National Institute for Health and Care Excellence

Final

Atrial fibrillation: diagnosis and management

Evidence review L: Treatment strategies for atrial fibrillation after cardiothoracic surgery

NICE guideline NG196

Intervention evidence review

April 2021

Final

Developed by the National Guideline Centre, Royal College of Physicians

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patientand, where appropriate,their carer or guardian.

Local commissioners andproviders have a responsibility to enable the guideline to be applied when individual health professionals and theirpatients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

Contents

1 Treatment strategies for atrial fibrillation after cardiothoracic surgery

1.1 Review question: What is the most clinical and cost effective treatment strategy (rate or rhythm control,or no treatment) for peoplewith atrial fibrillation after cardiothoracic surgery?

1.2 Introduction

Atrial fibrillation remains one of the most common adverse events to occur following cardiac surgery. Despite the improvement in the rate of other perioperative morbidities and mortality, however, the reported incidence of post-operative AF following cardiac surgery remains high (up to 30-50%) and has not changed significantly over recent years. Its incidence increases in those with an increased age, undergoing surgery of increased complexity or with a past history of AF, and is associated with a significant increase in perioperative morbidity, hospital length of stay, utilisation of health care resources and mortality.

The exact mechanisms of initiation and maintenance of post-cardiac surgery AF, however, are not fully understood and associated with this, a number of different treatment modalities and strategies (rate or rhythm control) have been proposed. A rate control strategy includes using medications (such as beta-blockers or calcium channel blockers) that reduce conduction across the atrioventricular node to slow the heart rate, whereas rhythm control strategies include using pharmacological agents (such as amiodarone) or electrical cardioversion in an attempt to restore sinus rhythm. Other considerations for these patients include identification and treatment of any triggers of atrial fibrillation, such as restoration of serum potassium and magnesium levels; anticoagulation, whilst balancing bleeding risks with thromboembolic risks; and the haemodynamic status of the patient, where early electrical cardioversion may be required in patients with hypotension or marked tachycardia.

Due to the absence of robust clinical studies, the implementation of these different management strategies varies considerably. This chapter intends to examine the clinical evidence surrounding the different therapeutic options used in the treatment of atrial fibrillation following cardiac surgery and develop some recommendations regarding how best to manage these patients.

1.3 PICO table

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

Table 1: PICO characteristics of review question

Population	People aged over 18 who have had cardiothoracic surgery and who have post-operative AF (stratified by pre-existing AF vs. no pre-existing AF)
Interventions	**Rate control strategies (lists below are not exhaustive):** • Beta blockers -for example, bisoprolol, acebutolol, metoprolol, nadolol, pindolol, betaspace, propranolol, esmalol • Ca2+ channel blockers – for example, diltiazem hydrochloride, verapamil • Digoxin • Amiodarone*

	Rhythm control strategies (lists below are not exhaustive): • Na+ channel blockers – such as procainamide, disopyramide, quinidine sulphate, flecainide, propafenone • K+ channel blockers – such as amiodarone*, dronedarone, ibutilide, sotalol • DC cardioversion *amiodarone may be used for rate or rhythm control.
Comparisons	• Placebo • No treatment • To each other (between classes of intervention – i.e. beta blockers vs Ca channel blockers, or digoxin versus DC cardioversion). • RCTs where individuals in the intervention group may be prescribed different rate or rhythm drugs are allowed. No comparisons within classes will be included (i.e. bisoprolol versus pindolol, or procainamide versus flecainide)
Outcomes	**Critical** • health-related quality of life • mortality • stroke or thromboembolic complications • Need for rescue DC cardioversion • Rehospitalisation (all cause) • Rehospitalisation for AF • Achievement of sinus rhythm • Adverse events **Important** • freedom from anticoagulation • freedom from AAD use • Hospital length of stay • ICU length of stay
Study design	Randomised controlled trials and systematic reviews of RCTs

1.4 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual.[83]Methods specific to this review question are described in the review protocol in Appendix A:.

1.5 Clinical evidence

1.5.1 Included studies

A search was conducted to identify randomised controlled trials or systematic reviews of randomised controlled trials comparing different strategies for treating atrial fibrillation after cardiothoracic surgery, including rate control (beta-blockers, calcium channel blockers, digoxin and amiodarone), rhythm control (Na+ blockers, K+ blockers and DC cardioversion) and no treatment strategies. The population could include those developing atrial fibrillation after surgery and also those with pre-existing atrial fibrillation prior to the surgery – population strata were used to stratify for the presence or absence of pre-existing atrial

fibrillation prior to surgery from the outset of the review. Fifteen studies (from sixteen papers) were included in the review;[12, 13, 15, 31, 35, 37, 51, 64, 67, 68, 84, 89, 100, 101, 110, 111]these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (Tables3-17).

See also the study selection flow chart in Appendix C:, study evidence tables in Appendix D:, forest plots in Appendix E:andGRADE tables in Appendix F:.

The majority of studies (eleven studies from twelve papers) included in this review were within the no pre-existing atrial fibrillation stratum, where in most cases the presence of atrial fibrillation prior to the cardiothoracic surgery was an exclusion criterion. Of the remaining four papers, three were within the pre-existing atrial fibrillation stratum and one was assigned to the mixed/unclear stratum as there were limited details to assign it to one of the two other strata.

The included studies covered the following comparisons between the interventions listed in the protocol for this review:

Mixed/unclear stratum:

- One study compared calcium channel blockers (intravenous verapamil) with intravenous placebo;[37]

No pre-existing AF stratum:

- One study compared DC cardioversion with K+ blockers (intravenous amiodarone); [31]
- One study compared K+ blockers (intravenous amiodarone) with intravenous digoxin;[15]
- Two studies compared K+ blockers (intravenous followed by oral amiodarone) with K+ blockers + ranolazine (intravenous amiodarone and oral ranolazine, followed by oral amiodarone and oral ranolazine);[100, 101]
- One study compared a mixed rate control strategy (specific drugs not stated, oral administration likely but not clear) with K+ blockers (amiodarone recommended, oral administration) +/-a rate control agent (specific drugs not stated, oral administration likely but not clear);[35]
- One study (covered by two papers) compared a mixed rhythm control strategy (such as sotalol, propafenone or procainamide, route of administration dependent on drug used) +/- electrical cardioversion with a mixed rate control strategy (such as diltiazem, verapamil, metoprolol, atenolol, propranolol, esmolol or digoxin - route of administration dependent on drug used and patient);[67, 68]
- One study compared Na+ blockers (intravenous flecainide) with intravenous digoxin[111]
- One study compared Na+ blockers (oral propafenone) with K+ blockers (intravenous amiodarone);[84]
- One study compared calcium channel blockers(intravenous verapamil)with intravenous placebo;[51]
- One study compared K+ blockers (intravenous vernakalant) with intravenous placebo;[64]
- One study compared K+ blockers (amiodarone) with routine medical treatment alone;[12]

Pre-existing AF stratum:

- One study compared DC cardioversion (oral amiodarone for four days prior to cardioversion) with K+ blockers + captopril + simvastatin (oral amiodarone with captopril and simvastatin);[13]

- One study compared a mixed rate control strategy (digoxin and/or diltiazem, route unclear but likely to be oral based on study length) with K+ blockers + captopril + simvastatin(oral amiodarone with captopril and simvastatin);[89]
- One study compared K+ blockers(intravenous followed by oral amiodarone) + DC cardioversion with placebo (unclear if given intravenously followed by orally as with amiodarone) + DC cardioversion;[110]

It is also noted that studies which included intravenous use of certain drugs (including diltiazem, sotalol, disopyramide and propafenone) that are only available in the UK in oral form and not used intravenously were not included in the review. One study(from two papers)that compared a mixed rhythm control strategy +/- electrical cardioversion with a mixed rate control strategy was downgraded for intervention indirectness, as one of the options within the mixed rate control strategy was the use of intravenous diltiazem but the proportion of patients that received this as their rate control strategy was unclear[67, 68].

1.5.2 Excluded studies

See the excluded studies list in Appendix I:.

1.5.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Chen2013[13] RCT N=115 Conducted in China	**DC cardioversion:** Initial 200mg amiodarone three times daily for four days. Electrical defibrillation was performed on fifth day. Once unconscious, patients received direct-current synchronized electrical cardioversion using an initial energy level of 200 J. If the first shock failed, two 300 J shocks were given. Electrical treatment was stopped if sinus rhythm was not restored within three shocks. After reversion to normal rhythm, 200 mg amiodarone was taken daily for 30 days **K+ blockers + captopril + simvastatin:** Oral amiodarone with captoptri land simvastatin. Three months combination therapy with oral amiodarone at a dose of 600 mg/day for 3 days, 400 mg/day for the following 3 days and then 200 mg/day, oral captopril at a dose of 12.5 mg twice daily before	**Pre-existing AF stratum: those with pre-existing permanent AF prior to mitral valve replacement operation.** Inclusion criteria: • Age >18 years with permanent AF • Undergone prosthetic mitral valve replacement with or without aortic valve replacement • Cardiothoracic ratio ≤0.5 on cardiac anterioposterior X-radiography and a left atrial diameter ≤50 mm on Doppler ultrasound for ≥6 months post-surgery Exclusion criteria: • New York Heart Association heart failure class IV • History of sick sinus syndrome or second-	• Mortality • Rehospitalisation for AF • Achievement of sinus rhythm • Adverse events	All patients received standard long-term anticoagulant therapy with warfarin and/or digoxin following surgery.

