for one or more hospitalisations, as Section 6.4.1.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* cites Sinclair and Bracken 1994, and Sackett 1996 in stating that "odds ratios, like odds, are more difficult to interpret" and recommends using risk ratio (Higgins 2022). An exception to this was three outcomes found to have very low event rates: all-cause mortality, adverse events: thromboembolic events, and adverse events: new diagnosis of heart failure, which ranged between 0.6% to 0.1%. For such cases, Section 16.9.5 of the *Cochrane Handbook* cites Sweeting 2004, stating that "at event rates below 1% the Peto one-step odds ratio method [is] the least biased and most powerful method, and provides the best confidence interval coverage". Consequently, for these outcomes we have presented our results using this methodology (Higgins 2011b).

As the median follow-up of Kaitani 2016 was 387 days, beyond this at the longest follow-up of 450 days only a minority of participants had data reported. In reality, the longest follow-up for this paper was 365 days, and the data beyond this are included in the analysis of this paper in error. Consequently, we did not use the longest follow-up in this case, and instead used the 365-day follow-up time point to mitigate against this potential bias.

Only three studies reported hospitalisation for atrial tachyarrhythmia (Darkner 2014; Hayashi 2014; Roux 2009), yet two other studies reported similar data on cardioversion rates, Kaitani 2016, and all-cause rehospitalisation, Ad 2016. We thought that these data could yield relevant insights and so included them in sensitivity analysis.