Atrial fibrillation (acute onset)

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ABSTRACT

INTRODUCTION: Acute atrial fibrillation is rapid, irregular, and chaotic atrial activity of recent onset. Various definitions of acute atrial fibrillation have been used in the literature, but for the purposes of this review we have included studies where atrial fibrillation may have occurred up to 7 days previously. Risk factors for acute atrial fibrillation include increasing age, cardiovascular disease, alcohol, diabetes, and lung disease. Acute atrial fibrillation increases the risk of stroke and heart failure. The condition resolves spontaneously within 24 to 48 hours in more than 50% of people; however, many people will require interventions to control heart rate or restore sinus rhythm. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of interventions to prevent embolism, for conversion to sinus rhythm, and to control heart rate in people with recent-onset atrial fibrillation (within 7 days) who are haemodynamically stable? We searched: Medline, Embase, The Cochrane Library, and other important databases up to April 2014 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 26 studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review, we present information relating to the effectiveness and safety of the following interventions: amiodarone, antithrombotic treatment before cardioversion, atenolol, bisoprolol, carvedilol, digoxin, diltiazem, direct current cardioversion, flecainide, metoprolol, nebivolol, propafenone, sotalol, timolol, and verapamil.

QUESTIONS

INTERVENTIONS

Footnote

*Categorisation based on consensus.

Key points

- Acute atrial fibrillation is rapid, irregular, and chaotic atrial activity of less than 48 hours' duration. It resolves spontaneously within 24 to 48 hours in more than 50% of people. In this review, we have included studies on patients with onset up to 7 days previously.

  Risk factors for acute atrial fibrillation include increasing age, CVD, alcohol abuse, diabetes, and lung disease.

  Acute atrial fibrillation increases the risk of stroke and heart failure.

- The consensus is that people with haemodynamically unstable atrial fibrillation should have immediate direct current cardioversion. In people who are haemodynamically stable, direct current cardioversion increases reversion to sinus rhythm compared with intravenous propafenone.

  There is consensus that antithrombotic treatment with heparin should be given before cardioversion of recent-onset atrial fibrillation to reduce the risk of embolism in people who are haemodynamically stable, but we found no studies to show whether this is beneficial.

- Oral or intravenous flecainide, propafenone, or amiodarone increase the likelihood of reversion to sinus rhythm compared with placebo in people with haemodynamically stable acute atrial fibrillation.
- CAUTION: Flecainide and propafenone should not be used in people with ischaemic heart disease as they can cause (life-threatening) arrhythmias.
- We don't know whether sotalol increases reversion to sinus rhythm in people with haemodynamically stable atrial fibrillation, as few adequate trials have been conducted.

  Digoxin does not seem to increase reversion to sinus rhythm compared with placebo. We don't know whether verapamil increases reversion to sinus rhythm compared with placebo.

- No one drug has been shown to be more effective at controlling heart rate. However, there is general consensus that intravenous bolus amiodarone is more effective than digoxin.
- Treatment with digoxin may control heart rate in people with haemodynamically stable atrial fibrillation, despite its being unlikely to restore sinus rhythm.
- We don't know whether diltiazem, timolol, and verapamil are effective at controlling heart rate, but they are unlikely to restore sinus rhythm.

  We don't know whether sotalol, bisoprolol, metoprolol, atenolol, nebivolol, or carvedilol are effective at controlling heart rate in people with acute atrial fibrillation who are haemodynamically stable. However, sotalol may cause arrhythmias at high doses.

Clinical context

DEFINITION

Acute atrial fibrillation is rapid, irregular, and chaotic atrial activity of recent onset. Various definitions of acute atrial fibrillation have been used in the literature, but for the purposes of this review we have included studies where atrial fibrillation may have occurred up to 7 days previously. Acute atrial fibrillation includes both the first symptomatic onset of chronic or persistent atrial fibrillation and episodes of paroxysmal atrial fibrillation. It is sometimes difficult to distinguish new-onset atrial fibrillation from previously undiagnosed long-standing atrial fibrillation. By contrast, chronic atrial fibrillation is more sustained and can be described as paroxysmal (with spontaneous termination and sinus rhythm between recurrences), persistent, or permanent atrial fibrillation. This review deals with people with acute and recent-onset atrial fibrillation who are haemodynamically stable. The consensus is that people who are not haemodynamically stable should be treated with immediate direct current cardioversion. We have excluded studies in people with atrial fibrillation arising during or soon after cardiac surgery. **Diagnosis** Acute atrial fibrillation should be suspected in people presenting with dizziness, syncope, dyspnoea, or palpitations. Moreover, atrial fibrillation can contribute to a large number of other non-specific symptoms. Palpation of an irregular pulse is generally only considered sufficient to raise suspicion of atrial fibrillation; diagnosis requires confirmation with ECG. However, in those with paroxysmal atrial fibrillation, ambulatory monitoring may be required. [1] [2]

INCIDENCE/ PREVALENCE

We found limited evidence on the incidence or prevalence of acute atrial fibrillation. Extrapolation from the Framingham study suggests an incidence in men of 3/1000 person-years at age 55 years, rising to 38/1000 person-years at age 94 years. [3] In women, the incidence was 2/1000 person-years at age 55 years and 32.5/1000 person-years at age 94 years. The prevalence of atrial fibrillation ranged from 0.5% for people aged 50 to 59 years to 9% in people aged 80 to 89 years. Among acute emergency medical admissions in the UK, 3% to 6% had atrial fibrillation, and about 40% of these were newly diagnosed. [4] [5] Among acute hospital admissions in New Zealand, 10% (95% CI 9% to 12%) had documented atrial fibrillation. [6]

AETIOLOGY/ RISK FACTORS

Common precipitants of acute atrial fibrillation are acute MI and the acute effects of alcohol. Age increases the risk of developing acute atrial fibrillation. Men are more likely than women to develop atrial fibrillation (38 years' follow-up from the Framingham Study; RR, after adjustment for age and known predisposing conditions, 1.5). [7] Atrial fibrillation can occur in association with underlying disease (both cardiac and non-cardiac) or can arise in the absence of any other condition. Epidemiological surveys found that risk factors for the development of acute atrial fibrillation include ischaemic heart disease, hypertension, heart failure, valve disease, diabetes, alcohol abuse, thyroid disorders, and disorders of the lung and pleura. [3] In a British survey of acute hospital admissions of people with atrial fibrillation, a history of ischaemic heart disease was present in 33%, heart

failure in 24%, hypertension in 26%, and rheumatic heart disease in 7%. [5] In some populations, the acute effects of alcohol explain a large proportion of the incidence of acute atrial fibrillation. Paroxysms of atrial fibrillation are more common in athletes. [8]

PROGNOSIS

Spontaneous reversion: observational studies and placebo arms of RCTs found that more than 50% of people with acute atrial fibrillation revert spontaneously within 24 to 48 hours, especially if atrial fibrillation is associated with an identifiable precipitant such as alcohol or MI. **Progression to chronic atrial fibrillation**: we found no evidence about the proportion of people with acute atrial fibrillation who develop more chronic forms of atrial fibrillation (e.g., paroxysmal, persistent, or permanent atrial fibrillation). **Mortality**: we found little evidence about the effects on mortality of acute atrial fibrillation where no underlying cause is found. Acute atrial fibrillation during MI is an independent predictor of both short- and long-term mortality. [9] **Heart failure**: onset of atrial fibrillation reduces cardiac output by 10% to 20%, irrespective of the underlying ventricular rate, [10] [11] and can contribute to heart failure. People with acute atrial fibrillation who present with heart failure have worse prognoses. **Stroke**: acute atrial fibrillation is associated with a risk of imminent stroke. [12] [13] [14] [15] One case series using transoesophageal echocardiography in people who had developed acute atrial fibrillation within the preceding 48 hours found that 15% had atrial thrombi. [16] An ischaemic stroke associated with atrial fibrillation is more likely to be fatal, have a recurrence, or leave a serious functional deficit among survivors than a stroke not associated with atrial fibrillation. [17]

AIMS OF INTERVENTION

To reduce symptoms, morbidity, and mortality with minimum adverse effects.

OUTCOMES

Major outcomes include: thromboembolism, stroke or transient ischaemic attack, major bleeding, mortality, and adverse effects of treatment. Proxy measures include heart rhythm, ventricular rate, and time to restoration of sinus rhythm. The following outcomes are reported in this review: for the question on interventions to prevent embolism: **thromboembolic events** (thromboembolism, stroke, TIA); for the question on interventions for conversion to sinus rhythm: **conversion to sinus rhythm**; for the question on interventions to control heart rate: **control of heart rate**; for all questions: **mortality**, **adverse effects**. Frequent spontaneous reversion to sinus rhythm makes it difficult to interpret short-term studies of rhythm; treatments may accelerate restoration of sinus rhythm without increasing the proportion of people who eventually convert. The clinical importance of changes in mean heart rate is also unclear.

METHODS

Clinical Evidence search April 2014. The following databases were used to identify studies for this systematic review: Medline 1966 to April 2014, Embase 1980 to April 2014, and The Cochrane Database of Systematic Reviews 2014, issue 4 (1966 to date of issue). Additional searches were carried out in the Database of Abstracts of Reviews of Effects (DARE) and the Health Technology Assessment (HTA) database. We also searched for retractions of studies included in the review. Titles and abstracts of the studies retrieved from the initial search, run by an information specialist, were first assessed against predefined criteria by an evidence scanner. Full texts for potentially relevant studies were discussed with an expert contributor. All data relevant to the review were then extracted by an evidence analyst. Study design criteria for inclusion in this review were: published RCTs and systematic reviews of RCTs in the English language, at least single-blinded, and containing at least 20 individuals (at least 10 per arm), of whom at least 80% were followed up. There was no minimum length of follow-up required to include studies. We excluded all studies described as 'open', 'open label', or not blinded unless blinding was impossible. We included RCTs and systematic reviews of RCTs where harms of an included intervention were studied, applying the same study design criteria for inclusion as we did for benefits. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 42). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION **What are the effects of interventions to prevent embolism in people with recent-onset atrial fibrillation who are haemodynamically stable?**

OPTION ANTITHROMBOTIC TREATMENT BEFORE CARDIOVERSION

- For GRADE evaluation of interventions for Atrial fibrillation (acute onset), see table, p 42 .
- There is consensus that antithrombotic treatment with heparin should be given before cardioversion to reduce risk of embolism in people who are haemodynamically stable, but we found no RCT evidence to show whether this is effective.

Benefits and harms

Antithrombotic treatment before cardioversion:

We found no systematic review or RCTs on the use of antithrombotic treatment versus placebo before cardioversion in people with acute atrial fibrillation of less than 7 days' duration.

Comment:

One RCT compared low molecular weight heparin with unfractionated heparin (155 people with atrial fibrillation of between 2 and 19 days' duration, undergoing a transoesophageal echocardiography-guided cardioversion strategy). [18] The RCT found no significant difference between low molecular weight heparin and unfractionated heparin in rates of thrombus observation, stroke, systemic embolism, or bleeding. However, low molecular weight heparin did allow earlier hospital discharge.

Clinical guide: There is consensus to give heparin to people who have cardioversion within 48 hours of the onset of arrhythmia, but we found insufficient evidence from trials to support this. The decision to give anticoagulation both in the short-term and after cardioversion is usually based on an individual's intrinsic risk of thromboembolism. [19] Warfarin is not used as an anticoagulant in acute atrial fibrillation because of its slow onset of action. One transoesophageal echocardiography study in people with a recent embolic event found left atrial thrombus in 15% of people with acute atrial fibrillation of less than 3 days' duration. [16] This would suggest that such people may benefit from formal anticoagulation, or need to be evaluated by transoesophageal echocardiography before cardioversion.