Study	Intervention and comparison	Population	Outcomes	Comments
	food and oral simvastatin at a dose of 15 mg/day at night.	or third-degree atrioventricular block • Severe hepatic and/or renal dysfunction • Hyperthyroidism • Contraindications to treatment with amiodarone Population characteristics: • Mean (SD) duration of AF: 54.2 (25.9) vs. 53.5 (25.4) months • Mean (SD) LVEF: 58.6 (6.5) vs. 58.2 (6.2)%		
Chen 2019[12] RCT N=84 Conducted in China	**K+ blockers(amiodarone):**On the day of the operation, a micro infusion pump administered 600 mg amiodarone at 50 mg/h for 12 h. On postoperative day 1, amiodarone taken orally following recovery of diet 3 times daily. A week later, patients took amiodarone 2 times daily. Another week later, the dose was reduced to once daily. Treatment course was 1 month. Also received routine medical treatment as described in the control group. **Routine medical treatment:**	**No pre-existing AF stratum: states AF developed following valve replacement** Inclusion criteria: • Elective valvular replacement • Rheumatic heart disease with continuous atrial fibrillation • Cardiac function no higher than grade III • Satisfied application indication for amiodarone	• Achievement of sinus rhythm • Hospital length of stay • ICU length of stay	

Study	Intervention and comparison	Population	Outcomes	Comments
	Routine treatment consisted of oral administration of drugs for diuresis, anticoagulation and routine application of antibiotics.	• Normal levels of electrolytes and acidity and alkalinity • Heart rate <70 bpm Exclusion criteria: • Presence of other types of arrhythmia Population characteristics: • Mean (SD) duration of AF: 30 (14.93) vs. 31.06 (15.02) months • Mean (SD) left ventricular ejection fraction: 46.7 (4.32) vs. 47.5 (4.03)% • Mean (SD) New York Heart Association score: 2.50 (0.51) vs. 2.58 (0.50)		
Cochrane 1994[15] RCT N=30 Conducted in Australia	**K+ blockers:** Intravenous amiodarone. Loading dose of 5 mg/kg (max. 400 mg) in 100 ml of 5% dextrose infused intravenously over 30 min. At 30 min after loading dose complete, infusion of 25 mg/h initiated. Infusion increased to 40 mg/h if ventricular rate still	**No pre-existing AF stratum: AF prior to surgery was an exclusion criterion** Inclusion criteria: • People that developed AF persisting for >20 min with systolic	• Need for rescue DC cardioversion • Achievement of sinus rhythm • Adverse events	

Study	Intervention and comparison	Population	Outcomes	Comments
	exceeded 120 beats/min after 6 h. Treatment continued for 24 h after reversion to sinus rhythm. If no reversion following 24 h of intravenous amiodarone infusion, digoxin was added at half the dose used in the digoxin treatment group **Digoxin:** Intravenous digoxin. Loading dose of 1 mg given intravenously over 9 h as follows: 0.5 mg over 30 min at start of treatment, followed by 0.25 mg after 2 h and 0.125 mg after 5 h and 9 h. Oral maintenance therapy started within 12 h at a dose suitable for body weight and renal function. If reversion did not occur during 24 h treatment period amiodarone was added at dose described for amiodarone group and digoxin continued at half the previous dose	blood pressure of ≥85 mmHg without inotropic support, while recovering from open heart surgery Exclusion criteria: • AF prior to surgery • Poor ventricular contractility on preoperative left venticulogram • Postoperative administration of beta-blockers Population characteristics: • Operation type: coronary artery bypass grafting(73 vs. 67%), aortic valve replacement(20 vs. 20%), mitral valvotomy(7 vs. 0%)or combined procedures(0 vs. 13%) • Pre-operative beta-blockade: 47 vs. 53%		

Study	Intervention and comparison	Population	Outcomes	Comments
Fitzgerald 2008[31] RCT N=18 Conducted in Austria	**DC cardioversion** ALERT catheter for intracardiac conversion. Sedation with midazolam (3-5 mg intravenously) and intracardiac cardioversion. ALERT system provides temporary pacing, sensing and delivery of stimuli for internal cardioversion. First shock with 3 J. Following each shock, 12-lead ECG was obtained to assess sinus rhythm. If rhythm was not converted, shock energy was increased by increments of 3 J to a maximum of 15 J. If no response after 15 J shock, the patient was classified as being not responsive. When awake and haemodynamically stable patients were returned to the ward. Non-responders received treatment according to the preference of the doctor in charge and were excluded from further evaluation **K+ blockers** Standard pulmonary artery catheter for delivery of intravenous amiodarone. Bolus	**No pre-existing AF stratum: chronic AF and conduction disorders were exclusion criteria** Inclusion criteria: • Undergoing coronary artery bypass grafting or valve surgery • Postoperative AF development Exclusion criteria: • Chronic atrial fibrillation • Conduction disorders • Patients with pacemakers Population characteristics: • Type of surgery: CABG (44 vs. 56%), aortic valve (22 vs. 22%), mitral valve (11 vs. 11%), CABG + valve (22 vs. 11%) • NYHA class: I (11 vs. 11%), II (56 vs. 67%), III (22 vs.	• Need for rescue DC cardioversion • Achievement of sinus rhythm	**In both groups:** Patients allowed treatment with intravenous digoxin if tachycardia led to haemodynamic instability at any time prior to the intervention. If this treatment was not successful in establishing stability and further treatment was required, patients were excluded from further evaluation

Study	Intervention and comparison	Population	Outcomes	Comments
	dose of 250 mg followed by continuous infusion of 0.6 mg/kg/h. Duration unclear.	11%), IV (11 vs. 11%) • Median (range) ejection fraction: 53 (31-74) vs. 59 (36-68)%		
Gillinov2016[35] RCT N=523 Conducted in Canada and USA	**Mixed rate control** Received medications to slow heart rate with aim of achieving a resting heart rate <100 beats/min. Patients in whom sinus rhythm was not restored after rate control could be switched to rhythm control if provider thought necessary to improve haemodynamic status or alleviate symptoms. Duration 60 days. No further details on the interventions given. **K+ blocker with/without rate control agent** Amiodarone with or without rate-slowing agent. If atrial fibrillation persisted for 24-48 h after randomisation, direct current cardioversion was recommended.	**No pre-existing AF: History of AF was an exclusion criterion** Inclusion criteria: • Haemodynamically stable adults • Undergone elective surgery to treat coronary artery disease or heart valve disease • Postoperative atrial fibrillation persisting for >60 min or recurrent episodes of atrial fibrillation during index hospitalisation Exclusion criteria: • History of atrial fibrillation Patient characteristics: • Diabetes: 31.3 vs. 30.3%	• Rehospitalisation, all-cause • Mortality • Stroke or thromboembolic complications • Need for rescue DC cardioversion • Rehospitalisation for AF • Achievement of sinus rhythm • Adverse events • Hospital length of stay • Freedom from anticoagulation	**For both groups:** If patients remained in atrial fibrillation or had recurrent atrial fibrillation 48 hafter randomization, anticoagulation with warfarin (target international normalized ratio, 2 to 3) was recommended, and bridging with low-molecular-weight heparin was allowed. Anticoagulation was recommended to be continued for 60 days, unless complications occurred

Study	Intervention and comparison	Population	Outcomes	Comments
	Recommended dose of amiodarone was 3 g of oral amiodarone before hospital discharge with a maintenance dose of 200 mg/day or less if direct current cardioversion was successful. It was recommended that the use of amiodarone be extended for 60 days, but discontinuation was allowed for amiodarone-related adverse events, such as bradycardia, corrected QT interval >480 msec or neuropathy	• Heart failure: 13.4 vs. 12.6% • Hypertension: 73.7 vs. 75.9% • Previous myocardial infarction: 19.1 vs. 18.4% • Previous stroke: 6.5 vs. 5.7% • Medication: ACE inhibitor (34 vs. 32.2%), ARB (19.5 vs. 18%), beta-blocker (61.8 vs. 55.6%), calcium channel blocker (19.8 vs. 22.2%), diuretic (30.2 vs. 31%), nitrate (22.9 vs. 21.1%) • Index operation: CABG only (42.7 vs. 38.3%), valve repair only (14.9 vs. 16.5%), CABG + valve repair (3.8 vs. 2.7%), valve replacement only (22.9 vs. 25.3%), CABG + valve replacement (15.6 vs. 17.2%)		
Gray 1982[37] RCT	**Calcium channel blockers** Intravenous verapamil. Low-dose verapamil (0.075 mg/kg	**Mixed/unclear stratum: 18.1% had history of atrial tachyarrhythmias**	• Adverse events	Those that did not achieve positive response with first drug were switched over to the other

Study	Intervention and comparison	Population	Outcomes	Comments
N=22 Conducted in USA	body weight, up to maximum of 10 mg) administered as bolus intravenous injection over 1 min. **Placebo** Intravenous placebo. Volume of placebo similar to that used in verapamil administration was administered as bolus intravenous injection over 1 min.	Inclusion criteria: • Development of supraventricular tachyarrhythmias (atrial fibrillation, atrial flutter or atrial tachycardias) following open heart surgery. Exclusion criteria: • Age >74 years or <21 years • Evidence of renal or hepatic failure • Received propanolol24 h previously Patient characteristics (not given separately for each group): • Arrhythmia type: Atrial fibrillation, 81.8%; atrial flutter, 18.2% • Type of surgery: CABG, 86.4%; double valve (aortic and mitral) replacement, 9.09%; mitral commissurotomy		drug, which may affect outcomes. Analysed as randomised in review unless stated otherwise. For both groups: • A positive response was observed if the patient converted to sinus rhythm or the heart rate decreased below 100 bpm (120 bpm in digoxin-treated patients). • If no positive response was seen within 10 min, a higher dose of the initial intervention was administered consisting of 0.15 mg/kg verapamil or placebo equivalent. • If no response was seen after 15 min, drug B (placebo or verapamil) was administered first in low dose and then in high dose as described for each intervention. Digoxin had been given in 20 patients (mean dose 0.5 mg) within the 24 h prior to verapamil administration (when verapamil used either as first drug or when used as second drug if placebo failed)

Study	Intervention and comparison	Population	Outcomes	Comments
		and aortic valve replacement, 4.56% • Digoxin had been given in 20 patients (mean dose 0.5 mg) within the 24 h prior to verapamil administration (when verapamil used either as first drug or when used as second drug if placebo failed)		
Hwang 1984[51] RCT N=14 Conducted in USA	**Calcium channel blockers** Intravenous verapamil. First dose of0.075 mg/kg given intravenously over 1 min. If therapeutic end point was not achieved after 15 min, administration of verapamil was repeated at a dose of 0.15 mg/kg, up to a maximum of 10 mg. After a further 30 min, if therapeutic end point not achieved, the second drug (placebo) was administered in a similar fashion **Placebo** Intravenous placebo. First dose of 0.075 mg/kg placebo given intravenously over 1 min.	**No pre-existing AF stratum: being in normal sinus rhythm prior to and immediately after surgery was inclusion criterion.** Inclusion criteria: • Presence of sinus rhythm prior to and immediately following surgery • Development of supraventricular tachycardia with a ventricular response >120 beats/min during postoperative period and persisting for at least 1 h Exclusion criteria:	• Achievement of sinus rhythm • Adverse events	Those that did not achieve positive response with first drug were switched over to the other drug, which may affect outcomes. Analysed as randomised in review unless stated otherwise.

Study	Intervention and comparison	Population	Outcomes	Comments
	If therapeutic end point was not achieved after 15 min, administration of placebo was repeated at a dose of 0.15 mg/kg, up to a maximum of 10 mg. After a further 30 min, if therapeutic end point not achieved, the second drug (verapamil) was administered in a similar fashion	• Preoperative left ventricular ejection fraction <45% or clinical postoperative cardiac failure • Hypotension (<systolic pressure below 90 mmHg) • Notable valvular heart disease • Impaired atrioventricular conduction or evidence of depressed sinus node automaticity • Impaired hepatic or renal function • Administration of beta-blocking drugs or disopyramide within previous 48 h Patient characteristics (not given separately for each group): • Arrhythmia type: atrial fibrillation, 78.6%; atrial flutter, 21.4% • Mean (range) preoperative LVEF: 62 (49-74)% • Type of surgery: aortocoronary		

Study	Intervention and comparison	Population	Outcomes	Comments
		bypass, 85.7%; aortocoronary bypass + thymectomy, 7.1%; atrial septal defect closure, 7.1%		
Kowey2009[64]	**K+ blockers** Infusion of 3.0 mg/kg vernakalant over 10 min followed by 15 min observation period. Second infusion of 2.0 mg/kg vernakalant performed over 10 min if did not convert to sinus rhythm. **Placebo** Infusion of 3.0 mg/kg placebo (normal saline) over 10 min followed by 15 min observation period. Second infusion of 2.0 mg/kg placebo performed over 10 min if did not convert to sinus rhythm.	**No pre-existing AF stratum: being in normal sinus rhythm prior to and immediately after surgery was inclusion criterion.** Inclusion criteria: • ≥18 years old with sustained AF or flutter occurring between 24 h and 7 days following surgery. • Haemodynamically stable • Sinus rhythm before and after surgery • Weight between 46 and 136 kg Exclusion criteria: • Pregnancy or nursing • Uncorrected QT interval >500 ms • Ventricular response rate to AF <45 bpm	• Mortality • Achievement of sinus rhythm • Adverse events (serious and treatment-emergent)	Infusion was discontinued if one of various adverse effects were observed, such as uncorrected QT interval ≥550 ms or prolongation of the uncorrected QT interval >25%

Study	Intervention and comparison	Population	Outcomes	Comments
		• QRS interval >140 ms without pacemaker • Second or third-degree AV block • History of torsadesde pointes • Unstable class IV congestive heart failure, serious hepatic or renal disease, or end-stage disease states • Reversible cause of AF (e.g. hyperthyroidism or pulmonary embolism) • Uncorrected electrolyte imbalance • Digoxin toxicity • Received another investigational drug or IV vernakalant in past 30 days, received oral amiodarone with past 3 months, received IV amiodarone within past 24 h, or received class I or III antiarrhythmic drugs following cardiac surgery		

Study	Intervention and comparison	Population	Outcomes	Comments
Lee 2000[68]and Lee 2003[67] RCT N=50 Conducted in Canada	**Mixed rhythm control with/without electrical cardioversion** Antiarrhythmic drug therapy with or without electrical cardioversion. Aimed at restoration of sinus rhythm within 48 h. Preferred initial treatment was with sotalol or propafenone, taking into consideration left ventricular function, history of coronary artery disease and contraindications to beta-blockers. Sotalol prescribed at dose of 120-360 mg/day; amiodarone at 200 mg/day after a loading dose of 1200-1600 mg for 4-5 days; and propafenone at dose of 300-900 mg/day. Procainamide given as intravenous load of 500-1000 mg followed by continuous infusion of 1-4 mg/h or 2-3 g/day in divided oral doses. If sinus rhythm was not achieved within 48 h, patients were electrically cardioverted Rate control therapy used in rate control group were	**No pre-existing AF stratum: those with history of paroxysmal AF or conduction disturbances at randomisation excluded** Inclusion criteria: • Development of atrial fibrillation lasting at least 1 h following heart surgery • Ability to give informed consent • 18 years of age or above Exclusion criteria: • History of paroxysmal atrial fibrillation • Received antiarrhythmic therapy within 5 half-lives of the time of randomisation • Had beta-blockers withdrawn after surgery • Were in cardiogenic shock • Creatinine level of >200 µg/mmol	• Mortality • Achievement of sinus rhythm • Hospital length of stay	**For both groups:** Intravenous heparin and oral warfarin started within 24 h after randomisation. • Dose of heparin was titrated to maintain a partial thromboplastin time between 80 and 100 seconds. • Warfarin doses adjusted to obtain an INR between 2 and 3. • Anticoagulation continued until end of study

Study	Intervention and comparison	Population	Outcomes	Comments
	permitted if clinically indicated (e.g. ventricular rates ≥110 per min) and in patients who received propafenone because of potential for 1:1 AV conduction during atrial fibrillation. **Mixed rate control** Preferred initial treatment was IVdiltiazem for those requiring IVagent on basis of symptom severity and beta-blockers in those treated with oral agents. • IV diltiazem administered as initial bolus of 5-20 mg followed by continuous infusion of 5-15 mg/h. • Oral diltiazem given at 120-360 mg/day and verapamil given orally in similar fashion. • Metoprolol given at dose of 25-100 mg/day in 2 divided doses • Atenolol given at dose of 25-100 mg/day • Propanolol given at a dose of 30-120 mg in 3 divided doses • Esmolol given at 0.05 mg/kg per minute intravenous loading	• Serum aspartate aminotransferase or alanine aminotransferase concentrations 4 times the upper limit of normal; • Conduction disturbances before randomisation • Contraindications to anticoagulation Patient characteristics: • Mean (SD) LVEF: 49 (1) vs. 47(11)% • Preoperative beta-blockers: 63 vs. 61% • Preoperative calcium channel blockers: 63 vs. 36% • Valvular surgery: 30 vs. 30% • Diabetes: 19 vs. 23% • Hypertension: 48 vs. 52%		

Study	Intervention and comparison	Population	Outcomes	Comments
	followed by maintenance dose of 0.05-0.2 mg/kg per minute. • Digoxin loading administered either intravenously or orally: ○ Oral loading dose of 0.25-0.5 mg digoxin was given followed by 0.25 mg every 4-6 hours until a loading dose of1 mg had been given. ○ Intravenous digoxin administered in similar fashion. ○ Daily maintenance dose of 0.25 mg was administered thereafter for digoxin			
Nemati 2016[84] RCT N=122 Conducted in Iran	**Na+ blockers** Oral propafenone. 600 mg loading dose and 150 mg every 8 h for 10 days after onset of atrial fibrillation.	**No pre-existing AF stratum: History of AF within previous 6 months an exclusion criterion. <10% with AF history before this period.** Inclusion criteria:	• Need for rescue DC cardioversion • Achievement of sinus rhythm • Adverse events	If the treatment strategy patients were assigned to did not resolve the AF after 10 days, treatment with drug could be repeated or switched to other drug, which could affect outcomes. Analysed as randomised in the review unless otherwise stated.

Study	Intervention and comparison	Population	Outcomes	Comments
	If AF did not resolve after this first dosing strategy, it could be repeated or switched to amiodarone **K+ blockers** Intravenous amiodarone. 300 mg intravenous loading dose followed by continuous intravenous infusion of 600 mg over 12-24 h after the onset of atrial fibrillation. If AF did not resolve after this first dosing strategy, it could be repeated or switched to propafenone	• Development of postoperative atrial fibrillation (continuous AF for at least 30 min or AF requiring treatment for symptoms or hemodynamic compromise) following elective coronary artery bypass grafting Exclusion criteria: • Patients that underwent concomitant cardiac operations at same time as coronary artery bypass grafting • Bradycardia (<50 beats/min in resting position) • Patients with > type I second-degree heart block • Symptomatic sick sinus syndrome without a pacemaker • Taking class I or III antiarrhythmic medications • History of AF within past 6 months		

Study	Intervention and comparison	Population	Outcomes	Comments
		• Sensitivity to propafenone • Cardiogenic shock • Ejection fraction <30% • Marked hypotension (systolic blood pressure <90 mmHg) • Electrolyte imbalances Patient characteristics: • All underwent CABG surgery • Hypertension: 70.9 vs. 77.6% • Hyperlipidaemia: 69.1 vs. 67.2% • Diabetes mellitus: 50.9 vs. 49.3% • Congestive heart failure: 0 vs. 3.1% • Previous atrial fibrillation: 9.1 vs. 3.2% • Drugs: beta-blockers (87.3 vs. 80.6%), calcium channel blockers (9.1 vs. 12.5%), ACE inhibitor (34.5 vs. 25.8%)		

Study	Intervention and comparison	Population	Outcomes	Comments
Qian 2008[89] RCT N=99 Conducted in China	**Mixed rate control** Control of ventricular rate using digoxin and diltiazem, either alone or in combination. Doses of drugs not stated. Appears to be oral dosing based on length of the study but not explicitly stated Duration, 12 months. **K+ blockers + captopril +simvastatin** Pharmacological cardioversion with low-dose oral amiodarone (2 mg/kg), captopril (0.25 mg/kg) and simvastatin (0.3 mg/kg) administered daily. Heart rate was maintained at 60-80 beats/min under quiescent conditions. If needed, digoxin and/or diltiazem were also administered in these patients Duration, 12 months.	**Pre-existing AF: duration of AF longer than time since surgery, indicating AF present prior to surgery** Inclusion criteria: • >18 years of age • Permanent atrial fibrillation for at least 6 months following prosthetic mitral valve replacement Exclusion criteria: • Moderate or severe tricuspid regurgitation • NYHA heart failure class IV • History of sick sinus syndrome or second- or third-degree atrioventricular block • Significant thyroid, pulmonary or hepatic disease • Contraindications to treatment with amiodarone • Significant impairment of renal function • Pregnancy or females shortly	• Achievement of sinus rhythm • Adverse events	

Study	Intervention and comparison	Population	Outcomes	Comments
		intending to become pregnant • Any other medical condition that in the opinion of the investigators could make the patient inappropriate for the study Patient characteristics: • All received mitral valve surgery • Mean (SD) duration of AF: 35.7 (16.1) vs. 36.3 (17.5) months • Mean (SD) LVEF: 46 (13.1) vs. 45.7 (12.1)%		
Simonpoulos2014[101] RCT N=41 Conducted in Greece	**K+ blockers** IVamiodarone. 300 mg in 30 min followed by 750 mg in 24 h. After conversion to sinus rhythm the amiodarone infusion was stopped but received amiodarone orally at a dose of 200 mg twice daily for a week and 200 mg once daily for the second week, or according to their cardiologist's advice following discharge **K+ blockers + ranolazine**	**No pre-existing AF stratum: history of AF an exclusion criterion** Inclusion criteria: • Development of postoperative atrial fibrillation following elective on-pump coronary artery bypass grafting Exclusion criteria: • History of AF	• Achievement of sinus rhythm	**For both groups:** All patients after extubation and until discharge received a standard drug regimen that included acetylsalicylic acid (100 mg daily), atorvastatin (20-40 mg daily), the beta-blocker metoprolol (50-100 mg daily), and the angiotensin-converting enzyme inhibitor perindopril (5-10 mg daily), in addition to each patient's individual treatment based on his or her personal medical history

Study	Intervention and comparison	Population	Outcomes	Comments
	IV amiodarone at 300 mg in 30 min followed by 750 mg in 24 h. Oral ranolazine regimen consisted of 500 mg loading dose followed by 375 mg 6 hours later and then 375 mg twice daily. After conversion to sinus rhythm the amiodarone infusion was stopped but received amiodarone orally at a dose of 200 mg twice daily for a week and 200 mg once daily for the second week, or according to their cardiologist's advice following discharge. Ranolazine 375 mg twice daily was also continued.	• Prior antiarrhythmic therapy Patient characteristics: • CABG surgery in all patients • Mean (SD) LVEF: 52.6 (8.6) vs. 53.8 (9.4)% • Diabetes: 40 vs. 38% • Renal insufficiency: 15 vs. 14.28%		
Simonpoulos2018[100] RCT N=812 Conducted in Greece	**K+ blockers** IV amiodarone. Loading dose of 300 mg in 30 min followed by 750 mg in 24 h. If arrhythmia was sustained after 24 h, further 375 mg given in 12 h. Maximum recording period of 36 h. After conversion to sinus rhythm amiodarone infusion was discontinued and treatment with amiodarone 200 mg t.i.d was continued until hospital discharge	**No pre-existing AF stratum: persistent or permanent AF in previous 6 months exclusion criterion** Inclusion criteria: • Those that underwent coronary artery bypass grafting • Development of atrial fibrillation 2-3 days following operation	• Achievement of sinus rhythm	**For both groups:** On first postoperative day, all given LMWH and acetylsalicylic acid 100 mg once daily, which was continued during the AF and conversion to sinus rhythm. Where sinus rhythm was not restored with 36 h, anticoagulation was changed to acenocoumarol4 mg and adjusted according to INR