QUESTION **What are the effects of interventions for conversion to sinus rhythm in people with recent-onset atrial fibrillation who are haemodynamically stable?**

OPTION FLECAINIDE FOR RHYTHM CONTROL

- For GRADE evaluation of interventions for Atrial fibrillation (acute onset), see table, p 42 .
- Oral or intravenous flecainide increases the likelihood of reversion to sinus rhythm compared with placebo in people with haemodynamically stable acute atrial fibrillation.
- Flecainide is associated with serious adverse events, such as severe hypotension and torsades de pointes.
- **CAUTION:**
  Flecainide should not be used in people with ischaemic heart disease as it can cause (life-threatening) arrhythmias. Amiodarone should be used in preference to flecainide in people with structural heart disease.

Benefits and harms

Flecainide versus placebo:

We found five RCTs. [20] [21] [22] [23] [24]

Conversion to sinus rhythm

Flecainide compared with placebo Oral or intravenous (iv) flecainide is more effective at increasing the rate of conversion to sinus rhythm at 1 to 24 hours in people with acute atrial fibrillation (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Rate of conversion to sinus rhythm					
[20] RCT **3-armed trial**	62 people, aged >75 years, onset of atrial fibrillation 7 days or less	**Conversion to sinus rhythm , 8 hours** 20/22 (91%) with oral flecainide 10/21 (48%) with placebo The remaining arm evaluated amiodarone	P <0.01	○○○	flecainide
[21] RCT **3-armed trial**	98 people, onset of atrial fibrillation 72 hours or less	**Conversion to sinus rhythm , 2 hours** 20/34 (59%) with iv flecainide 7/32 (22%) with placebo The remaining arm evaluated iv amiodarone	RR 2.69 95% CI 1.32 to 5.48	●●○	flecainide
[22] RCT	102 people with recent-onset atrial fibrillation of <72 hours	**Conversion to sinus rhythm , 1 hour** 29/51 (57%) with iv flecainide 7/51 (14%) with placebo Participants were monitored in intensive care or coronary care units; iv digoxin was given to all people who had not previously received digoxin	OR 8.3 95% CI 2.9 to 24.8	●●●	flecainide
[22] RCT	102 people with recent-onset atrial fibrillation of <72 hours	**Conversion to sinus rhythm , 6 hours** 34/51 (67%) with iv flecainide 18/51 (35%) with placebo Participants were monitored in intensive care or coronary care units; iv digoxin was given to all people who had not previously received digoxin	OR 3.67 95% CI 1.50 to 9.10	●●○	flecainide
[23] RCT **5-armed trial**	417 people admitted to hospital with recent-onset atrial fibrillation of 7 days or less	**Conversion to sinus rhythm , 8 hours** 75% with oral flecainide 37% with placebo Absolute numbers not reported The remaining arms evaluated iv amiodarone, iv propafenone, and oral propafenone	Significance not assessed		
[24] RCT **3-armed trial**	352 people with recent-onset atrial fibrillation of <72 hours	**Conversion to sinus rhythm , 1 hour** 72% with iv flecainide 22% with control Absolute numbers not reported The remaining arm evaluated iv propafenone	P <0.0001	○○○	flecainide
[24] RCT **3-armed trial**	352 people with recent-onset atrial fibrillation of <72 hours	**Conversion to sinus rhythm , 3 hours** 80% with iv flecainide 28% with control Absolute numbers not reported The remaining arm evaluated iv propafenone	P <0.0001	○○○	flecainide

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[24] RCT **3-armed trial**	352 people with recent-onset atrial fibrillation of <72 hours	**Conversion to sinus rhythm , 6 hours** 86% with iv flecainide 35% with control Absolute numbers not reported The remaining arm evaluated iv propafenone	P <0.0005	○○○	flecainide
[24] RCT **3-armed trial**	352 people with recent-onset atrial fibrillation of <72 hours	**Conversion to sinus rhythm , 24 hours** 90% with iv flecainide 46% with control Absolute numbers not reported The remaining arm evaluated iv propafenone	P <0.0001	○○○	flecainide

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[21] RCT **3-armed trial**	98 people, onset of atrial fibrillation 72 hours or less	**Hypotension** 8/34 (24%) with iv flecainide 8/32 (25%) with placebo The remaining arm evaluated iv amiodarone	Reported as not significant P value not reported	⟷	Not significant
[22] RCT	102 people with recent-onset atrial fibrillation of <72 hours	**Severe hypotension** 11/51 (22%) with iv flecainide 3/51 (6%) with placebo Severe hypotension defined by study as a decrease in systolic arterial pressure by 33% or more Participants were monitored in intensive care or coronary care units; iv digoxin was given to all people who had not previously received digoxin	OR 4.40 95% CI 1.03 to 18.60	●●○	placebo
[20] RCT **3-armed trial**	62 people, aged >75 years, onset of atrial fibrillation 7 days or less	**Adverse effects** with oral flecainide with placebo The remaining arm evaluated amiodarone	There were no adverse effects leading to interruption of the study: 1 person who took oral flecainide had an asymptomatic pause of 9.3 seconds, and another person who took oral flecainide had mild light-headedness		
[21] RCT **3-armed trial**	98 people, onset of atrial fibrillation 72 hours or less	**Adverse effects** with iv flecainide with placebo The remaining arm evaluated iv amiodarone	1 person in the iv flecainide group with no history of ventricular arrhythmia and a normal QT interval developed torsades de pointes		
[24] RCT **3-armed trial**	352 people with recent-onset atrial fibrillation of <72 hours	**Adverse effects** 10% with iv flecainide 4% with control	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Absolute numbers not reported The remaining arm evaluated iv propafenone			
[23] RCT **5-armed trial**	417 people admitted to hospital with recent-onset atrial fibrillation of 7 days or less	**Adverse effects** with oral flecainide with placebo Absolute numbers not reported The remaining arms evaluated iv amiodarone, iv propafenone, and oral propafenone	Adverse effects of oral flecainide in 3 people: 1 with left ventricular decompensation, and 2 with atrial flutter with rapid ventricular response; 1 person in the placebo group had atrial flutter with rapid ventricular response		

Flecainide versus amiodarone:

We found four RCTs. [20] [21] [23] [25]

Conversion to sinus rhythm

Flecainide compared with amiodarone Oral or intravenous (iv) flecainide may be more effective than iv amiodarone at increasing conversion rates to sinus rhythm at 1 to 12 hours (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Rate of conversion to sinus rhythm					
[23] RCT **5-armed trial**	417 people admitted to hospital with recent-onset atrial fibrillation of 7 days or less	**Conversion to sinus rhythm , 1 hour** 9/69 (13%) with oral flecainide 3/51 (6%) with iv amiodarone The remaining arms evaluated iv propafenone, oral propafenone, and placebo	Significance not assessed		
[23] RCT **5-armed trial**	417 people admitted to hospital with recent-onset atrial fibrillation of 7 days or less	**Conversion to sinus rhythm , 3 hours** 39/69 (57%) with oral flecainide 13/51 (25%) with iv amiodarone The remaining arms evaluated iv propafenone, oral propafenone, and placebo	Significance not assessed		
[23] RCT **5-armed trial**	417 people admitted to hospital with recent-onset atrial fibrillation of 7 days or less	**Conversion to sinus rhythm , 8 hours** 52/69 (75%) with oral flecainide 29/51 (57%) with iv amiodarone The remaining arms evaluated iv propafenone, oral propafenone, and placebo	Significance not assessed		
[20] RCT **3-armed trial**	62 people aged >75 years, onset of atrial fibrillation 7 days or less	**Conversion to sinus rhythm , 8 hours** 20/22 (91%) with oral flecainide 7/19 (37%) with iv amiodarone The remaining arm evaluated placebo	RR 2.47 95% CI 1.35 to 4.51	●●○	flecainide

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[21] RCT **3-armed trial**	98 people, onset of atrial fibrillation 72 hours or less	**Conversion to sinus rhythm , 2 hours** 20/34 (59%) with iv flecainide 11/32 (34%) with iv amiodarone The remaining arm evaluated placebo	RR 1.71 95% CI 0.98 to 2.98	⟷	Not significant
[25] RCT **3-armed trial**	150 people, onset of atrial fibrillation 48 hours or less	**Conversion to sinus rhythm , 1 hour** 29/50 (58%) with iv flecainide 7/50 (14%) with iv amiodarone The remaining arm evaluated propafenone	RR 4.14 95% CI 2.00 to 8.57	●●○	flecainide
[25] RCT **3-armed trial**	150 people, onset of atrial fibrillation 48 hours or less	**Conversion to sinus rhythm , 8 hours** 41/50 (82%) with iv flecainide 21/50 (42%) with iv amiodarone The remaining arm evaluated propafenone	RR 1.95 95% CI 1.38 to 2.77	●○○	flecainide
[25] RCT **3-armed trial**	150 people, onset of atrial fibrillation 48 hours or less	**Conversion to sinus rhythm , 12 hours** 45/50 (90%) with iv flecainide 32/50 (64%) with iv amiodarone The remaining arm evaluated propafenone	RR 1.41 95% CI 1.12 to 1.77	●○○	flecainide

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[21] RCT **3-armed trial**	98 people, onset of atrial fibrillation 72 hours or less	**Severe hypotension** 8/34 (24%) with iv flecainide 5/32 (16%) with iv amiodarone The remaining arm evaluated placebo	Significance not assessed P value not reported		
[23] RCT **5-armed trial**	417 people admitted to hospital with recent-onset atrial fibrillation of 7 days or less	**Adverse effects** with oral flecainide with iv amiodarone Absolute numbers not reported The remaining arms evaluated iv propafenone, oral propafenone, and placebo	Adverse effects of oral flecainide reported in 3 people: 1 had left ventricular decompensation, and 2 had atrial flutter with rapid ventricular response		
[25] RCT **3-armed trial**	150 people, onset of atrial fibrillation 48 hours or less	**Adverse effects** 6/50 (12%) with iv flecainide 3/50 (6%) with iv amiodarone The remaining arm evaluated propafenone	Adverse effects included transient junctional rhythm and symptomatic hypotension with flecainide, and rash and symptomatic hypotension with amiodarone Reported as not significant	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[20] RCT **3-armed trial**	62 people aged >75 years, onset of atrial fibrillation 7 days or less	**Adverse effects** with oral flecainide with amiodarone The remaining arm evaluated placebo	There were no adverse effects leading to interruption of the study: 1 person who took oral flecainide had an asymptomatic pause of 9.3 seconds and 1 person had mild light-headedness; 2 people receiving iv amiodarone had superficial phlebitis		
[21] RCT **3-armed trial**	98 people, onset of atrial fibrillation 72 hours or less	**Adverse effects** with iv flecainide with iv amiodarone The remaining arm evaluated placebo	Overall, adverse effects were more common with flecainide compared with amiodarone		

Flecainide versus propafenone:

We found three RCTs. [23] [24] [25]