Study	Intervention and comparison	Population	Outcomes	Comments
	K+ blockers + ranolazine IVamiodarone + oral ranolazine. Amiodarone loading dose of 300 mg in 30 min followed by 750 mg in 24 h. If arrhythmia was sustained after 24 h, further 375 mg given in 12 h. Maximum recording period of 36 h. 500 mg ranolazine was administered once at time of randomisation, followed by 375 mg 6 h later and subsequently 375 mg twice daily. After conversion to sinus rhythm amiodarone infusion was discontinued and treatment with amiodarone 200 mg t.i.dand375 mg b.i.dranolazine was continued until hospital discharge	Exclusion criteria: • Previously documented persistent of permanent AF in last 6 months prior to surgery • ReceivingCYP3A inhibitors or inducers • History of hepatic or renal failure Patient characteristics: • All underwent CABG surgery • Mean (SD) LVEF: 42.65 (8.98) vs. 43.24 (9.7)% • Prior myocardial infarction: 53.8 vs. 59% • Type II diabetes: 54.6 vs. 53.8% • Hypertension: 58.5 vs. 54.3% • Medications: • Beta-blockers: 84.0 vs. 81.8% • Digoxin: 0.2 vs. 0% • ACE inhibitors/ARBs: 65.9 vs. 66.8% • Statins: 58.3 vs. 68.6%		

Study	Intervention and comparison	Population	Outcomes	Comments
		• Dihydropyridines: 24.7 vs. 32.9%		
Vilvanathan2016[110] RCT N=89 Conducted in India	**K+ blockers + DC cardioversion** Amiodarone + DC cardioversion. DC cardioversion performed 48 h after balloon mitral valvuloplasty. Cardioversion: • Prior to DC cardioversion, patients sedated and given analgesia. • Synchronised DC cardioversion was given using biphasic defibrillators using the following protocol: 100J, 200J, 300J and 360 J. • Unsuccessful DC cardioversion was considered to include those who did not revert with 360J. K+ blockers: • Amiodarone was given as an intravenous bolus of 150 mg followed by a 1 g intravenous infusion for	**Pre-existing AF stratum: all had permanent AF for at least 3 months prior to mitral valvuloplasty** Inclusion criteria: • Aged >18 years • Underwent successful balloon mitral valvuloplasty • ECG evidence of atrial fibrillation for >3 months Exclusion criteria: • Prior history of cardioversion • Significant mitral, tricuspid or aortic regurgitation • Significant tricuspid or aortic stenosis • Left atrial thrombus (detected by transoesophageal echocardiography) • Left atrial diameter ≥6 cm • Inability to comply with 12 months follow-up period	• Health-related quality of life • Achievement of sinus rhythm • Adverse events	**For both groups:** Patients were anticoagulated with warfarin and INR was required to be between 2 and 3 for at least 1 month prior to DC cardioversion

Study	Intervention and comparison	Population	Outcomes	Comments
	12 h prior to DC cardioversion. • Following cardioversion, oral amiodarone was started initially 200 mg three times a day for 2 weeks, followed by 200 mg twice daily for 2 weeks and subsequently 200 mg once daily for 12 months **Placebo + DC cardioversion** Cardioversion: • DC cardioversion was performed 48 h after balloon mitral valvuloplasty. • Prior to DC cardioversion, patients were sedated and received analgesia. • Synchronised DC cardioversion was given using biphasic defibrillators using the following protocol: 100J, 200J, 300J and 360 J. • Unsuccessful DC cardioversion was considered to include	• Contraindications to anticoagulation or amiodarone Patient characteristics: • Mean (SD) duration of AF: 10.05 (5.718) vs. 10.27 (5.495) months • Hypertension: 4.5 vs. 6.7% • Diabetes: 4.5 vs. 2.2% • Hypertension + diabetes: 2.3 vs. 4.4% • Diabetes + coronary heart disease: 2.3 vs. 0% • NYHA class: I (20.5 vs. 4.4%), II (63.6 vs. 75.6%), III (11.4 vs. 13.3%) and IV (4.5 vs. 6.7%) • Concomitant drugs: • Beta-blockers: 48.9 vs. 43.2% • Calcium channel blockers: 24.4 vs. 22.7% • Digoxin: 64.4 vs. 68.2%		

Study	Intervention and comparison	Population	Outcomes	Comments
	those who did not revert with 360J. Placebo: • No preloading with amiodarone prior to DC cardioversion • Following DC cardioversion, patients received placebo for 12 months			
Wafa1989[111] RCT N=29 Conducted in UK	**Na+ blockers** Intravenous flecainide. Bolus of 1 mg/kg body weight over 10 min followed by an infusion of 1.5 mg/kg/h for 1 h and another infusion of 0.25 mg/kg/h for the rest of the 24 h study period A single dose of verapamil (10 mg intravenously) was given over a 5 min period if after 45 min reversion to sinus rhythm and adequate ventricular rate control (<100 beats/min) had not been achieved. **Digoxin** Intravenous digoxin. Bolus of 0.5 mg over 10 min followed after 6 and 12 h by bolus doses of 0.25 mg over 10 min	**No pre-existing AF: preoperative atrial arrhythmias an exclusion criterion** Inclusion criteria: • 18-80 years of age • CABG complicated within 96 h after surgery by atrial tachyarrhythmias (atrial fibrillation, atrial flutter or atrial tachycardia) lasting at least 15 min with a ventricular rate >120 beats/min Exclusion criteria: • Preoperative atrial arrhythmia	• Achievement of sinus rhythm • Adverse events	

Study	Intervention and comparison	Population	Outcomes	Comments
	A single dose of verapamil (10 mg intravenously) was given over a 5 min period if after 45 min reversion to sinus rhythm and adequate ventricular rate control (<100 beats/min) had not been achieved.	• Second- or third-degree atrioventricular block • Presence or history of bifascicular block or bundle branch block with any degree of atrioventricular block • Known sinus node dysfunction in the absence of a pacing wire • Impaired left ventricular dysfunction (as detected clinically and angiographically) • Treatment with other antiarrhythmics (including verapamil) during anaesthesia or since return to intensive care unit • Treatment with digoxin or beta-blockers in the 24h before entry into the study • Serious renal or hepatic disease • Receipt of any investigational drug		

Study	Intervention and comparison	Population	Outcomes	Comments
		during the 4-weeks prior to the study • Receipt of any antiarrhythmic agents within 3 elimination half-lives of the date of inclusion in the study Patient characteristics: • Type of operation: CABG alone (93.3 vs. 92.9%) and CABG + aortic valve replacement (6.7 vs. 7.1%) • Arrhythmia type: atrial fibrillation (100 vs. 85.7%) and atrial flutter (0 vs. 14.3%) • Coronary artery disease: 100% vs. 100% • Aortic valve disease: 6.7 vs. 7.1%		

See Appendix D:for full evidence tables.

1.5.4 Quality assessment of clinical studies included in the evidence review

Table 3: Clinical evidence summary: Evidence not suitable for GRADE analysis

Study	Intervention and comparator	Outcome	Intervention results	Intervention group (n)	Comparatorresults	Comparatorgroup (n)	Risk of bias
Gillinov2016[35]	**No pre-existing AF stratum:** Mixed rate control vs. K+ blocker with/without rate control agent	Hospital length of stay at 60 days	Median (IQR): 5.1 (3-7.4) days	262	Median (IQR): 5.0 (3.2-7.5) days	261	High
Hwang1984[51]	**No pre-existing AF stratum:** Calcium channel blockers vs. placebo	Achievement of sinus rhythm at end of hospital stay – note results given 'as received'. All patients in placebo group switched to verapamil as treatment failed within required time-frame. Study reports total number of all participants in study that were in sinus rhythm after treatment with verapamil	At end of study,3/14 remained in sinus rhythm at the end of their hospital stay. Of these, 2 had been receiving oral doses of digoxin or propanololhydrochloride, but none maintained on oral doses of verapamil	14 (those originally assigned to calcium channel blockers and all those assigned to placebo switched following failure)	NA	NA	Very high

Table 4: Clinical evidence summary: Mixed/unclear stratum– calcium channel blockers vs. placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with Calcium channel blockers (95% CI)
Adverse events (adverse reaction or unusual haemodynamic response)	22 (1 study) 24 hours	⨁⊖⊖⊖ VERY LOW[b,c,d] due to risk of bias, indirectness, imprecision	RD: 0 (-0.16 to 0.16)	Moderate	
				0 per 1000	0 fewer per 1000 (from 160 fewer to 160 more)[a]

[a]Absolute effect calculated manually using risk difference as zero events in both arms of the study.
[b]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[c]>10% with atrial flutter rather than atrial fibrillation
[d]Imprecision assessed using sample size as zero events in both arms of the study. Sample size <70 so very serious imprecision.

Table 5: Clinical evidence summary: No pre-existing AFstratum– DC cardioversion vs. K+ blockers

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with K+ blockers	Risk difference with DC cardioversion (95% CI)
Achievement of sinus rhythm (sinus rhythm at 24 h)	18 (1 study) 24 hours	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.33 (0.09 to 1.23)	Moderate	
				667 per 1000	447 fewer per 1000 (from 607 fewer to 153 more)
Need for rescue DC cardioversion (need for transthoracic cardioversion post-24 h - follow-up unclear)	11 (1 study)	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	PetoOR 0.16 (0 to 8.19)	Moderate	
				167 per 1000	167 fewer per 1000 (from 543 fewer to 209 more)[c]

[a]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with K+ blockers	Risk difference with DC cardioversion (95% CI)
[b]Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs [c]Absolute effect calculated manually using risk difference as zero events in one arm of single study.					

Table 6: Clinical evidence summary: No pre-existing AFstratum– K+ blockers vs. digoxin

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Digoxin	Risk difference with K+ blockers (95% CI)
Achievement of sinus rhythm (sinus rhythm at 24 h)	30 (1 study) 24 hours	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 1.17 (0.88 to 1.55)	Moderate	
				800 per 1000	136 more per 1000 (from 96 fewer to 440 more)
Adverse events (clinically significant hypotension or cardiac conduction abnormalities)	30 (1 study) 24 hours	⨁⊖⊖⊖ VERY LOW[a,d] due to risk of bias, imprecision	RD: 0 (-0.12 to 0.12)	Moderate	
				0 per 1000	0 fewer per 1000 (from 120 fewer to 120 more)[c]
Need for rescue DC cardioversion (direct current reversion post-24 h - follow-up unclear)	30 (1 study)	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	PetoOR 0.14 (0 to 6.82)	Moderate	
				67 per 1000	67 fewer per 1000 (from 233 fewer to 100 more)[e]
[a]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias [b]Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs [c]Absolute effect calculated manually using risk difference as zero events in both arms of the study. [d]Imprecision assessed using sample size as zero events in both arms of the study. Sample size <70so very serious imprecision. [e]Absolute effect calculated manually using risk difference as zero events in one arm of the study.					