Conversion to sinus rhythm

Flecainide compared with propafenone Oral or intravenous (iv) flecainide may be as effective as oral or iv propafenone at conversion to sinus rhythm at 1 to 12 hours (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Rate of conversion to sinus rhythm					
[23] RCT **5-armed trial**	417 people admitted to hospital with recent-onset atrial fibrillation of 7 days or less	**Conversion to sinus rhythm , 1 hour** 9/69 (13%) with oral flecainide 10/119 (8%) with oral propafenone The remaining arms evaluated iv amiodarone, iv propafenone, and placebo	Significance not assessed		
[23] RCT **5-armed trial**	417 people admitted to hospital with recent-onset atrial fibrillation of 7 days or less	**Conversion to sinus rhythm , 3 hours** 39/69 (57%) with oral flecainide 54/119 (45%) with oral propafenone The remaining arms evaluated iv amiodarone, iv propafenone, and placebo	Significance not assessed		
[23] RCT **5-armed trial**	417 people admitted to hospital with recent-onset atrial fibrillation of 7 days or less	**Conversion to sinus rhythm , 8 hours** 52/69 (75%) with oral flecainide 91/119 (76%) with oral propafenone The remaining arms evaluated iv amiodarone, iv propafenone, and placebo	Significance not assessed		
[23] RCT **5-armed trial**	417 people admitted to hospital with recent-onset atrial fibrillation of 7 days or less	**Conversion to sinus rhythm , 1, 3, and 8 hours** with oral flecainide with iv propafenone Absolute results not reported	Intravenous propafenone increased the rate of conversion to sinus rhythm within 1 hour, but had similar conversion rates at 3 and 8 hours (conversion rate of about 75% at 8 hours)		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		The remaining arms evaluated iv amiodarone, oral propafenone, and placebo	Significance not assessed		
[24] RCT **3-armed trial**	352 people with recent-onset atrial fibrillation of <72 hours	**Conversion to sinus rhythm , 1 hour** 72% with iv flecainide 54% with iv propafenone Absolute numbers not reported The remaining arm evaluated control	P = 0.05	○○○	flecainide
[25] RCT **3-armed trial**	150 people, onset of atrial fibrillation 48 hours or less	**Conversion to sinus rhythm , 1 hour** 29/50 (58%) with iv flecainide 30/50 (60%) with iv propafenone The remaining arm evaluated iv amiodarone	RR 0.97 95% CI 0.70 to 1.34	⟷	Not significant
[25] RCT **3-armed trial**	150 people, onset of atrial fibrillation 48 hours or less	**Conversion to sinus rhythm , 8 hours** 41/50 (82%) with iv flecainide 34/50 (68%) with iv propafenone The remaining arm evaluated iv amiodarone	RR 1.21 95% CI 0.96 to 1.51	⟷	Not significant
[25] RCT **3-armed trial**	150 people, onset of atrial fibrillation 48 hours or less	**Conversion to sinus rhythm , 12 hours** 45/50 (90%) with iv flecainide 36/50 (72%) with iv propafenone The remaining arm evaluated iv amiodarone	RR 1.25 95% CI 1.03 to 1.52	●○○	flecainide

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[23] RCT **5-armed trial**	417 people admitted to hospital with recent-onset atrial fibrillation of 7 days or less	**Adverse effects** with oral flecainide with oral propafenone Absolute numbers not reported The remaining arms evaluated iv amiodarone, iv propafenone, and placebo	Adverse effects of oral flecainide in 3 people: 1 had left ventricular decompensation, 2 had atrial flutter with rapid ventricular response; 1 person receiving iv propafenone had left ventricular decompensation		
[24] RCT **3-armed trial**	352 people with recent-onset atrial fibrillation of <72 hours	**Adverse effects** 10% with iv flecainide 10% with iv propafenone Absolute numbers not reported The remaining arm evaluated placebo	Significance not assessed		
[25] RCT	150 people, onset of atrial fibrillation 48 hours or less	**Adverse effects** 6/50 (12%) with iv flecainide	Adverse effects reported were transient junctional rhythm and symptomatic hypotension with	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
3-armed trial		7/50 (14%) with iv propafenone The remaining arm evaluated iv amiodarone	flecainide, and transient junctional rhythm and atrial tachycardia with propafenone Reported as not significant		

Comment: Multi-arm RCTs reported in this option are also reported in the amiodarone and propafenone options, where relevant. [20] [21] [23] [24] [25]

Clinical guide:
Following the increased mortality observed in people who have had an MI randomised to flecainide or encainide in the Cardiac Arrhythmia Suppression Trial, flecainide is not used for the treatment of atrial fibrillation in people with known ischaemic heart disease, because of the risk of pro-arrhythmia. [26] One systematic review on atrial fibrillation concluded that flecainide is the drug of choice to perform pharmacological cardioversion in those without evidence of structural heart disease (coronary artery disease or left ventricular dysfunction). However, this drug should not be used in people with haemodynamic compromise. In the presence of structural heart disease, amiodarone is first-line treatment. [27]

OPTION PROPAFENONE FOR RHYTHM CONTROL

- For GRADE evaluation of interventions for Atrial fibrillation (acute onset), see table, p 42 .
- Oral or intravenous propafenone increases the likelihood of reversion to sinus rhythm compared with placebo in people with haemodynamically stable acute atrial fibrillation.
- **CAUTION**
  Propafenone should not be used in people with ischaemic heart disease as it can cause (life-threatening) arrhythmia.

Benefits and harms

Propafenone versus placebo:

We found 10 RCTs. [23] [24] [28] [29] [30] [31] [32] [33] [34] [35] We found an additional RCT, which evaluated the safety of an oral-loading dose of propafenone (600 mg for >60 kg body weight, then 300 mg, if persistent) compared with that of digoxin plus propafenone, digoxin plus quinidine, and placebo. [36]

Conversion to sinus rhythm

Propafenone compared with placebo Oral or intravenous (iv) propafenone is more effective at increasing the proportion of people who convert to sinus rhythm within 24 hours in people with acute atrial fibrillation (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Rate of conversion to sinus rhythm					
[23] RCT **5-armed trial**	417 people admitted to hospital with recent-onset atrial fibrillation of 7 days or less	**Conversion to sinus rhythm , 1 hour** 8/29 (28%) with iv propafenone 1/29 (3%) with oral propafenone 1/29 (3%) with placebo Other arms included amiodarone and flecainide	P <0.05 for iv propafenone *v* placebo	○○○	propafenone
[23] RCT	417 people admitted to hospital with recent-onset atrial	**Conversion to sinus rhythm , 3 hours** 12/29 (41%) with iv propafenone	P <0.02 for iv propafenone *v* placebo	○○○	propafenone

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
5-armed trial	fibrillation of 7 days or less	16/29 (55%) with oral propafenone 3/29 (10%) with placebo Other arms included amiodarone and flecainide			
[23] RCT **5-armed trial**	417 people admitted to hospital with recent-onset atrial fibrillation of 7 days or less	**Conversion to sinus rhythm , 8 hours** 19/29 (66%) with iv propafenone 20/29 (69%) with oral propafenone 7/29 (24%) with placebo Other arms included amiodarone and flecainide	P <0.005 for iv propafenone *v* placebo	○○○	propafenone
[24] RCT **3-armed trial**	352 people, mean age 59 years, with recent-onset atrial fibrillation of <72 hours	**Conversion to sinus rhythm , 1 hour** 89/164 (54%) with iv propafenone 12/50 (22%) with placebo The remaining arm evaluated iv flecainide	P <0.005	○○○	propafenone
[24] RCT **3-armed trial**	352 people, mean age 59 years, with recent-onset atrial fibrillation of <72 hours	**Conversion to sinus rhythm , 3 hours** 112/164 (68%) with iv propafenone 15/50 (28%) with placebo The remaining arm evaluated iv flecainide	P <0.001	○○○	propafenone
[24] RCT **3-armed trial**	352 people, mean age 59 years, with recent-onset atrial fibrillation of <72 hours	**Conversion to sinus rhythm , 6 hours** 123/164 (75%) with iv propafenone 19/50 (35%) with placebo The remaining arm evaluated iv flecainide	P <0.0005	○○○	propafenone
[24] RCT **3-armed trial**	352 people, mean age 59 years, with recent-onset atrial fibrillation of <72 hours	**Conversion to sinus rhythm , 24 hours** 151/164 (92%) with iv propafenone 25/50 (46%) with placebo The remaining arm evaluated iv flecainide	P <0.0001	○○○	propafenone
[29] RCT	240 people, mean age 59 years, duration of atrial fibrillation <7 days	**Conversion to sinus rhythm , 3 hours** 54/119 (45%) with oral propafenone 22/121 (18%) with placebo	ARR 27% 95% CI 17% to 39%	○○○	propafenone
[29] RCT	240 people, mean age 59 years, duration of atrial fibrillation <7 days	**Conversion to sinus rhythm , 8 hours** 91/119 (76%) with oral propafenone 45/121 (37%) with placebo	ARR 39% 95% CI 29% to 52%	○○○	propafenone

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[30] RCT	55 people, mean age 59 years, duration of atrial fibrillation <7 days	**Conversion to sinus rhythm , 2 hours** 12/29 (41%) with oral propafenone 2/26 (8%) with placebo	P = 0.005	○○○	propafenone
[30] RCT	55 people, mean age 59 years, duration of atrial fibrillation <7 days	**Conversion to sinus rhythm , 6 hours** 65% with oral propafenone 31% with placebo Absolute numbers not reported	P = 0.015	○○○	propafenone
[30] RCT	55 people, mean age 59 years, duration of atrial fibrillation <7 days	**Conversion to sinus rhythm , 12 hours** 69% with oral propafenone 31% with placebo Absolute numbers not reported	P = 0.06	⟷	Not significant
[30] RCT	55 people, mean age 59 years, duration of atrial fibrillation <7 days	**Conversion to sinus rhythm , 24 hours** 79% with oral propafenone 73% with placebo Absolute numbers not reported	P = 0.75	⟷	Not significant
[31] RCT	156 people, aged 18–80 years, onset of atrial fibrillation <72 hours	**Conversion to sinus rhythm , 2 hours** 57/81 (70%) with iv propafenone 13/75 (17%) with placebo	RR 4.06 95% CI 2.43 to 6.79	●●○	propafenone
[32] RCT **3-armed trial**	123 people, onset of atrial fibrillation <72 hours	**Conversion to sinus rhythm , 1 hour** 25/81 (31%) with iv or oral propafenone 7/42 (17%) with placebo The remaining arm evaluated digoxin	Significance not assessed		
[32] RCT **3-armed trial**	123 people, onset of atrial fibrillation <72 hours	**Conversion to sinus rhythm , 4 hours** 49/81 (61%) with iv or oral propafenone 14/42 (33%) with placebo	Significance not assessed		
[32] RCT **3-armed trial**	123 people, onset of atrial fibrillation <72 hours	**Conversion to sinus rhythm , 8 hours** 53/81 (65%) with iv or oral propafenone 20/42 (48%) with placebo	Significance not assessed		
[28] RCT **3-armed trial**	123 people, aged 18–75 years, onset of atrial fibrillation <72 hours	**Conversion to sinus rhythm , 1 hour** 20/41 (49%) with iv propafenone 6/42 (14%) with placebo The remaining arm evaluated digoxin	RR 3.42 95% CI 1.53 to 7.63	●●○	propafenone

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[33] RCT **3-armed trial**	143 people (77 men), mean age 63 (±12 years), recent-onset atrial fibrillation 48 hours or less	**Conversion to sinus rhythm , 1 hour** 36/46 (78%) with iv propafenone 27/49 (55%) with placebo The remaining arm evaluated amiodarone	RR 1.42 95% CI 1.06 to 1.91	●○○	propafenone
[34] RCT	75 people, aged 18–70 years, recent-onset atrial fibrillation <72 hours	**Conversion to sinus rhythm , within 3 hours or until conversion occurred** 24/41 (59%) with iv propafenone 10/34 (29%) with placebo	OR 3.2 95% CI 1.3 to 7.9 P <0.01	●●○	propafenone
[35] RCT **4-armed trial**	362 people, aged 34–86 years, with recent-onset atrial fibrillation 48 hours or less	**Rate of conversion to sinus rhythm , 24 hours** 73/91 (80%) with iv propafenone 55/90 (61%) with placebo The remaining arms evaluated iv procainamide and iv amiodarone The level of blinding in the trial is unclear	P <0.05	○○○	propafenone