Table 7: Clinical evidence summary: No pre-existing AF stratum– K+ blockers vs. K+ blockers + ranolazine

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with K+ blocker + ranolazine	Risk difference with K+ blockers alone (95% CI)
Achievement of sinus rhythm (sinus rhythm at 36 h/unclear)	853 (2 studies)	⨁⨁⊖⊖ LOW[a] due to risk of bias	RR 1 (0.99 to 1.01)	Moderate	
				1000 per 1000	0 fewer per 1000 (from 10 fewer to 10 more)
[a]Downgraded by 1 increment if the majority o fthe evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias					

Table 8: Clinical evidence summary: No pre-existing AF stratum– mixed rate control vs. K+ blockers with/without rate control agent

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with K+ blocker with/without rate control agent	Risk difference with mixed rate control (95% CI)
Achievement of sinus rhythm (sinus rhythm at hospital discharge)	518 (1 study)	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, indirectness	RR 0.96 (0.91 to 1.01)	Moderate	
				934 per 1000	37 fewer per 1000 (from 84 fewer to 9 more)
Adverse events (serious and non-serious adverse events, other than cerebrovascular/non-cerebral thromboembolism)	523 (1 study) 60 days	⨁⊖⊖⊖ VERY LOW[a,b,e] due to risk of bias, indirectness, imprecision	Rate ratio 0.96 (0.77 to 1.2)	Patients could have more than one event included in rate count. Event rate per 100 patient-months: 31.4.	1.3 fewer per 100 patient-months(from 8.22 fewer to 5.58 more)[c,d]
Freedom from anticoagulation (no warfarin prescription at hospital discharge)	523 (1 study)	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, indirectness	RR 1.01 (0.87 to 1.17)	Moderate	
				567 per 1000	6 more per 1000 (from 74 fewer to 96 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with K+ blocker with/without rate control agent	Risk difference with mixed rate control (95% CI)
Mortality (mortality at 60 days)	523 (1 study) 60 days	⨁⊖⊖⊖ VERY LOW[a,b,e] due to risk of bias, indirectness, imprecision	PetoOR 1.49 (0.26 to 8.66)	Moderate	
				8 per 1000	4 more per 1000 (from 6 fewer to 57 more)
Need for rescue DC cardioversion (direct current cardioversion at 60 days)	523 (1 study) 60 days	⨁⊖⊖⊖ VERY LOW[a,b,e] due to risk of bias, indirectness, imprecision	RR 0.66 (0.41 to 1.08)	Moderate	
				138 per 1000	47 fewer per 1000 (from 81 fewer to 11 more)
Rehospitalisation, all-cause (readmission due to any cause at 60 days)	523 (1 study) 60 days	⨁⊖⊖⊖ VERY LOW[a,b,e] due to risk of bias, indirectness, imprecision	Rate ratio 1.0 (0.73to 1.37)	Patients could have more than one event included in rate count. Event rate per 100 patient-months: 18.5.	0 fewer per 100-patient-months(from 5.77fewer to 5.74 more)[c,d]
Rehospitalisation for AF (readmission due to treatment of AF at 60 days)	523 (1 study) 60 days	⨁⊖⊖⊖ VERY LOW[a,b,e] due to risk of bias, indirectness, imprecision	Rate ratio 0.67 (0.31 to 1.42)	Patients could have more than one event included in rate count. Event rate per 100 patient-months: 3.9	1.3 fewer per 100 patient-months(from 3.71 fewer to 1.12 more)[c,d]
Stroke or thromboembolic complications (serious and non-serious cerebrovascular, inc, stroke and TIA, and/or non-cerebral thromboembolism at 60 days)	523 (1 study) 60 days	⨁⊖⊖⊖ VERY LOW[a,b,e] due to risk of bias, indirectness, imprecision	Rate ratio 2.33 (0.6to 9.02)	Patients could have more than one event included in rate count. Event rate per 100 patient-months: 0.6	0.8more per 100 patient-months(from 0.44fewer to 2.04more)[c,d]

[a]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with K+ blocker with/without rate control agent	Risk difference with mixed rate control (95% CI)

[b]Unclear which rate control agents were included - could include some not listed in our protocol
[c]Per100 patient-months.
[d]Absolute effect calculated manually using difference in rates per 100 patient months
[e]Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 9: Clinical evidence summary: No pre-existing AF stratum– mixed rhythm control +/- electrical cardioversion vs. mixed rate control

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with mixed rate control	Risk difference with mixed rhythm control +/- electrical cardioversion (95% CI)
Achievement of sinus rhythm (sinus rhythm at 8 weeks post-hospital discharge)	50 (1 study) 8 weeks post-hospital discharge	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, indirectness	RR 1.05 (0.91 to 1.22)	Moderate	
				913 per 1000	46 more per 1000 (from 82 fewer to 201 more)
Mortality (mortality at 8 weeks post-hospital discharge)	50 (1 study) 8 weeks post-hospital discharge	⨁⊖⊖⊖ VERY LOW[a,b,d] due to risk of bias, indirectness, imprecision	PetoOR 6.62 (0.4 to 109.94)	Moderate	
				0 per 1000	74 more per 1000 (from 46 fewer to 194 more)[c]
Hospital length of stay (from surgery to discharge)	50 (1 study)	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, indirectness	NA	The mean hospital length of stay (from surgery to discharge) in the control groups was 9.7 days	The mean hospital length of stay (from surgery to discharge) in the intervention groups was 2.3 lower (2.72 to 1.88 lower)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with mixed rate control	Risk difference with mixed rhythm control +/- electrical cardioversion (95% CI)
					Note: MID was deemed to be 0.5days (based on 0.5 x median sd[1.0] in mixed rate control group)

[a]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[b]Serious indirectness as some in the mixed rate control arm could have received intravenous diltiazem - not available in UK in this form. Proportion unclear.
[c]Absolute effect calculated manually using risk difference as zero events in control group
[d]Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 10: Clinical evidence summary: No pre-existing AF stratum– Na+ blockers vs. digoxin

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with digoxin	Risk difference with Na+ blockers (95% CI)
Achievement of sinus rhythm (sinus rhythm at 24 h)	29 (1 study) 24 hours	⊕⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 1.31 (0.91 to 1.87)	Moderate	
				714 per 1000	221 more per 1000 (from 64 fewer to 621 more)
Adverse events (adverse reactions at 24 h)	29 (1 study) 24 hours	⊕⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	PetoOR 8.02 (0.76 to 84.1)	Moderate	
				0 per 1000	200 more per 1000 (from 22 fewer to 422 more)[c]

[a]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[b]Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[c]Absolute effect calculated manually using risk difference as zero events in control group

Table 11: Clinical evidence summary: No pre-existing AF stratum– Na+ blockers vs. K+ blockers

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with K+ blockers	Risk difference with Na+ blockers (95% CI)
Achievement of sinus rhythm (without electrical cardioversion at end of study - includes those switching drug)	122 (1 study)	⨁⨁⊖⊖ LOW[a] due to risk of bias	RR 1.01 (0.94 to 1.09)	Moderate	
				955 per 1000	10 more per 1000 (from 57 fewer to 86 more)
Adverse events (significant side effects at end of study)	122 (1 study)	⨁⊖⊖⊖ VERY LOW[a,c] due to risk of bias, imprecision	RD: 0 (-0.03 to 0.03)	Moderate	
				0 per 1000	0 fewer per 1000 (from 30 fewer to 30 more)[b]
Need for rescue DC cardioversion (cardioversion at end of study)	122 (1 study)	⨁⊖⊖⊖ VERY LOW[a,d] due to risk of bias, imprecision	RR 0.81 (0.14 to 4.69)	Moderate	
				45 per 1000	9 fewer per 1000 (from 39 fewer to 166 more)

[a]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[b]Absolute effect calculated manually using risk difference as zero events in both arms of the study.
[c]Imprecision assessed using sample size as zero events in both arms of the study. Sample size >70 and <350 so serious imprecision.
[d]Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 12: Clinical evidence summary: No pre-existing AFstratum– Calcium channel blockers vs. placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with calcium channel blockers (95% CI)
Adverse events (adverse events requiring premature termination of study, such as hypotension or bradycardia - in-hospital)	14 (1 study)	⨁⊖⊖⊖ VERY LOW[b,c,d] due to risk of bias, indirectness, imprecision	RD 0 (-0.24 to 0.24)	Moderate	
				0 per 1000	0 fewer per 1000 (from 240 fewer to 240 more)[a]

[a]Absolute effect calculated manually using risk difference as zero events in both arms of the study.
[b]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[c]>10% with atrial flutter rather than atrial fibrillation
[d]Imprecision assessed using sample size as zero events in both arms of the study. Sample size <70 so very serious imprecision.

Table 13: Clinical evidence summary: No pre-existing AFstratum– K+ blockers (vernakalant) vs. placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with No pre-existing AF stratum: K+ blockers (vernakalant) (95% CI)
Mortality	160 (1 study) 30 days	⨁⨁⊖⊖ LOW[b,c] due to risk of bias, imprecision	RD 0 (-0.03 to 0.03)	Moderate	
				0 per 1000	0 fewer per 1000 (from 30 fewer to 30 more)[a]
Achievement of sinus rhythm	161 (1 study) 90 min	⨁⨁⊖⊖ LOW[b] due to risk of bias	RR 3.03 (1.54 to 5.94)	Moderate	
				148 per 1000	300 more per 1000 (from 80 more to 731 more)
Serious adverse events	161 (1 study) 30 days	⨁⊖⊖⊖ VERY LOW[b,d] due to risk of bias, imprecision	RR 0.84 (0.32 to 2.19)	Moderate	
				111 per 1000	18 fewer per 1000 (from 75 fewer to 132 more)
				Moderate	

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with No pre-existing AF stratum: K+ blockers (vernakalant) (95% CI)
Treatment-emergent adverse events	161 (1 study) 24 h	⨁⊖⊖⊖ VERY LOW[b,d] due to risk of bias, imprecision	RR 1.22 (0.77 to 1.93)	315 per 1000	69 more per 1000 (from 72 fewer to 293 more)

[a]Absolute risk calculated manually using risk difference as zero events in both arms of the study
[b]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[c]Imprecision assessed using sample size as zero events in both arms of the study. Sample size >70 and <350 so serious imprecision
[d]Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 14: Clinical evidence summary: No pre-existing AF stratum– K+ blockers (amiodarone) vs. routine medical treatment alone

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with routine medical treatment alone	Risk difference with K+ blockers (amiodarone) (95% CI)
Achievement of sinus rhythm	84 (1 study) unclear	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 1.43 (0.84 to 2.43)	Moderate	
				333 per 1000	143 more per 1000 (from 53 fewer to 476 more)
Hospital length of stay	84 (1 study)	⨁⨁⨁⊖ MODERATE[a] due to risk of bias		The mean hospital length of stay in the control groups was 14.07 days	The mean hospital length of stay in the intervention groups was 3.83 lower (4.32 to 3.34 lower) Note: MID was deemed to be 0.59days (based on 0.5 x median sd[1.17] in routine medical treatment group)
ICU length of stay	84 (1 study)	⨁⨁⨁⊖ MODERATE[a] due to risk of bias		The mean ICU length of stay in the control groups was 2.83 days	The mean ICU length of stay in the intervention groups was

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with routine medical treatment alone	Risk difference with K+ blockers (amiodarone) (95% CI)
					1.14 lower (1.54 to 0.74 lower) Note: MID was deemed to be 0.48days (based on 0.5 x median sd[0.95] in routine medical treatment group)

[a]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[b]Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 15: Clinical evidence summary: Pre-existing AF stratum– DC cardioversion vs. K+ blockers + captopril + simvastatin

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with K+ blockers+ captopril + simvastatin	Risk difference with DC cardioversion (95% CI)
Achievement of sinus rhythm (sinus rhythm at end of treatment)	115 (1 study)	⊕⊕⊕⊖ MODERATE[a] due to risk of bias	RR 3.67 (2.38 to 5.67)	Moderate	
				268 per 1000	716 more per 1000 (from 370 more to 1000 more)
Adverse events (severe complications at follow-up)	115 (1 study) 3-34 months	⊕⊖⊖⊖ VERY LOW[a,c] due to risk of bias, imprecision	RD 0 (-0.03 to 0.03)	Moderate	
				0 per 1000	0 fewer per 1000 (from 30 fewer to 30 more)[b]
Adverse events (severe cough during treatment)	115 (1 study)	⊕⊖⊖⊖ VERY LOW[a,e] due to risk of bias, imprecision	PetoOR 0.13 (0.01 to 2.04)	Moderate	
				36 per 1000	36 fewer per 1000 (from 94 fewer to 22 more)[d]
				Moderate	

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with K+ blockers+ captopril + simvastatin	Risk difference with DC cardioversion (95% CI)
Adverse events (sinus bradycardia with heart rate of 43-52 bpm during treatment)	115 (1 study)	⊕⊖⊖⊖ VERY LOW[a,e] due to risk of bias, imprecision	PetoOR 7.14 (0.44 to 115.75)	0 per 1000	34 more per 1000 (from 22 fewer to 90 more)[f]
Mortality (mortality at follow-up)	115 (1 study) 3-34 months	⊕⊕⊖⊖ LOW[a,c] due to risk of bias, imprecision	RD 0 (-0.03 to 0.03)	Moderate	
				0 per 1000	0 fewer per 1000 (from 30 fewer to 30 more)[b]
Rehospitalisation for AF (recurrence of AF at follow-up)	73 (1 study) 3-34 months	⊕⊖⊖⊖ VERY LOW[a,e] due to risk of bias, imprecision	RR 0.52 (0.05 to 5.33)	Moderate	
				67 per 1000	32 fewer per 1000 (from 64 fewer to 290 more)

[a]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[b]Absolute effect calculated manually using risk difference as zero events in both arms of the study
[c]Imprecision assessed using sample size as zero events in both arms. Sample size >70 and <350 so serious imprecision.
[d]Absolute effect calculated manually using risk difference as zero events in one arm of single study
[e]Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[f]Absolute effect calculated manually using risk difference as zero events in the control group

Table 16: Clinical evidence summary: Pre-existing AF stratum– Mixed rate control vs. K+ blockers + captopril + simvastatin

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with K+ blockers+ captopril + simvastatin	Risk difference with mixed rate control (95% CI)
				Moderate	

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with K+ blockers+ captopril + simvastatin	Risk difference with mixed rate control (95% CI)
Achievement of sinus rhythm (sinus rhythm conversion at 12 months)	99 (1 study) 12 months	⨁⨁⨁⨀ MODERATE[a] due to risk of bias	RR 0.15 (0.05 to 0.49)	388 per 1000	330 fewer per 1000 (from 198 fewer to 369 fewer)
Adverse events (adverse events requiring discontinuation of one or more study drugs at 12 months)	98 (1 study) 12 months	⨁⨁⨀⨀ LOW[a] due to risk of bias	PetoOR 0.11 (0.02 to 0.52)	Moderate	
				146 per 1000	146 fewer per 1000 (from 250 fewer to 42 more)[b]

[a]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[b]Absolute effect calculated manually using risk difference as zero events in one arm of the study

Table 17: Clinical evidence summary: Pre-existing AF stratum– K+ blockers + DC cardioversion vs. placebo + DC cardioversion

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo + DC cardioversion	Risk difference with K+ blockers + DC cardioversion (95% CI)
Achievement of sinus rhythm (sinus rhythm at 12 months)	73 (1 study) 12 months	⨁⨁⨀⨀ LOW[a] due to risk of bias	RR 3.23 (1.58 to 6.61)	Moderate	
				189 per 1000	421 more per 1000 (from 110 more to 1000 more)
Adverse events (dose reduction due to adverse events at 12 months)	89 (1 study) 12 months	⨁⨁⨀⨀ LOW[a] due to risk of bias	PetoOR 9.25 (2.35 to 36.43)	Moderate	
				0 per 1000	205 more per 1000 (from 82 more to 328 more)[b]

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo + DC cardioversion	Risk difference with K+ blockers + DC cardioversion (95% CI)
Health-related quality of life (mental component score SF-8 at 12 months) Scale from: 0 to 100.	73 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW[a,c] due to risk of bias, imprecision	NA	The mean health-related quality of life (mental component score sf-8 at 12 months) in the control groups was 50.15 Baseline value, mean (SD, n): 43.94 (5.276, n=45)	The mean health-related quality of life (mental component score sf-8 at 12 months) in the intervention groups was 3.74 higher (1.1 to 6.38 higher) Baseline value, mean (SD, n): 45.08 (4.928, n=44) Note: MID was deemed to be 2.61(based on 0.5 x median sd[5.216] in placebo + DC cardioversion group)
Health-related quality of life (physical component score SF-8 at 12 months) Scale from: 0 to 100.	73 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW[a,d] due to risk of bias, imprecision	NA	The mean health-related quality of life (physical component score sf-8 at 12 months) in the control groups was 46.62 Baseline value, mean (SD, n): 46.46 (4.628, n=45)	The mean health-related quality of life (physical component score sf-8 at 12 months) in the intervention groups was 3.17 higher (0.24 to 6.1 higher) Baseline value, mean (SD, n): 48.03 (5.005, n=44); Note: MID was deemed to be 2.96(based on 0.5 x median sd[5.917] in placebo + DC cardioversion group)

[a]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[b]Absolute effect calculated manually using risk difference as zero events in control group of study
[c]Downgraded by 1 increment as the confidence intervals crossed the upper MID of 2.61

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo + DC cardioversion	Risk difference with K+ blockers + DC cardioversion (95% CI)
[d]Downgraded by 1 increment as the confidence intervals crossed the upper MID of 2.96					

See Appendix F: for full GRADE tables.

Click here to enter text.

1.6 Economic evidence

1.6.1 Included studies

No health economic studies were included.

1.6.2 Excluded studies

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

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

1.6.3 Unit costs

Relevant drug unit costs are provided in Table 18to aid consideration of costeffectiveness.

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

Table 18: Drug unit costs

Class	Drug (preparation)	Dose range	Cost range per day	Cost range per year
Class IC (Na+ channel blockers)	Disopyramide (capsules)	300mg to 800 mg daily in divided doses	£0.79 to £2.10	£287.22 to £765.92
	Flecainide acetate (tablet)	50mg bd to 300mg daily	£0.16 to £0.26	£59.13 to £93.26
	Propafenone hydrochloride(tablet)	150mg tid to 300mg tid	£0.25 to £0.49	£89.67 to £179.34
Class II (beta-blockers)	Acebutolol (tablet)	0.4g to 1.2 g daily in 2–3 divided doses.	£0.67 to £2	£242.73 to £728.18
	Atenolol (tablet)	50mg to 100mg daily	£0.02 to £0.05	£8.21 to £16.43
	Bisoprolol fumarate (tablet)	5mg to 10mg od	£0.02 to £0.04	£7.69 to £15.38
	Esmolol hydrochloride (IV)	50–200 micrograms/kg/minute	Cost per infusion bag: £89.69 (b)	
	Metoprolol tartare (tablet)	50 mg bd to 300mg daily.	£0.06 to £0.10	£20.08 to £34.81
	Nadolol (tablet)	160mg od	£0.43	£156.43
	Propranolol (tablet)	10–40 mg 3–4 times a day	£0.13 to £0.14	£49.01 to £52.40
Class II & III (beta blockers/K+ channel blocker)	Sotalol hydrochloride (tablet)	80 mg to 320 mg daily in 2 divided doses	£0.08 to £0.28	£28.94 to £102.98
Class III (K+ channel blocker)	Amiodarone (tablet)	200mg od	£0.12	£42.50
	Amiodarone (IV infusion)	Maximum 1.2 g per day	£5.87	N/A
	Dronedarone (tablet)	400mg bd	£2.25	£821.25
	Vernakalant (IV infusion)	Maximum 565 mg per day	£327.70 per day	N/A

Class	Drug (preparation)	Dose range	Cost range per day	Cost range per year
Class IV (calcium channel blocker)	Diltiazem hydrochloride	120mg to 360mg daily	£0.13 to £0.38	£46.60 to £139.81
	Verapamil hydrochloride (tablet)	40mg to 120 mg tid	£0.06 to £0.14	£20.34 to £52.40
	Verapamil hydrochloride (slow IV injection)	5–10 mg to be given over 2 minutes	£2.16 to £4.33	N/A
Class V (Positive ionotropic drug)	Digoxin (tablet)	125–250 micrograms daily	£0.06 to £0.11	£20.34 to £40.67

(a) Source of cost and dose: BNF[7], last accessed January 2020. With exception of diltiazem hydrochloride as this is an unlicensed indication. GC expert advice provided for dosage.

(b) Breviblocpre mixed 2.5mg/250ml infusion bags

Abbreviations: bd: twice daily; IV: intravenous; N/A: not applicable; od: once daily; tid: three times daily.

Direct current cardioversion (X501) and external cardioversion electrical cardioversion (X502) are not coded separately as a HRG, and therefore the day case unit cost for Arrhythmia or Conduction Disorders (EB07) is the closest proxy, which has a weighted cost of £670taking comorbidities and or complications into account.[22]

The weighted average cost for excess bed days for patients who have had elective and non-elective CABG are provided in **Table 19**and **Table 20**.