Mortality

No data from the following reference on this outcome. [23] [24] [28] [29] [30] [31] [32] [33] [34] [35] [36]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[23] RCT **5-armed trial**	417 people admitted to hospital with recent-onset atrial fibrillation of 7 days or less	**Cardiovascular adverse effects** 1/29 (3%) with iv propafenone 1/29 (3%) with placebo Other arms included oral propafenone, amiodarone, and flecainide	The adverse effects were left ventricular depression in 1 person receiving propafenone, and atrial flutter with rapid ventricular response in 1 person receiving placebo Significance not assessed		
[29] RCT **5-armed trial**	240 people, mean age 59 years, duration of atrial fibrillation <7 days	**Sustained atrial flutter or tachycardia , lasting <1 minute** 8/119 (7%) with oral propafenone 7/121 (6%) with placebo	Reported as not significant P <0.2	⟷	Not significant
[29] RCT	240 people, mean age 59 years, duration of atrial fibrillation <7 days	**Pauses of <2 seconds** 1/119 (1%) with oral propafenone 3/121 (2%) with placebo	Reported as not significant P <0.2	⟷	Not significant
[36] RCT **4-armed trial**	246 people with onset of atrial fibrillation of <48 hours	**Transient atrial flutter** 13/66 (20%) with propafenone 3/40 (8%) with placebo	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		The remaining arms evaluated digoxin plus propafenone and digoxin plus quinidine			
[24] RCT **3-armed trial**	352 people, mean age 59 years, with recent-onset atrial fibrillation <72 hours	**Adverse effects** 10% with iv propafenone 4% with placebo Absolute numbers not reported The remaining arm evaluated iv flecainide	Significance not assessed		
[33] RCT **3-armed trial**	143 people (77 men), mean age 63 (±12 years), recent-onset atrial fibrillation 48 hours or less	**Adverse effects** with iv propafenone with placebo The remaining arm evaluated amiodarone	The RCT reported discontinuation of propafenone in 2 people due to excessive QRS widening		
[30] [31] [32] [34] RCT	People with recent-onset atrial fibrillation (number unclear)	**Adverse effects** with propafenone with placebo Absolute results not reported	The RCTs reported no serious adverse effects		
[36] RCT **4-armed trial**	246 people with onset of atrial fibrillation <48 hours	**Serious adverse effects** with propafenone with placebo The remaining arms evaluated digoxin plus propafenone and digoxin plus quinidine	The RCT found no serious adverse events		
[36] RCT **4-armed trial**	246 people with onset of atrial fibrillation of <48 hours	**Non-serious, non-cardiac adverse effects** with propafenone with placebo Absolute results not reported The remaining arms evaluated digoxin plus propafenone and digoxin plus quinidine	The RCT found no significant difference between groups in non-cardiac adverse events, such as nausea, headache, gastrointestinal disturbance, dizziness, and paraesthesia	⟷	Not significant
[35] RCT **4-armed trial**	362 people, aged 34–86 years, with recent-onset atrial fibrillation 48 hours or less	**Pro-arrhythmic effects** with iv propafenone with placebo Absolute results not reported The remaining arms evaluated iv procainamide and iv amiodarone The level of blinding in the trial is unclear	The RCT did not directly compare adverse effects of propafenone *v* placebo; it reported no pro-arrhythmic effects, defined as the new onset of sustained ventricular tachycardia, ventricular fibrillation, or torsades de pointes, but treatment was discontinued in 4 people receiving propafenone because of excessive QRS widening		

Propafenone versus digoxin:

We found one RCT. [28]

Conversion to sinus rhythm

Propafenone compared with intravenous digoxin Intravenous (iv) propafenone may be as effective at increasing conversion to sinus rhythm at 1 hour (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Conversion to sinus rhythm					
[28] RCT **3-armed trial**	123 people, aged 18–75 years, onset of atrial fibrillation <72 hours	**Conversion to sinus rhythm , 1 hour** 49% with iv propafenone 32% with iv digoxin Absolute numbers not reported The remaining arm evaluated placebo	OR 1.50 95% CI 0.87 to 2.59	⟷	Not significant

Mortality

No data from the following reference on this outcome. [28]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[28] RCT **3-armed trial**	123 people, aged 18–75 years, onset of atrial fibrillation <72 hours	**Hypotension , 1 hour** with iv propafenone with iv digoxin Absolute numbers not reported The remaining arm evaluated placebo	P = 0.12	⟷	Not significant
[28] RCT **3-armed trial**	123 people, aged 18–75 years, onset of atrial fibrillation <72 hours	**Adverse effects (other than hypotension) , 1 hour** with iv propafenone with iv digoxin Absolute numbers not reported The remaining arm evaluated placebo	Asymptomatic atrial flutter with 2:1 atrioventricular conduction (ventricular rates between 105 beats/minute and 130 beats/minute) in 3 people: 1 receiving propafenone as first treatment, 1 receiving propafenone after digoxin, and 1 receiving digoxin after propafenone	⟷	Not significant

Propafenone versus amiodarone:

We found no systematic review but found four RCTs. [23] [25] [33] [35]

Conversion to sinus rhythm

Propafenone compared with amiodarone We don't know how propafenone and amiodarone compare at increasing conversion to sinus rhythm at 1 to 48 hours in people with acute atrial fibrillation (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Rate of conversion to sinus rhythm					
[33] RCT **3-armed trial**	143 people, mean age 63 years, recent-onset atrial fibrillation of 48 hours or less	**Conversion to sinus rhythm , 1 hour** 36/46 (78%) with iv propafenone 40/48 (83%) with iv amiodarone The remaining arm evaluated placebo Intravenous digoxin was given to all people who had not previously received digoxin	RR 0.94 95% CI 0.77 to 1.15	⟷	Not significant
[23] RCT **5-armed trial**	417 people admitted to hospital with recent-onset atrial fibrillation of 7 days or less	**Conversion to sinus rhythm , 8 hours** 75% with iv propafenone 76% with oral propafenone 57% with iv amiodarone Absolute numbers not reported The remaining arms evaluated oral flecainide and placebo	Significance not assessed		
[25] RCT **3-armed trial**	150 people, onset of atrial fibrillation 48 hours or less	**Conversion to sinus rhythm , 12 hours** 36/50 (72%) with iv propafenone 32/50 (64%) with iv amiodarone The remaining arm evaluated iv flecainide	P = 0.39	⟷	Not significant
[35] RCT **4-armed trial**	362 people, aged 34–86 years, with recent-onset atrial fibrillation 48 hours or less	**Rate of conversion to sinus rhythm , 24 hours** 73/91 (80%) with iv propafenone 82/92 (89%) with iv amiodarone The remaining arms evaluated iv procainamide and placebo The level of blinding in the trial is unclear	Reported as not significant P value not reported	⟷	Not significant
Time to conversion to sinus rhythm					
[25] RCT **3-armed trial**	150 people, onset of atrial fibrillation 48 hours or less	**Median time to conversion to sinus rhythm** 30 minutes with iv propafenone 333 minutes with iv amiodarone The remaining arm evaluated iv flecainide	P <0.001	○○○	propafenone

Mortality

No data from the following reference on this outcome. [23] [25] [33] [35]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[33] RCT **3-armed trial**	143 people (77 men), mean age 63 (±12 years), recent-onset atrial fibrillation 48 hours or less	**Adverse effects** with iv propafenone with placebo The remaining arm evaluated amiodarone	The RCT reported discontinuation of propafenone in 2 people due to excessive QRS widening; 1 person discontinued amiodarone due to allergy		
[23] RCT **5-armed trial**	417 people admitted to hospital with recent-onset atrial fibrillation of 7 days or less	**Adverse effects** with iv propafenone with oral propafenone with iv amiodarone Absolute numbers not reported The remaining arms evaluated oral flecainide and placebo	The RCT reported left ventricular decompensation in 1 person receiving propafenone		
[25] RCT **3-armed trial**	150 people, onset of atrial fibrillation 48 hours or less	**Adverse effects** 7/50 (14%) with iv propafenone 3/50 (6%) with iv amiodarone The remaining arm evaluated iv flecainide	Reported as not significant P value not reported	⟷	Not significant
[35] RCT **4-armed trial**	362 people, aged 34–86 years, with recent-onset atrial fibrillation 48 hours or less	**Cardiac adverse effects** with iv propafenone with iv amiodarone The remaining arms evaluated iv procainamide and placebo	The RCT did not directly compare adverse effects of propafenone *v* amiodarone; it reported no pro-arrhythmic effects, defined as the new onset of sustained ventricular tachycardia, ventricular fibrillation, or torsades de pointes, but treatment was discontinued in 4/91 (4%) people receiving propafenone because of excessive QRS widening The RCT also reported significant decrease in systolic blood pressure (<90 mmHg) in 15/92 (16%) people receiving amiodarone the first hour of iv administration		
[35] RCT **4-armed trial**	362 people, aged 34–86 years, with recent-onset atrial fibrillation 48 hours or less	**Phlebitis** with iv propafenone with iv amiodarone The remaining arms evaluated iv procainamide and placebo The level of blinding in the trial is unclear	The RCT did not directly compare adverse effects of propafenone *v* amiodarone; it reported that 17/92 (18%) of people developed phlebitis over the site of amiodarone infusion; in all these cases, the amiodarone administration was continued at a more central site		

Propafenone versus flecainide:

See option on Flecainide, p 4 .

Propafenone versus digoxin plus propafenone:

We found one RCT, which evaluated the safety of an oral-loading dose of propafenone (600 mg for >60 kg body weight, then 300 mg, if persistent) compared with that of digoxin plus propafenone, digoxin plus quinidine, and placebo. [36]

Conversion to sinus rhythm

No data from the following reference on this outcome. [36]

Mortality

No data from the following reference on this outcome. [36]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[36] RCT **4-armed trial**	246 people with onset of atrial fibrillation of <48 hours	**Serious adverse effects** with propafenone with digoxin plus propafenone The remaining arms evaluated digoxin plus quinidine and placebo	The RCT found no serious adverse events		
[36] RCT **4-armed trial**	246 people with onset of atrial fibrillation of <48 hours	**Transient atrial flutter** 13/66 (20%) with propafenone 12/70 (17%) with digoxin plus propafenone The remaining arms evaluated digoxin plus quinidine and placebo	Significance not assessed		
[36] RCT **4-armed trial**	246 people with onset of atrial fibrillation of <48 hours	**Transient left bundle branch block** 3/66 (5%) with propafenone 2/70 (3%) with digoxin plus propafenone The remaining arms evaluated digoxin plus quinidine and placebo	Significance not assessed		
[36] RCT **4-armed trial**	246 people with onset of atrial fibrillation of <48 hours	**Non-serious non-cardiac adverse effects** with propafenone with digoxin plus propafenone The remaining arms evaluated digoxin plus quinidine and placebo	The RCT found no significant difference between groups for non-cardiac adverse events, such as nausea, headache, gastrointestinal disturbance, dizziness, and paraesthesia	⟷	Not significant

Further information on studies

[23] Subgroup analysis of the RCT found that, after stratification by age (up to 60 years, or >60 years of age), conversion to sinus rhythm with propafenone was more likely in people aged less than 60 years compared with older people (in people aged >60 years: OR 3.78, 95% CI 1.80 to 7.92 at 3 hours *v* OR 4.74, 95% CI 2.12 to

10.54 at 8 hours; in people aged up to 60 years: OR 5.03, 95% CI 2.08 to 12.12 at 3 hours *v* OR 6.75, 95% CI 3.38 to 73.86 at 8 hours).

[29] The RCT also compared intravenous (iv) propafenone versus oral propafenone and found that the time to conversion to sinus rhythm was significantly shorter with iv propafenone compared with oral propafenone.

Comment: Multi-arm RCTs reported in this option are also reported in the amiodarone, digoxin, and flecainide options, where relevant. [23] [25] [28] [33]

One systematic review (search date 1997, 27 controlled clinical trials including some non-randomised trials, 1843 people) did not analyse the data for patients with acute and chronic atrial fibrillation separately. [37] In the trials included in the systematic review, propafenone was given either intravenously (initial bolus followed by infusion) or orally. The systematic review reported that people treated with propafenone were more likely to convert to sinus rhythm at 4 and 8 hours after initial treatment compared with people treated with placebo, but there was no significant difference at 24 hours. The systematic review gave no information on adverse effects. The number of RCTs was not reported clearly. [37] One subsequent RCT (86 people, onset of atrial fibrillation <2 weeks) reported a faster rate of conversion to sinus rhythm with oral propafenone compared with oral amiodarone. However the RCT reported no increase in the proportion of people who converted to sinus rhythm at 24 and 48 hours. The RCT found no serious adverse events. [38]

Clinical guide:
Extrapolation of the results of the Cardiac Arrhythmia Suppression Trial, in which flecainide or encainide increased mortality in people who had had an MI, has meant that other class 1c anti-arrhythmic agents, including propafenone, tend not to be used in people with ischaemic heart disease because of concerns over a possible increase in pro-arrhythmic effects in this group of people. [26] In addition, the increased frequency of cardiac adverse events with long-term propafenone, noted in people with structural heart disease, means that trials in acute atrial fibrillation have, for the main part, excluded people with significant heart disease. [39]

OPTION AMIODARONE FOR RHYTHM CONTROL

- For GRADE evaluation of interventions for Atrial fibrillation (acute onset), see table, p 42 .
- Amiodarone increases the likelihood of reversion to sinus rhythm compared with placebo in people with haemodynamically stable acute atrial fibrillation.
- Amiodarone is associated with adverse effects including bradycardia and hypotension.

Benefits and harms

Amiodarone versus placebo:

We found two systematic reviews (search dates 2001 [40] [41]), which identified two RCTs [20] [21] comparing amiodarone as a single agent with placebo (104 people with acute-onset atrial fibrillation). We also found one additional RCT [23] and three subsequent RCTs. [33] [35] [42]

Conversion to sinus rhythm

Amiodarone compared with placebo Amiodarone may be more effective than placebo at increasing conversion to sinus rhythm at 1 to 8 hours in people with acute atrial fibrillation who are haemodynamically stable (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Rate of conversion to sinus rhythm					
[20] RCT	40 people with acute-onset atrial fibrillation In review [40]	**Conversion to sinus rhythm , 8 hours** 37% with amiodarone 48% with placebo Absolute numbers not reported	Reported as not significant	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[21] RCT	64 people with acute-onset atrial fibrillation In review [41]	**Conversion to sinus rhythm , 8 hours** 59% with iv amiodarone 56% with placebo Absolute numbers not reported	Reported as not significant	⟷	Not significant
[23] RCT **5-armed trial**	417 people admitted to hospital with recent-onset atrial fibrillation of 7 days or less	**Conversion to sinus rhythm , 8 hours** 57% with iv amiodarone 37% with placebo Absolute numbers not reported The remaining arms evaluated iv propafenone, oral propafenone, and oral flecainide	Reported as significant P value not reported	○○○	amiodarone
[42] RCT	72 people Results reported for 62/72 (86%) people	**Conversion to sinus rhythm , 8 hours** 50% with oral amiodarone 20% with placebo Absolute numbers not reported	P <0.0001	○○○	amiodarone
[33] RCT **3-armed trial**	143 people, mean age 63 years, recent-onset atrial fibrillation of 48 hours or less	**Conversion to sinus rhythm , 1 hour** 40/48 (83%) with iv amiodarone 27/49 (55%) with placebo The remaining arm evaluated iv propafenone Intravenous digoxin was given to all people who had not previously received digoxin	P <0.02	○○○	amiodarone
[35] RCT **4-armed trial**	362 people, aged 34–86 years, with recent-onset atrial fibrillation of 48 hours or less	**Rate of conversion to sinus rhythm , 24 hours** 82/92 (89%) with iv amiodarone 55/90 (61%) with placebo The remaining arms evaluated iv procainamide and iv propafenone	P <0.05	○○○	amiodarone

Mortality

No data from the following reference on this outcome. [20] [21] [23] [33] [35] [42]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[41] Systematic review	104 people with acute-onset atrial fibrillation	**Adverse effects** 17% with amiodarone 11% with placebo Absolute numbers not reported	The most common adverse effects of iv amiodarone were phlebitis, hypotension, and bradycardia Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[42] RCT	72 people Results reported for 62/72 (86%) participants	**Adverse effects** 6/31 (19%) with amiodarone 6/31 (19%) with placebo	Adverse effects reported with amiodarone were rapid ventricular response, diarrhoea, nausea, and fainting; adverse effects reported with placebo were diarrhoea, nausea, sinus arrest, and transient ischaemic attack Significance not assessed		
[23] RCT **5-armed trial**	417 people admitted to hospital with recent-onset atrial fibrillation of 7 days or less	**Adverse effects** with iv amiodarone with placebo Absolute numbers not reported The remaining arms evaluated iv propafenone, oral propafenone, and oral flecainide	The RCT found no serious adverse effects in the iv amiodarone group		
[33] RCT **3-armed trial**	143 people, mean age 63 years, recent-onset atrial fibrillation of 48 hours or less	**Adverse effects** 1/48 (2%) with amiodarone 0/49 (0%) with placebo The remaining arm evaluated iv propafenone	Amiodarone was discontinued in 1 person because of an allergic reaction Significance not assessed		
[35] RCT **4-armed trial**	362 people, aged 34–86 years, with recent-onset atrial fibrillation of 48 hours or less	**Cardiac adverse effects** with iv amiodarone with placebo The remaining arms evaluated iv procainamide and propafenone	The RCT did not directly compare adverse effects of amiodarone *v* placebo; it reported no pro-arrhythmic effects, defined as the new onset of sustained ventricular tachycardia, ventricular fibrillation, or torsades de pointes, but it reported a significant decrease in systolic blood pressure (<90 mmHg) in 15/92 (16%) people receiving amiodarone the first hour of iv administration		
[35] RCT **4-armed trial**	362 people, aged 34–86 years, with recent-onset atrial fibrillation of 48 hours or less	**Phlebitis** with iv amiodarone with placebo The remaining arms evaluated iv procainamide and propafenone	The RCT did not directly compare adverse effects of amiodarone versus placebo The RCT reported that 17/92 (18%) of people developed phlebitis over the site of amiodarone infusion; in all these cases, the amiodarone administration was continued at a more central site		

Amiodarone versus digoxin:

We found two systematic reviews (search date 2001, 3 RCTs; [40] search date 2001, 3 RCTs [41]) and two subsequent RCTs. [43] [44] The reviews identified some RCTs in common and together they identified four small RCTs (34, 45, 50, and 30 people, respectively). [45] [46] [47] [48]

Conversion to sinus rhythm

Amiodarone compared with digoxin Amiodarone may be as effective at increasing conversion to sinus rhythm within 1 to 48 hours (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Rate of conversion to sinus rhythm					
[40] Systematic review	148 people with acute-onset atrial fibrillation 3 RCTs in this analysis	**Conversion to sinus rhythm , 24–48 hours** with amiodarone with digoxin Absolute results not reported	No statistical pooling of results Reported as no significant difference in any of the RCTs	⟷	Not significant
[41] Systematic review	114 people 3 RCTs in this analysis	**Conversion to sinus rhythm , 24–48 hours** with amiodarone with digoxin Absolute results not reported	No statistical pooling of results Reported as no significant difference in any of the RCTs	⟷	Not significant
[43] RCT	100 people with recent-onset atrial fibrillation, heart rate <135 beats/minute at presentation	**Conversion to sinus rhythm , 30 minutes** 14/50 (28%) with iv amiodarone 3/50 (6%) with iv digoxin If the person remained tachycardic after 30 minutes, a further dose of amiodarone or digoxin was administered to each group	P = 0.003	○○○	amiodarone
[43] RCT	100 people with recent-onset atrial fibrillation, heart rate <135 beats/minute at presentation	**Conversion to sinus rhythm , 60 minutes** 21/50 (42%) with iv amiodarone 9/50 (18%) with iv digoxin If the person remained tachycardic after 30 minutes, a further dose of amiodarone or digoxin was administered to each group	P = 0.012	○○○	amiodarone
[43] RCT	100 people with recent-onset atrial fibrillation, heart rate <135 beats/minute at presentation	**Conversion to sinus rhythm , 24 hours** with iv amiodarone with iv digoxin Absolute results not reported Similar rates in both groups	P value not reported		
[44] RCT **3-armed trial**	140 people, mean age 55 years, presenting with recent-onset atrial fibrillation	**Conversion to sinus rhythm** 51% with iv amiodarone 50% with iv digoxin Absolute numbers not reported The remaining arm evaluated iv sotalol If pharmacological cardioversion had not occurred by 12 hours, then direct current cardioversion was attempted; in those people in whom subsequent direct current cardioversion was required, there was no significant difference in success rate between groups	Reported as not significant among groups P value not reported		

Mortality

No data from the following reference on this outcome. [43] [44] [45] [46] [47] [48]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[44] RCT **3-armed trial**	140 people, mean age 55 years, presenting with recent-onset atrial fibrillation	**Symptomatic hypotension** 5 people with iv amiodarone Not reported with iv digoxin Not reported with iv sotalol	P = 0.035 for amiodarone *v* digoxin or sotalol	○○○	digoxin or sotalol
[44] RCT **3-armed trial**	140 people, mean age 55 years, presenting with recent-onset atrial fibrillation	**Serious adverse effects** with iv amiodarone with iv digoxin Absolute numbers not reported The remaining arm evaluated iv sotalol	There was a trend to more serious adverse effects with amiodarone, including 1 person with profound bradycardia after amiodarone infusion and 1 person with viral cardiomyopathy, who subsequently developed cardiogenic shock requiring inotropic and ventilatory support		
[48] RCT	75 people with recent-onset atrial fibrillation	**Adverse effects** 3/39 (8%) with amiodarone 8/36 (22%) with digoxin	Significance not assessed		
[45] RCT	34 people with recent-onset atrial fibrillation	**Adverse effects** 1/18 (6%) with amiodarone 0/16 (0%) with digoxin	Significance not assessed		
[46] RCT	30 people with recent-onset atrial fibrillation	**Adverse effects** 0/15 (0%) with amiodarone 0/15 (0%) with digoxin	Significance not assessed		
[47] RCT	50 people with recent-onset atrial fibrillation	**Adverse effects** 3/26 (12%) with amiodarone 0/24 (0%) with digoxin	Significance not assessed		
[44] RCT **3-armed trial**	140 people, mean age 55 years, presenting with recent-onset atrial fibrillation	**Non-serious adverse effects** with iv amiodarone with iv digoxin Absolute numbers not reported The remaining arm evaluated iv sotalol	Non-serious adverse effects included nausea and vomiting, and paraesthesia over the infusion site		

Amiodarone versus sotalol:

We found one RCT. [44]

Conversion to sinus rhythm

Amiodarone compared with sotalol Amiodarone may be as effective at increasing conversion to sinus rhythm at 3 hours (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Rate of conversion to sinus rhythm					
[44] RCT **3-armed trial**	140 people, mean age 55 years, presenting with recent-onset atrial fibrillation	**Conversion to sinus rhythm** 51% with iv amiodarone 44% with iv sotalol Absolute numbers not reported The remaining arm evaluated iv digoxin If pharmacological cardioversion had not occurred by 12 hours, then direct current cardioversion was attempted; there was no significant difference in success rate between groups for people who required subsequent direct current cardioversion	Reported as not significant among groups P value not reported		

Mortality

No data from the following reference on this outcome. [44]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[44] RCT **3-armed trial**	140 people, mean age 55 years, presenting with recent-onset atrial fibrillation	**Symptomatic hypotension** 5 people with iv amiodarone Not reported with iv sotalol Not reported with iv digoxin	P = 0.035 for amiodarone *v* digoxin or sotalol	○○○	digoxin or sotalol
[44] RCT **3-armed trial**	140 people, mean age 55 years, presenting with recent-onset atrial fibrillation	**Serious adverse effects** with iv amiodarone with iv sotalol Absolute numbers not reported The remaining arm evaluated iv digoxin	There was a trend to more serious adverse effects with amiodarone, including 1 person with profound bradycardia after amiodarone infusion, and 1 person with viral cardiomyopathy, who subsequently developed cardiogenic shock requiring inotropic and ventilatory support		
[44] RCT **3-armed trial**	140 people, mean age 55 years, presenting with recent-onset atrial fibrillation	**Non-serious adverse effects** with iv amiodarone with iv sotalol Absolute numbers not reported The remaining arm evaluated iv digoxin	Non-serious adverse effects included nausea and vomiting, and paraesthesia over the infusion site		

Amiodarone versus verapamil:

We found one RCT. [49]

Conversion to sinus rhythm

Amiodarone compared with verapamil Amiodarone is more effective at increasing conversion to sinus rhythm at 3 hours (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Rate of conversion to sinus rhythm					
[49] RCT	24 people with atrial fibrillation of <48 hours' duration, aged 71 (±9.6 years)	**Conversion to sinus rhythm , 3 hours** 10/13 (77%) with iv amiodarone 0/11 (0%) with iv verapamil	P <0.001	○○○	amiodarone

Mortality

No data from the following reference on this outcome. [49]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[49] RCT	24 people with atrial fibrillation of <48 hours' duration, aged 71 (±9.6 years)	**Adverse effects , 3 hours** with iv amiodarone with iv verapamil	The RCT reported slowing of ventricular rate to 45 beats/minute and transitory hypotension in 1 person receiving verapamil, and hypotension without bradycardia, lasting for about 4 minutes, in 1 person receiving amiodarone		

Amiodarone versus flecainide:

See option on Flecainide, p 4 .