Table 19: Elective inpatient excess bed days cost

Currency Code	Currency Description	Excess Bed Days	National Average Unit Cost
ED26A	Complex Coronary Artery Bypass Graft with CC Score 10+	272	£312
ED26B	Complex Coronary Artery Bypass Graft with CC Score 5-9	157	£312
ED26C	Complex Coronary Artery Bypass Graft with CC Score 0-4	12	£325
ED27A	Major Coronary Artery Bypass Graft with CC Score 10+	4	£352
ED27B	Major Coronary Artery Bypass Graft with CC Score 5-9	110	£377
ED27C	Major Coronary Artery Bypass Graft with CC Score 0-4	17	£311
ED28A	Standard Coronary Artery Bypass Graft with CC Score 10+	381	£304
ED28B	Standard Coronary Artery Bypass Graft with CC Score 5-9	196	£393
ED28C	Standard Coronary Artery Bypass Graft with CC Score 0-4	198	£276
Weighted average			**£322**

Source: National reference costs 2017-2018[22]

Table 20: Non-elective inpatient excess bed days cost

Currency Code	Currency Description	Excess Bed Days	National Average Unit Cost
ED26A	Complex Coronary Artery Bypass Graft with CC Score 10+	422	£346
ED26B	Complex Coronary Artery Bypass Graft with CC Score 5-9	135	£411
ED26C	Complex Coronary Artery Bypass Graft with CC Score 0-4	51	£264
ED27A	Major Coronary Artery Bypass Graft with CC Score 10+	217	£331
ED27B	Major Coronary Artery Bypass Graft with CC Score 5-9	81	£297
ED27C	Major Coronary Artery Bypass Graft with CC Score 0-4	132	£311

Currency Code	Currency Description	Excess Bed Days	National Average Unit Cost
ED28A	Standard Coronary Artery Bypass Graft with CC Score 10+	549	£254
ED28B	Standard Coronary Artery Bypass Graft with CC Score 5-9	679	£303
ED28C	Standard Coronary Artery Bypass Graft with CC Score 0-4	362	£385
Weighted average			**£318**

Source: National reference costs 2017-2018[22]

1.7 The committee's discussion of the evidence

1.7.1 Interpreting the evidence

1.7.1.1 The outcomes that matter most

In this review, the following outcomes were considered to be critical for decision-making: health-related quality of life, mortality, stroke or thromboembolic complications, need for rescue DC cardioversion, rehospitalisation (all-cause), rehospitalisation for AF, achievement of sinus rhythm and adverse events.

Additional outcomes that were considered to be important for decision-making were freedom from anticoagulation, freedom from antiarrhythmic drug use, hospital length of stay and intensive care unit length of stay.

In this review, no clinical evidence was identified for the following critical outcomes: freedom from antiarrhythmic drug use and intensive care unit length of stay.

1.7.1.2 The quality of the evidence

The quality of the evidence for all outcomes included in this review ranged from very low quality to moderate, with the majority of outcomes for all comparisons being rated very low quality based on GRADE quality assessment. For those rated very low quality, the main factors contributing to the quality rating were a very high or high risk of bias and imprecision in the effect estimates due to very small study sample sizes. There were only four studies where the population size was >100 participants, and the number of participants within the other nine studies ranged from 14 to 99, which made imprecision an issue with the majority of outcomes from these smaller studies. This made it difficult for the committee to interpret these outcomes and decide whether any clinically important differences were present due to the uncertainty surrounding the effect estimates. For the majority of outcomes only one study was available and meta-analysis was therefore not performed.

In addition, there were some outcomes presented that could not be analysed and assessed by GRADE due to insufficient detail reported within the studies. This comprised two outcomes, one where only the median and interquartile range was given for the length of hospital stay in both groups and the other where data was not given for separately for each randomised group. These outcomes were reported separate to other outcomes and are presented in Table 3 of the evidence review.

1.7.1.3 Benefits and harms

The evidence included in this review was obtained from thirteen RCTs (covered by fourteen papers) and was stratified from the outset based on whether or not the AF was pre-existing before cardiothoracic surgery was performed within the individual studies.

For the no pre-existing AF stratum, where AF was new-onset following cardiothoracic surgery, nine RCTs were included, which covered the following comparisons: DC cardioversion vs. K+ blockers, K+ blockers vs. digoxin, K+ blockers vs. K+ blockers + ranolazine, mixed rate control vs. K+ blockers with/without rate control, mixed rhythm control with/without electrical cardioversion vs. mixed rate control, Na+ blockers vs. digoxin, Na+ blockers vs. K+ blockers and calcium channel blockers vs. placebo.

For the pre-existing AF stratum, where AF was present prior to the cardiothoracic surgery, three RCTs were included, which covered the following comparisons: DC cardioversion vs. K+ blockers + captopril + simvastatin, mixed rate control vs. K+ blockers + captopril + simvastatin and K+ blockers + DC cardioversion vs. placebo + DC cardioversion.

There was an additional study that could not be classified into either of the above strata as there was no information about preoperative AF – this was included separately under a mixed/unclear stratum and covered the comparison between calcium channel blockers and placebo.

No pre-existing AF

For the majority of the evidence within this stratum, the committee agreed that there was insufficient evidence to favour particular interventions and that many of the studies were old with very small participant numbers and covered drugs that are not commonly used in practice anymore. For the comparisons between individual drug classes (such as Na+ blockers vs. K+ blockers) there was only one, small study for each and there was substantial uncertainty in the effect estimate for most outcomes due to imprecision, meaning the committee felt that there was insufficient evidence to favour a particular drug class.

However, the committee noted the inclusion of a larger RCT that compared a mixed rate control strategy vs. K+ blockers (amiodarone) with/without rate control that reported numerous outcomes listed in the protocol, all of which appeared to suggest no clinical difference (or there was uncertainty around the effect estimate and the true effect size) between the two groups, particularly concerning the presence of sinus rhythm at discharge, freedom from warfarin at discharge and all-cause hospital readmission at 60 days. There was also no difference in hospital length of stay based on median values reported in the study.

There were some outcomes where the point estimate of the relative effect suggested a benefit of K+ blockers with/without rate control (mortality and stroke or thromboembolic complications); however the committee did not consider these to be clinically important differences based on the absolute effect estimates, the presence of imprecision and the low number of events. The adverse event outcome (serious and non-serious events) reported in this study appeared to suggest a slight benefit of mixed rate control, which the committee agreed may be due to the side effects associated with amiodarone use, however this was also considered not to be a clinically important difference based on the size of the effect. Need for rescue DC cardioversion also suggested a benefit of mixed rate control over amiodarone treatment, however, DC cardioversion was a recommended procedure in the amiodarone group if patients did not respond (and this was not mentioned within the mixed

rate control group procedure), which may partially explain the increased number in the amiodarone group.

Although this RCT was not without its limitations, such as no details provided about the types of rate control drugs included in the mixed rate control group, the committee noted that this was the best available evidence within the review to inform changes to the existing recommendation covering the post-cardiothoracic surgery population.

Overall, the committee considered that for those with no pre-existing AF prior to cardiothoracic surgery, there was insufficient evidence to keep the existing strong recommendation to offer a rhythm control strategy as the initial management option for postoperative atrial fibrillation following cardiothoracic surgery, and therefore agreed that this should be changed to a consider recommendation, which would give less emphasis on rhythm control strategies and allow rate control strategies to be considered if the clinician felt this was more appropriate for the individual patient. The committee agreed that this may lead to a change in practice as in their experience the use of amiodarone to treat new-onset AF following cardiothoracic surgery is routine. The committee noted that this routine use of amiodarone may be unnecessary based on the results of the review and the possibility that postoperative AF may resolve naturally in many patients with watchful waiting, meaning that a rate control strategy rather than a rhythm control strategy may often be sufficient to resolve the atrial fibrillation. This contributed to the committee's decision to change the recommendation to a consider recommendation. The committee also noted that if a rate control strategy was initially selected instead of a rhythm control strategy, rhythm control would remain an option if this initial management failed. A benefit of a watchful waiting strategy could include avoiding side effects associated with rate and rhythm control drugs (particularly amiodarone), though side effects are considered to be less of an issue with the short term use of these drugs. However, limited evidence was included in this review comparing rate or rhythm control drugs with a watchful waiting strategy, and therefore no recommendation was made concerning this strategy.

The committee agreed that if a rhythm control strategy was chosen as the initial management, the need for this should be reviewed, alongside the need for any associated anticoagulation, at approximately 6 weeks and not continued automatically for long periods of time. 6 weeks is in line with current practice and is an appropriate time point to assess the person's recovery including for example prosthetic valve function and to check if sinus rhythm has been restored. The committee agreed that the adverse events associated with the use of amiodarone are usually following medium to long-term use and were less concerned about these adverse events for the treatment of new-onset AF following cardiothoracic surgery, providing amiodarone use is not continued for long periods unnecessarily.

Pre-existing AF

The committee agreed that there was insufficient evidence within this stratum to make any specific recommendations for those with pre-existing AF before cardiothoracic surgery that remained following surgery. The evidence was obtained from three studies, which covered three separate comparisons.

There was some evidence from one study that DC cardioversion improved clinical outcomes compared with a group where K+ blockers were used, and evidence from another study that suggested K+ blockers with DC cardioversion was better than DC cardioversion alone in terms of achieving sinus rhythm. However, these studies were substantially smaller than the

largest RCT included for the no pre-existing AF stratum and the committee felt unable to make recommendations based on his.

In addition to the lack of evidence, the committee noted that all three studies in this stratum covered the patients that were undergoing mitral valve surgery and that in this situation most patients with pre-existing AF prior to mitral valve surgery would undergo simultaneous left atrial surgery at the time of valve intervention, with the aim of resolving the AF and reducing the need for future intervention or treatment.

1.7.2 Cost effectiveness and resource use

No relevant health economic analyses were identified for this review. Relevant unit costs were presented for rate and rhythm strategies. The unit cost of rate and rhythm drugs was generally low and comparable. Although there were some more costly drugs within each class, these were considered by the committee to be less frequently used than the other lower cost drugs. This was because the low cost drugs generally work well in terms of acute conversion and there is no evidence of any gains of using the more expensive drugs currently. Furthermore, the aim of this review question was to compare rate versus rhythm strategies rather than making inter class comparisons, therefore this was not considered an issue. Finally, the committee noted that rate or rhythm drugs would be used for a short period of time in this context, usually over a period of days or weeks. The unit cost of direct current cardioversion was also presented. Direct current cardioversion (X501) and external cardioversion electrical cardioversion (X502) are not coded separately as an HRG, and therefore the day case unit cost for Arrhythmia or Conduction Disorders (EB07) is the closest proxy, which has a weighted cost of £670 taking comorbidities and or complications into account. The committee noted that the cost would likely be lower when done in the intensive care unit or in an outpatient setting. Finally, the unit cost of excess bed days for patients undergoing CABG was presented to illustrate the potential cost of strategies that increase length of stay.