Amiodarone versus propafenone:

See option on Propafenone, p 11 .

Amiodarone versus direct current cardioversion:

We found no RCTs.

Comment: The RCTs that found no significant difference between treatments may have lacked power to detect clinically important effects.

Multi-arm RCTs reported in this option are also reported in the flecainide and propafenone options where relevant. [23] [33]

Clinical guide:
One systematic review on atrial fibrillation management concluded that amiodarone should be the drug of choice to attempt pharmacological cardioversion in people with evidence of structural heart disease (coronary artery disease or left ventricular dysfunction). However, in the absence of structural heart disease, flecainide is the usual first choice. [27]

OPTION DIRECT CURRENT CARDIOVERSION FOR RHYTHM CONTROL

- For GRADE evaluation of interventions for Atrial fibrillation (acute onset), see table, p 42 .
- Electrical cardioversion is more effective than intravenous propafenone at increasing the proportion of people who converted to sinus rhythm with haemodynamically stable acute atrial fibrillation.
- Consensus is that direct current cardioversion should be used in people with haemodynamically unstable acute atrial fibrillation.

Benefits and harms

Direct current cardioversion versus chemical cardioversion:

We found one RCT, which compared direct current cardioversion with pharmacological cardioversion using intravenous propafenone for heart rhythm control in people with acute atrial fibrillation of less than 2 days' duration. [50]

Conversion to sinus rhythm

Direct current cardioversion versus chemical cardioversion Electrical cardioversion is more effective than intravenous propafenone at increasing the proportion of people who converted to sinus rhythm with haemodynamically stable atrial fibrillation lasting less than 48 hours (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Rate of conversion to sinus rhythm					
[50] RCT	247 people (mean age 67 years) with haemodynamically stable atrial fibrillation lasting <48 hours	**Successful cardioversion , within 6 hours** 108/121 (89%) with direct current cardioversion 93/126 (74%) with iv propafenone	HR 0.34 95% CI 0.17 to 0.68 P = 0.02 See Further information on studies	●●○	direct current cardioversion

Mortality

No data from the following reference on this outcome. [50]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[50] RCT	247 people (mean age 67 years) with haemodynamically stable atrial fibrillation lasting <48 hours	**Hypotension , up to discharge** 0/121 (0%) with electrical cardioversion 2/126 (2%) with iv propafenone	Significance not assessed		
[50] RCT	247 people (mean age 67 years) with haemodynamically stable atrial fibrillation lasting <48 hours	**Atrial flutter , up to discharge** 0/121 (0%) with electrical cardioversion 2/126 (2%) with iv propafenone	Significance not assessed		

Further information on studies

[50] Successful cardioversion was defined as "return to sinus rhythm within 6 hours from beginning of intravenous propafenone, as demonstrated by a rhythm strip and 12-lead ECG and consequent discharge from the emergency department". The 33 patients in the propafenone arm who failed to convert to sinus rhythm were offered electrical cardioversion, 28 of whom consented, with a 97% success rate. Recurrence of atrial fibrillation was reported in 165/247 patients (attrition = 33%), and no between-group difference was observed: 24/91 (26%) with electrical cardioversion versus 21/74 (28%) with propafenone; HR 0.9, 95% CI 0.45 to 1.8, P = 0.86.

Comment:

Clinical guide:
Direct current cardioversion seems to be more effective than pharmacological cardioversion with propafenone of recent-onset atrial fibrillation. This is in accordance with the evidence of the use of direct current cardioversion in chronic atrial fibrillation. Direct current cardioversion has been used for the treatment of atrial fibrillation since the 1960s. [51] It may be unethical to conduct RCTs of direct current cardioversion in people with acute atrial fibrillation and haemodynamic compromise. The consensus is that immediate direct current cardioversion for acute atrial fibrillation should be attempted if there are signs of haemodynamic compromise. [19] If the patient is haemodynamically stable, full anticoagulation is recommended (warfarin for 3 weeks before, and 4 weeks after, cardioversion) to reduce the risk of thromboembolism in people with atrial fibrillation of more than 48 hours' duration. [19] We found insufficient evidence on whether cardioversion or rate control is superior for the treatment of acute atrial fibrillation.

Adverse events from synchronised direct current cardioversion include those associated with a general anaesthetic, generation of a more serious arrhythmia, superficial burns, and thromboembolism.

OPTION SOTALOL FOR RHYTHM CONTROL

- For GRADE evaluation of interventions for Atrial fibrillation (acute onset), see table, p 42 .
- We don't know whether sotalol increases reversion to sinus rhythm in people with haemodynamically stable atrial fibrillation, as few adequate trials have been conducted.
- Sotalol can cause arrhythmias at high doses.

Benefits and harms

Sotalol versus placebo:

We found no systematic review or RCTs that compared sotalol with placebo for heart-rhythm control in people with acute atrial fibrillation of less than 7 days' duration.

Comment:

We found one systematic review (search date 1998), which compared beta-blockers versus placebo in people with acute or chronic atrial fibrillation. [52] See Comment on Timolol., p 37

Clinical guide:
It should be noted that sotalol is a beta-blocker that has class III anti-arrhythmic activity at high doses (240–480 mg/day). In UK clinical practice, sotalol is often used at low doses (80–160 mg/day), at which it essentially acts in a similar manner to a standard beta-blocker (class II) in terms of anti-arrhythmic activity. In people with low BMI, renal impairment, etc., some class III activity may be manifest at low doses. When used as an anti-arrhythmic agent, sotalol is often started at 80 mg twice-daily for the first week, and thereafter titrated to 160 mg twice-daily (or higher subsequently), after checking for adverse effects and QT prolongation on the ECG.

OPTION DIGOXIN FOR RHYTHM CONTROL

- For GRADE evaluation of interventions for Atrial fibrillation (acute onset), see table, p 42 .
- Digoxin does not seem to increase reversion to sinus rhythm compared with placebo.
- Digoxin can cause bradyarrhythmias.

Benefits and harms

Digoxin versus placebo:

We found four RCTs in people with atrial fibrillation of up to 7 days' duration. [28] [53] [54] [55]

Conversion to sinus rhythm

Digoxin compared with placebo Digoxin may be no more effective at increasing conversion to sinus rhythm at 1 to 16 hours in people with acute atrial fibrillation of up to 7 days' duration (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Rate of conversion to sinus rhythm					
[53] RCT	239 people within 7 days of onset of atrial fibrillation, mean age 66 years, mean ventricular rate 122 beats/minute	**Conversion to sinus rhythm , 16 hours** 51% with iv digoxin 46% with placebo Absolute numbers not reported	P = 0.37	⟷	Not significant
[54] RCT	40 people (23 men) within 7 days of onset of atrial fibrillation, mean age 64 years	**Conversion to sinus rhythm** 9/19 (47%) with iv digoxin 8/20 (40%) with placebo	P = 0.6	⟷	Not significant
[55] RCT	36 people within 7 days of the onset of atrial fibrillation	**Conversion to sinus rhythm , 18 hours** 50% with oral digoxin 44% with placebo Absolute numbers not reported	ARR +6% 95% CI –11% to +22%	⟷	Not significant
[28] RCT **3-armed trial**	123 people, aged 18–75 years, onset of atrial fibrillation <72 hours	**Conversion to sinus rhythm , 1 hour** 13/40 (33%) with iv digoxin 6/42 (14%) with iv placebo The remaining arm evaluated iv propafenone Treatments given as a 10-minute infusion	RR 2.28 95% CI 0.96 to 5.40	⟷	Not significant

Mortality

No data from the following reference on this outcome. [28] [53] [54] [55]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[53] RCT	239 people within 7 days of onset of atrial fibrillation, mean age 66 years, mean ventricular rate 122 beats/minute	**Adverse effects , 16 hours** with iv digoxin with placebo Absolute numbers not reported	The RCT reported that some people developed asymptomatic bradycardia, and 1 person with previously undiagnosed hypertrophic cardiomyopathy suffered circulatory distress		
[54] RCT	40 people (23 men) within 7 days of onset of atrial fibrillation, mean age 64 years	**Adverse effects** with iv digoxin with placebo	2 people developed bradyarrhythmias		
[28] RCT **3-armed trial**	123 people, aged 18–75 years, onset of atrial fibrillation <72 hours	**Adverse effects** with iv digoxin with iv placebo The remaining arm evaluated iv propafenone Treatments given as a 10-minute infusion	3 people reported asymptomatic atrial flutter with 2:1 atrioventricular conduction (ventricular rates between 105–130 beats/minute): 1 receiving propafenone as first treatment, 1 receiving propafenone after digoxin, and 1 receiving digoxin after propafenone		

Digoxin versus propafenone:

See option on Propafenone, p 11 .

Digoxin versus amiodarone:

See option on Amiodarone, p 20 .

Comment: The three-arm RCT reported in this option is also reported in the Propafenone, p 11 option. [28] In people with Wolff-Parkinson-White syndrome, digoxin may increase the ventricular rate of atrial fibrillation and can cause ventricular arrhythmias. [56]

Clinical guide:
The evidence suggests that digoxin is no better than placebo for restoring sinus rhythm in people with recent-onset atrial fibrillation. The peak action of digoxin (oral or iv) is delayed for up to 6 to 12 hours.

OPTION VERAPAMIL FOR RHYTHM CONTROL

- For GRADE evaluation of interventions for Atrial fibrillation (acute onset), see table, p 42 .
- We don't know whether verapamil increases reversion to sinus rhythm compared with placebo in people with haemodynamically stable atrial fibrillation.
- Verapamil has been associated with ventricular arrhythmias, hypotension, and exacerbation of heart failure.

Benefits and harms

Verapamil versus placebo:

We found no systematic review or RCTs on the use of verapamil versus placebo for heart-rhythm control in people with acute atrial fibrillation of less than 7 days' duration.

Verapamil versus amiodarone:

See option on Amiodarone, p 20 .

Comment:

In people with Wolff-Parkinson-White syndrome, verapamil may increase the ventricular rate and can cause ventricular arrhythmias. [57] Rate-limiting calcium channel blockers may exacerbate heart failure and hypotension.

We found one crossover RCT (double-blind, 20 people) in people with atrial fibrillation or atrial flutter for 2 hours to 2 years, which compared intravenous low-dose verapamil versus placebo. [58] A positive response was defined as conversion to sinus rhythm, or a decrease in the ventricular response to less than 100 beats a minute, or by more than 20% of the initial rate. If a positive response did not occur within 10 minutes, then a second bolus injection was given (placebo for people who initially received verapamil, and verapamil for people who initially received placebo). The RCT reported no significant difference in the proportion of people who converted to sinus rhythm within 30 minutes compared with placebo. The RCT reported development of 1:1 flutter in one person with previous Wolff-Parkinson-White syndrome and 2:1 flutter. [58]

Clinical guide:

One systematic review concluded that the available evidence suggests that calcium channel blockers, such as diltiazem and verapamil, reduce ventricular rate in acute- or recent-onset atrial fibrillation. However, these drugs are probably no better than placebo for restoring sinus rhythm. We found no studies of the effect of rate-limiting calcium channel blockers on exercise tolerance in people with acute- or recent-onset atrial fibrillation, but studies in people with chronic atrial fibrillation found improved exercise tolerance. [27]

QUESTION **What are the effects of interventions to control heart rate in people with recent-onset atrial fibrillation who are haemodynamically stable?**

OPTION AMIODARONE FOR RATE CONTROL

- For GRADE evaluation of interventions for Atrial fibrillation (acute onset), see table, p 42 .
- No one drug has been shown to be more effective at controlling heart rate. However, there is general consensus that intravenous bolus amiodarone is more effective than digoxin.

Benefits and harms

Amiodarone versus digoxin:

We found one RCT. [43]

Control of heart rate

Amiodarone compared with digoxin Amiodarone may be as effective at controlling heart rate at 30 minutes (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Control of heart rate					
[43] RCT	100 consecutive people, heart rate 135 beats/minute or more at presentation	**Control of heart rate , 5 minutes** with iv amiodarone with iv digoxin Absolute results reported graphically	P = 0.008	○○○	amiodarone

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		If the person remained tachycardic after 30 minutes, a further dose of amiodarone or digoxin was administered to each group The RCT showed that iv bolus amiodarone resulted in a slight reduction in systolic blood pressure up to 5 minutes after administration; this did not require treatment, but the numbers affected were not stated			

Mortality

No data from the following reference on this outcome. [43]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[43] RCT	100 consecutive people, heart rate 135 beats/minute or more at presentation	**Adverse effects** with iv amiodarone with iv digoxin Absolute results reported graphically The RCT showed that iv bolus amiodarone resulted in a slight reduction in systolic blood pressure up to 5 minutes after administration; this did not require treatment, but the numbers affected were not stated	One case of superficial phlebitis was reported with amiodarone, requiring local topical treatment		

Further information on studies

[43] Data presented for subsequent time-frames also included those people who had converted to sinus rhythm, and are therefore difficult to interpret. At 60 minutes, considering only people who remained in atrial fibrillation, no significant differences in heart rate were apparent between the two drugs (results presented graphically).

Comment: **Clinical guide:**
One systematic review on atrial fibrillation concluded that intravenous beta-blockers or rate-limiting calcium channel blockers should be used for people requiring urgent pharmacological rate control. Where these drugs are ineffective or contraindicated, amiodarone should be used. [27]

OPTION DIGOXIN FOR RATE CONTROL

- For GRADE evaluation of interventions for Atrial fibrillation (acute onset), see table, p 42 .

- Treatment with digoxin may control heart rate in people with haemodynamically stable atrial fibrillation, despite its being unlikely to restore sinus rhythm.

Benefits and harms

Digoxin versus placebo:

We found two RCTs in people with atrial fibrillation of up to 7 days' duration. [53] [54]

Control of heart rate

Digoxin compared with placebo Digoxin is more effective at controlling heart rate at 30 minutes to 2 hours in people with atrial fibrillation lasting up to 7 days (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Control of heart rate					
[53] RCT	239 people, <7 days of onset of atrial fibrillation, mean age 66 years, mean ventricular rate 122 beats/minute	**Mean ventricular rate , 2 hours** 105 beats/minute with iv digoxin 117 beats/minute with placebo	P = 0.0001	◌◌◌	digoxin
[54] RCT	40 people (23 men) with atrial fibrillation of <7 days' duration, mean age 64 years	**Ventricular rate , 30 minutes** with iv digoxin with placebo Absolute results reported graphically	P = 0.02	◌◌◌	digoxin

Mortality

No data from the following reference on this outcome. [53] [54]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[53] RCT	239 people, <7 days of onset of atrial fibrillation, mean age 66 years, mean ventricular rate 122 beats/minute	**Adverse effects** with iv digoxin with placebo	Adverse effects included asymptomatic bradycardia, and 1 person with previously undiagnosed hypertrophic cardiomyopathy suffered circulatory distress		
[54] RCT	40 people (23 men) with atrial fibrillation of <7 days' duration, mean age 64 years	**Adverse effects** with iv digoxin with placebo Absolute results reported graphically	2 people developed bradyarrhythmias		

No data from the following reference on this outcome. [53] [54]

Digoxin versus diltiazem:

See option on Diltiazem, p 34 .

Digoxin versus amiodarone:

See option on Amiodarone, p 31 .

Comment: **Clinical guide:**

We found one systematic review (search date 1998) [52] and two additional RCTs [59] [60] comparing digoxin with placebo in people with chronic atrial fibrillation, which found that control of the ventricular rate during exercise was poor unless a beta-blocker or rate-limiting calcium channel blocker (verapamil or diltiazem) was used in combination. One systematic review on atrial fibrillation concluded that intravenous beta-blockers or rate-limiting calcium channel blockers should be used for people requiring urgent pharmacological rate control. Where these drugs are ineffective or contraindicated, amiodarone should be used. [27] It is not clear whether these results can be extrapolated to people with acute atrial fibrillation.

OPTION DILTIAZEM FOR RATE CONTROL

- For GRADE evaluation of interventions for Atrial fibrillation (acute onset), see table, p 42 .
- We don't know whether diltiazem is effective at controlling heart rate, but it is unlikely to restore sinus rhythm.
- Rate-limiting calcium channel blockers may exacerbate heart failure and hypotension.

Benefits and harms

Diltiazem versus placebo:

We found no systematic review or RCTs on the effects of diltiazem to control heart rate in people with acute atrial fibrillation, of less than 7 days' duration, who are haemodynamically stable.

Diltiazem versus digoxin:

We found no systematic review or RCTs limited to people with acute atrial fibrillation.

Diltiazem versus verapamil:

See option on Verapamil, p 38 .

Comment: **Clinical guide:**

Diltiazem versus placebo One RCT (113 people; 89 with atrial fibrillation of unspecified duration and 24 with atrial flutter; ventricular rate of >120 beats/minute; systolic blood pressure 90 mmHg or more, without severe heart failure; 108 people with at least 1 underlying condition that may explain atrial arrhythmia; mean age 64 years) compared intravenous (iv) diltiazem with placebo. [61] After randomisation, a dose of iv diltiazem (0.25 mg/kg over 2 minutes), or equivalent placebo, was given. If the first dose had no effect after 15 minutes, then the code was broken and diltiazem 0.35 mg/kg every 2 minutes was given, regardless of randomisation. The RCT found no difference in response rate to diltiazem in people with atrial fibrillation compared with those with atrial flutter. In the diltiazem-treated group, seven people developed asymptomatic hypotension (systolic blood

pressure <90 mmHg), three developed flushing, three developed itching, and one developed nausea and vomiting. [61]

Diltiazem versus digoxin One RCT (30 consecutive people, 10 men, mean age 72 years, 26 with acute atrial fibrillation, 4 with atrial flutter, unspecified duration) compared iv diltiazem with iv digoxin versus both drugs given on admission to the emergency department. [62] Heart rate control was defined as a ventricular rate of <100 beats/minute. Intravenous digoxin (25 mg as a bolus at 0 and 30 minutes) and iv diltiazem (initially 0.25 mg/kg over the first 2 minutes, followed by 0.35 mg/kg at 15 minutes, and then a titratable infusion at a rate of 10–20 mg/hour) were given to maintain heart-rate control. The dosing regimens were the same whether the drugs were given alone or in combination. The RCT found that diltiazem decreased ventricular heart rate against baseline within 5 minutes, compared with digoxin, which was not significant until 180 minutes. No additional benefit was found with the combination of digoxin and diltiazem. The RCT was not large enough to assess adverse effects adequately, and none were apparent. The evidence suggests that calcium channel blockers, such as diltiazem and verapamil, reduce ventricular rate in acute- or recent-onset atrial fibrillation, but they are probably no better than placebo for restoring sinus rhythm. We found no studies of the effect of rate-limiting calcium channel blockers on exercise tolerance in people with acute- or recent-onset atrial fibrillation, but studies in people with chronic atrial fibrillation found improved exercise tolerance. One systematic review on atrial fibrillation concluded that iv beta-blockers or rate-limiting calcium channel blockers should be used for people requiring urgent pharmacological rate control. Where these drugs are ineffective or contraindicated, amiodarone should be used. [27]

OPTION BISOPROLOL FOR RATE CONTROL New

- For GRADE evaluation of interventions for Atrial fibrillation (acute onset), see table, p 42 .
- We don't know whether bisoprolol increases rate control in people with haemodynamically stable acute atrial fibrillation, as few adequate trials have been conducted.

Benefits and harms

Bisoprolol versus placebo:

We found no systematic review or RCTs on the effects of bisoprolol to control heart rate in people with acute atrial fibrillation, of up to 7 days' duration, who are haemodynamically stable.

Comment:

Clinical guide:

Beta-blockers or non-dihydropyridine calcium channel antagonists are recommended as first-line treatment for rate control of atrial fibrillation. [2] There is no RCT to compare the effects of bisoprolol or other drugs within the same class versus placebo in recent-onset atrial fibrillation. By extrapolating data from persistent and chronic atrial fibrillation, beta-blockers, as a class, seem to be a safe and effective treatment for rate control. Beta-blockers may exacerbate heart failure and hypotension in acute atrial fibrillation and can precipitate bronchospasm. [63] Co-administration of beta-blockers and rate-limiting calcium channel blockers (diltiazem and verapamil) may increase the risk of asystole and sinus arrest. [64] [65] [66]

OPTION METOPROLOL FOR RATE CONTROL New

- For GRADE evaluation of interventions for Atrial fibrillation (acute onset), see table, p 42 .
- We don't know whether metoprolol increases rate control in people with haemodynamically stable acute atrial fibrillation, as few adequate trials have been conducted.

Benefits and harms

Metoprolol versus placebo:

We found no systematic review or RCTs on the effects of metoprolol to control heart rate in people with acute atrial fibrillation, of up to 7 days' duration, who are haemodynamically stable.

Comment: **Clinical guide:**
Beta-blockers or non-dihydropyridine calcium channel antagonists are recommended as first-line treatment for rate control of atrial fibrillation. [2] There is no RCT to compare the effects of metoprolol or other drugs within the same class versus placebo in recent-onset atrial fibrillation. By extrapolating data from persistent and chronic atrial fibrillation, beta-blockers, as a class, seem to be a safe and effective treatment for rate control. Beta-blockers may exacerbate heart failure and hypotension in acute atrial fibrillation and can precipitate bronchospasm. [63] Co-administration of beta-blockers and rate-limiting calcium channel blockers (diltiazem and verapamil) may increase the risk of asystole and sinus arrest. [64] [65] [66]

OPTION ATENOLOL FOR RATE CONTROL New

- For GRADE evaluation of interventions for Atrial fibrillation (acute onset), see table, p 42 .
- We don't know whether atenolol increases rate control in people with haemodynamically stable acute atrial fibrillation, as few adequate trials have been conducted.

Benefits and harms

Atenolol versus placebo:

We found no systematic review or RCTs on the effects of atenolol to control heart rate in people with acute atrial fibrillation, of up to 7 days' duration, who are haemodynamically stable.

Comment: **Clinical guide:**
Beta-blockers or non-dihydropyridine calcium channel antagonists are recommended as first-line treatment for rate control of atrial fibrillation. [2] There is no RCT to compare the effects of atenolol or other drugs within the same class versus placebo in recent-onset atrial fibrillation. By extrapolating data from persistent and chronic atrial fibrillation, beta-blockers, as a class, seem to be a safe and effective treatment for rate control. Beta-blockers may exacerbate heart failure and hypotension in acute atrial fibrillation and can precipitate bronchospasm. [63] Co-administration of beta-blockers and rate-limiting calcium channel blockers (diltiazem and verapamil) may increase the risk of asystole and sinus arrest. [64] [65] [66]

OPTION NEBIVOLOL FOR RATE CONTROL New

- For GRADE evaluation of interventions for Atrial fibrillation (acute onset), see table, p 42 .
- We don't know whether nebivolol increases rate control in people with haemodynamically stable acute atrial fibrillation, as few adequate trials have been conducted.

Benefits and harms

Nebivolol versus placebo:

We found no systematic review or RCTs on the effects of nebivolol to control heart rate in people with acute atrial fibrillation, of up to 7 days' duration, who are haemodynamically stable.

Comment: **Clinical guide:**
Beta-blockers or non-dihydropyridine calcium channel antagonists are recommended as first-line treatment for rate control of atrial fibrillation. [2] There is no RCT to compare the effects of nebivolol or other drugs within the same class versus placebo in recent-onset atrial fibrillation. By extrapolating data from persistent and chronic atrial fibrillation, beta-blockers, as a class, seem to be a safe and effective treatment for rate control. Beta-blockers may exacerbate heart failure and hypotension

in acute atrial fibrillation and can precipitate bronchospasm. [63] Co-administration of beta-blockers and rate-limiting calcium channel blockers (diltiazem and verapamil) may increase the risk of asystole and sinus arrest. [64] [65] [66]

OPTION CARVEDILOL FOR RATE CONTROL New

- For GRADE evaluation of interventions for Atrial fibrillation (acute onset), see table, p 42 .
- We don't know whether carvedilol increases rate control in people with haemodynamically stable acute atrial fibrillation, as few adequate trials have been conducted.

Benefits and harms

Carvedilol versus placebo:

We found no systematic review or RCTs on the effects of carvedilol to control heart rate in people with acute atrial fibrillation, of up to 7 days' duration, who are haemodynamically stable.

Comment:

Clinical guide:

Beta-blockers or non-dihydropyridine calcium channel antagonists are recommended as first-line treatment for rate control of atrial fibrillation. [2] There is no RCT to compare the effects of carvedilol or other drugs within the same class versus placebo in recent-onset atrial fibrillation. By extrapolating data from persistent and chronic atrial fibrillation, beta-blockers, as a class, seem to be a safe and effective treatment for rate control. Beta-blockers may exacerbate heart failure and hypotension in acute atrial fibrillation and can precipitate bronchospasm. [63] Co-administration of beta-blockers and rate-limiting calcium channel blockers (diltiazem and verapamil) may increase the risk of asystole and sinus arrest. [64] [65] [66]

OPTION TIMOLOL FOR RATE CONTROL

- For GRADE evaluation of interventions for Atrial fibrillation (acute onset), see table, p 42 .
- We don't know whether timolol is effective at controlling heart rate, but it is unlikely to restore sinus rhythm.

Benefits and harms

Timolol:

We found no systematic review or RCTs on the effects of timolol to control heart rate in people with acute atrial fibrillation of up to 7 days' duration who are haemodynamically stable.

Comment:

Beta-blockers may exacerbate heart failure and hypotension in acute atrial fibrillation and can precipitate bronchospasm. [63] Beta-blockers plus rate-limiting calcium channel blockers (diltiazem and verapamil) may increase the risk of asystole and sinus arrest. [64] [65] [66]

Timolol versus placebo:

We found one RCT (61 people with atrial fibrillation of unspecified duration, ventricular rate >120 beats/minute), which compared intravenous (iv) timolol (a beta-blocker) versus iv placebo given immediately and repeated twice at 20-minute intervals if sinus rhythm was not achieved. [67] It found that, 20 minutes after the last injection, iv timolol increased the proportion of people who had a ventricular rate under 100 beats/minute compared with placebo. The most common adverse effects were bradycardia (2%) and hypotension (9%). [67] We found one systematic review comparing beta-blockers versus placebo in people with acute or chronic atrial fibrillation. [52] It found that, in 7/12 (58%) comparisons at rest, and in all during exercise, beta-blockers reduced ventricular rate compared with placebo.

OPTION VERAPAMIL FOR RATE CONTROL

- For GRADE evaluation of interventions for Atrial fibrillation (acute onset), see table, p 42 .
- We don't know whether verapamil is effective at controlling heart rate, but it is unlikely to restore sinus rhythm.
- Verapamil has been associated with ventricular arrhythmias, hypotension, and exacerbation of heart failure.

Benefits and harms

Verapamil versus placebo:

We found no systematic review or RCTs on the use of verapamil versus placebo for heart-rhythm control in people with acute atrial fibrillation of <7 days' duration.

Comment: See comment on Diltiazem, p 34 .

Verapamil versus placebo:

Two RCTs found that intravenous (iv) verapamil reduced heart rate at 10 and 30 minutes compared with placebo in people with atrial fibrillation or atrial flutter. [58] [68] The first RCT (duration of atrial fibrillation not stated) reported that iv verapamil caused a transient drop in systolic and diastolic blood pressure greater than with placebo (saline), which did not require treatment, but it did not state the number of people affected. [68] The second RCT reported development of 1:1 flutter in one person with previous Wolff-Parkinson-White syndrome and 2:1 flutter. [58]

Verapamil versus diltiazem:

We found one small, double-blind, crossover RCT (17 men, 5 with acute atrial fibrillation, 10 with atrial flutter, and 2 with a combination of atrial fibrillation and atrial flutter; ventricular rate at least 120 beats/minute, systolic blood pressure at least 100 mmHg), which compared iv verapamil versus iv diltiazem and found no difference in rate control or measures of systolic function. [69] In the RCT, three people who received verapamil developed symptomatic hypotension and were withdrawn from the study before crossover. [69] Two people recovered, but the episode in the third person was considered life-threatening. In people with Wolff-Parkinson-White syndrome, verapamil may increase ventricular rate, and can cause ventricular arrhythmias. [57] Rate-limiting calcium channel blockers may exacerbate heart failure and hypotension.

OPTION SOTALOL FOR RATE CONTROL

- For GRADE evaluation of interventions for Atrial fibrillation (acute onset), see table, p 42 .
- We found no clinically important results about the effects of sotalol on controlling heart rate in people with acute atrial fibrillation who are haemodynamically stable.
- We don't know whether sotalol is effective at controlling heart rate in people with acute atrial fibrillation who are haemodynamically stable.
- Sotalol may cause arrhythmias at high doses.

Benefits and harms

Sotalol:

We found no systematic review or RCTs on the effects of sotalol to control heart rate in people with acute atrial fibrillation of up to 7 days' duration who are haemodynamically stable.

Comment: See Comment on the Anti-arrhythmic effects of sotalol, p 28 .

GLOSSARY

Chronic atrial fibrillation Refers to more sustained or recurrent forms of atrial fibrillation, which can be subdivided into paroxysmal, persistent, or permanent atrial fibrillation.

Wolff–Parkinson–White syndrome Occurs when an additional electrical pathway exists between the atria and ventricles as a result of anomalous embryonic development. The extra pathway may cause rapid arrhythmias. Worldwide, it affects about 0.2% of the general population. In people with Wolff–Parkinson–White syndrome, beta-blockers, calcium channel blockers, and digoxin can increase the ventricular rate and cause ventricular arrhythmias.

Atrial flutter A similar arrhythmia to atrial fibrillation, but the atrial electrical activity is less chaotic and has a characteristic saw-tooth appearance on an electrocardiogram.

High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Paroxysmal atrial fibrillation If the atrial fibrillation recurs intermittently with sinus rhythm, with spontaneous recurrences or termination, it is designated as 'paroxysmal', and the objective of management is suppression of paroxysms and maintenance of sinus rhythm.

Permanent atrial fibrillation If cardioversion is inappropriate, and has not been indicated or attempted, atrial fibrillation is designated as 'permanent', where the objective of management is rate control and antithrombotic treatment.

Persistent atrial fibrillation When atrial fibrillation is more sustained than paroxysmal, atrial fibrillation is designated "persistent" and needs termination with pharmacological treatment or electrical cardioversion.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Bisoprolol for rate control New option. No evidence found. Categorised as unknown effectiveness.

Metoprolol for rate control New option. No evidence found. Categorised as unknown effectiveness.

Atenolol for rate control New option. No evidence found. Categorised as unknown effectiveness.

Nebivolol for rate control New option. No evidence found. Categorised as unknown effectiveness.

Carvedilol for rate control New option. No evidence found. Categorised as unknown effectiveness.

Direct current cardioversion for rhythm control New RCT added. [50] Categorisation unchanged (likely to be beneficial).

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Competing interests: GYHL has received research funding and honoraria from various pharmaceutical companies in relation to atrial fibrillation for meetings and educational symposia. In addition, he is a member of advisory boards and trial steering committees. He was clinical adviser to the NICE Guidelines on AF management, and on the writing group for the American College of Chest Physicians Guidelines on Antithrombotic Therapy. SA declares that he has no competing interests.
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Disclaimer

GRADE **Evaluation of interventions for Atrial fibrillation (acute onset).**

Important outcomes **Control of heart rate, Conversion to sinus rhythm, Mortality**

Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
What are the effects of interventions for conversion to sinus rhythm in people with recent-onset atrial fibrillation who are haemodynamically stable?									
5 (1031) [20] [21] [22] [23] [24]	Conversion to sinus rhythm	Flecainide versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
4 (727) [20] [21] [23] [25]	Conversion to sinus rhythm	Flecainide versus amiodarone	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results; directness point deducted for inclusion of different regimens
3 (919) [23] [24] [25]	Conversion to sinus rhythm	Flecainide versus propafenone	4	–1	–1	–1	0	Very low	Quality point deducted for incomplete reporting of results; consistency point deducted for conflicting results; directness point deducted for inclusion of different regimens
10 (1226) [23] [24] [28] [29] [30] [31] [32] [33] [34]	Conversion to sinus rhythm	Propafenone versus placebo	4	0	0	0	0	High	
1 (123) [28]	Conversion to sinus rhythm	Propafenone versus digoxin	4	–2	0	0	0	Low	Quality points deducted for sparse data and short follow-up
4 (at least 500) [23] [25] [33] [35]	Conversion to sinus rhythm	Propafenone versus amiodarone	4	0	–1	–1	0	Low	Consistency point deducted for conflicting results; directness point deducted for differences in endpoints and regimens
6 (at least 600) [20] [21] [23] [33] [35] [42]	Conversion to sinus rhythm	Amiodarone versus placebo	4	–1	–1	–1	0	Very low	Quality point deducted for incomplete reporting of results; consistency point deducted for conflicting results; directness point deducted for difference in regimens
6 (399) [43] [44] [45] [46] [47] [48]	Conversion to sinus rhythm	Amiodarone versus digoxin	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of results; consistency point deducted for conflicting results
1 (140) [44]	Conversion to sinus rhythm	Amiodarone versus sotalol	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (24) [49]	Conversion to sinus rhythm	Amiodarone versus verapamil	4	–2	0	0	+1	Moderate	Quality points deducted for sparse data and short follow-up; effect size point added for relative risk (RR) >2
1 (247) [50]	Conversion to sinus rhythm	Direct current cardioversion versus chemical cardioversion	4	0	0	0	0	High	
4 (396) [28] [53] [54] [55]	Conversion to sinus rhythm	Digoxin versus placebo	4	0	0	–2	0	Low	Directness points deducted for wide inclusion criteria and for use of different regimens
What are the effects of interventions to control heart rate in people with recent-onset atrial fibrillation who are haemodynamically stable?									

Important outcomes			Control of heart rate, Conversion to sinus rhythm, Mortality						
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
1 (100) [43]	Control of heart rate	Amiodarone versus digoxin	4	–2	–1	0	0	Very low	Quality points deducted for sparse data and incomplete reporting of results; consistency point deducted for different results at different endpoints
2 (333) [53] [54]	Control of heart rate	Digoxin versus placebo	4	0	0	–1	0	Moderate	Directness point deducted for wide inclusion criteria

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.