The committee considered these unit costs alongside the clinical evidence summarised above. For people with no pre-existing atrial fibrillation, they agreed that the limited clinical evidence available did not support the previous strong recommendation to offer rhythm control. Instead they made a weaker ‘consider’ recommendation reflecting the limited clinical evidence and lack of economic evidence. This was based primarily on a single large RCT which showed no difference between rate and rhythm strategies for a number of the protocol outcomes. This study included outcomes associated with resource use such as rehospitalisation and rescue direct current cardioversion. For all cause rehospitalisation, there was no difference between rate and rhythm strategies. For rescue cardioversion and AF rehospitalisation outcomes, they favoured rate control, however there was uncertainty surrounding the point estimate. Overall it was considered that this amendment to the recommendation may reduce the use of rhythm control with drugs such as amiodarone, and increase the use of rate control drugs. As the cost of the drugs is similar and there is no reported significant difference in downstream resource use from the clinical evidence, it was thought that this recommendation amendment is unlikely to have a significant resource impact.

For those with pre-existing AF, no specific recommendation was made for this population due to a lack of robust and relevant clinical evidence.

1.7.3 Other factors the committee took into account

The committee also considered the role of patient preference in the decision to use a rhythm or rate control strategy following the development of new-onset AF post-cardiothoracic surgery. The committee agreed that where possible the clinician would discuss with the patient their preferences, but also noted that in many cases the patient would be acutely unwell and unable to communicate their preferences to the clinician, meaning the clinician would have to make the decision without patient input in these cases.

References

1. Anonymous. Managing atrial fibrillation after coronary artery bypass graft surgery involves prophylaxis, cardioversion and/or ventricular rate control. Drugs and Therapy Perspectives. 2006; 22(9):12-15

2. Balser JR, Martinez EA, Winters BD, Perdue PW, Clarke AW, Huang W et al. Beta-adrenergic blockade accelerates conversion of postoperative supraventricular tachyarrhythmias. Anesthesiology. 1998; 89(5):1052-1059

3. Banach M, Okonski P, Zaslonka J. Atrial fibrillation following cardiosurgical operations - current guidelines of pharmacotherapy and invasive treatment. Polski Przeglad Chirurgiczny. 2005; 77(4):398-412

4. Bechtel JF, Christiansen JF, Sievers HH, Bartels C. Low-energy cardioversion versus medical treatment for the termination of atrial fibrillation after CABG. Annals of Thoracic Surgery. 2003; 75(4):1185-1188

5. Bernard EO, Schmid ER, Schmidlin D, Scharf C, Candinas R, Germann R. Ibutilide versus amiodarone in atrial fibrillation: a double-blinded, randomized study. Critical Care Medicine. 2003; 31(4):1031-1034

6. Blessberger H, Lewis S, Pritchard M, Fawcett L, Domanovits H, Schlager O et al. Perioperative beta-blockers for preventing surgery-related mortality and morbidity in adults undergoing cardiac surgery. Cochrane Database of Systematic Reviews 2019, Issue 9. Art. No.: CD013435. DOI: 10.1002/14651858.CD013435.

7. BMJ Group and the Royal Pharmaceutical Society of Great Britain. British National Formulary. Available from: https://www.evidence.nhs.uk/formulary/bnf/currentLast accessed: 21/01/2020.

8. Bockeria OL, Kanametov TN, Shvartz VA, Sokolskaya MA, Zhuginisov DS, Sanakoev MK et al. Epicardial application of hydrogel with amiodarone for prevention of postoperative atrial fibrillation in patients after coronary artery bypass grafting. Journal of Cardiovascular Translational Research. 2020; 13: 191-198

9. Burke SW, Solomon AJ. Atrial fibrillation in patients after cardiovascular surgery: incidence, risk factors, preventive and therapeutic strategies. American Journal of Cardiovascular Drugs. 2003; 3(2):95-100

10. Campbell TJ, Gavaghan TP, Morgan JJ. Intravenous sotalol for the treatment of atrial fibrillation and flutter after cardiopulmonary bypass. Comparison with disopyramide and digoxin in a randomised trial. British Heart Journal. 1985; 54(1):86-90

11. Campbell TJ, Morgan JJ. Treatment of atrial arrhythmias after cardiac surgery with intravenous disopyramide. Australian and New Zealand Journal of Medicine. 1980; 10(6):644-649

12. Chen K, Qin L, Lu X, Xia T, Gu Q. Amiodarone in the treatment of atrial fibrillation of patients with rheumatic heart disease after valve replacement. Pakistan Journal of Medical Sciences. 2019; 35(4):918-922

13. Chen WS, Gao BR, Chen WQ, Li ZZ, Xu ZY, Zhang YH et al. Comparison of pharmacological and electrical cardioversion in permanent atrial fibrillation after

prosthetic cardiac valve replacement: a prospective randomized trial. Journal of International Medical Research. 2013; 41(4):1067-1073

14. Cheng JW. Vernakalant in the management of atrial fibrillation. Annals of Pharmacotherapy. 2008; 42(4):533-542

15. Cochrane AD, Siddins M, Rosenfeldt FL, Salamonsen R, McConaghy L, Marasco S et al. A comparison of amiodarone and digoxin for treatment of supraventricular arrhythmias after cardiac surgery. European Journal of Cardio-Thoracic Surgery. 1994; 8(4):194-198

16. Connolly SJ, Mulji AS, Hoffert DL, Davis C, Shragge BW. Randomized placebo-controlled trial of propafenone for treatment of atrial tachyarrhythmias after cardiac surgery. Journal of the American College of Cardiology. 1987; 10(5):1145-1148

17. Conte SM, Florisson DS, De Bono JA, Davies RA, Newcomb AE. Management of atrial fibrillation after cardiac surgery. Internal Medicine Journal. 2019; 49(5):656-658

18. Crystal E, Kahn S, Roberts R, Thorpe K, Gent M, Cairns JA et al. Long-term amiodarone therapy and the risk of complications after cardiac surgery: results from the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT). Journal of Thoracic and Cardiovascular Surgery. 2003; 125(3):633-637

19. Dagres N, Iliodromitis EK, Lekakis JP, Simitsis P, Karatzas D, Rallidis LS et al. Ranolazine for the prevention or treatment of atrial fibrillation: a systematic review. Journal of Cardiovascular Medicine. 2014; 15(3):254-259

20. Daoud EG. Management of atrial fibrillation in the post-cardiac surgery setting. Cardiology Clinics. 2004; 22(1):159-166

21. De Vecchis R, Ariano C, Giasi A, Cioppa C. Antiarrhythmic effects of ranolazine used both alone for prevention of atrial fibrillation and as an add-on to intravenous amiodarone for its pharmacological cardioversion: a meta-analysis. Minerva Cardioangiologica. 2018; 66(3):349-359

22. Department of Health. NHS reference costs 2017-18. 2018. Available from: https://improvement.nhs.uk/resources/reference-costs/#rc1718Last accessed: 21/01/20.

23. deSouza IS, Tadrous M, Sexton T, Benabbas R, Carmelli G, Sinert R. Pharmacologic cardioversion of recent-onset atrial fibrillation and flutter in the emergency department: a systematic review and network meta-analysis. Annals of Emergency Medicine. 2020; 76(1):14-30

24. deSouza IS, Tadrous M, Sexton T, Benabbas R, Carmelli G, Sinert R. Pharmacologic cardioversion of recent-onset atrial fibrillation: a systematic review and network meta-analysis. Europace: European Pacing, Arrhythmias, and Cardiac Electrophysiology. 2020; 22(6):854-869

25. Di Biasi P, Scrofani R, Paje A, Cappiello E, Mangini A, Santoli C. Intravenous amiodarone vs propafenone for atrial fibrillation and flutter after cardiac operation. European Journal of Cardio-Thoracic Surgery. 1995; 9(10):587-591

26. Ding P, Li L, Zhang H, Chen LJ, Deng XJ, Yuan YQ. Comparison of amiodarone plus irbesartan regimen versus amiodarone alone on maintaining sinus rhythm in rheumatic heart disease patients with persistent atrial fibrillation post valve

replacement and cardioversion. Chinese Journal of Cardiovascular Diseases. 2009; 37(6):505-508

27. Duggan ST, Scott LJ. Intravenous vernakalant: a review of its use in the management of recent-onset atrial fibrillation. Drugs. 2011; 71(2):237-252

28. Dunning J, Khasati N, Prendergast B. What is the optimal medical treatment for stable cardiac surgical patients who go into atrial fibrillation after their operation? Interactive Cardiovascular and Thoracic Surgery. 2004; 3(1):46-51

29. Effert S, Merx W. On the treatment of atrial fibrillation following surgery of mitral stenosis. Deutsche Medizinische Wochenschrift. 1967; 92(15):691-695

30. Fellahi JL, Heringlake M, Knotzer J, Fornier W, Cazenave L, Guarracino F. Landiolol for managing atrial fibrillation in post-cardiac surgery. European Heart Journal Supplements. 2018; 20(Suppl A):A4-A9

31. Fitzgerald RD, Fritsch S, Wislocki W, Oczenski W, Waldenberger FR, Schwarz S. Transvenous, intracardial cardioversion for the treatment of postoperative atrial fibrillation. Annals of Cardiac Anaesthesia. 2008; 11(2):111-115

32. Frost L, Mortensen PE, Tingleff J, Platou ES, Christiansen EH, Christiansen N. Efficacy and safety of dofetilide, a new class III antiarrhythmic agent, in acute termination of atrial fibrillation or flutter after coronary artery bypass surgery. International Journal of Cardiology. 1997; 58(2):135-140

33. Gao L, Moodie M. Modelling the lifetime cost-effectiveness of catheter ablation for atrial fibrillation with heart failure. BMJ Open. 2019; 9(9):e031033

34. Gavaghan TP, Koegh AM, Kelly RP, Campbell TJ, Thorburn C, Morgan JJ. Flecainide compared with a combination of digoxin and disopyramide for acute atrial arrhythmias after cardiopulmonary bypass. British Heart Journal. 1988; 60(6):497-501

35. Gillinov AM, Bagiella E, Moskowitz AJ, Raiten JM, Groh MA, Bowdish ME et al. Rate control versus rhythm control for atrial fibrillation after cardiac surgery. New England Journal of Medicine. 2016; 374(20):1911-1921

36. Gong M, Zhang Z, Fragakis N, Korantzopoulos P, Letsas KP, Li G et al. Role of ranolazine in the prevention and treatment of atrial fibrillation: A meta-analysis of randomized clinical trials. Heart Rhythm. 2017; 14(1):3-11

37. Gray RJ, Conklin CM, Sethna DH, Mandel WJ, Matloff JM. Role of intravenous verapamil in supraventricular tachyarrhythmias after open-heart surgery. American Heart Journal. 1982; 104(4 Pt 1):799-802

38. Greenberg JW, Lancaster TS, Schuessler RB, Melby SJ. Postoperative atrial fibrillation following cardiac surgery: a persistent complication. European Journal of Cardio-Thoracic Surgery. 2017; 52(4):665-672

39. Gudbjartsson T, Helgadottir S, Sigurdsson MI, Taha A, Jeppsson A, Christensen TD et al. New-onset postoperative atrial fibrillation after heart surgery. Acta Anaesthesiologica Scandinavica. 2019;

40. Guerra F, Romandini A, Barbarossa A, Belardinelli L, Capucci A. Ranolazine for rhythm control in atrial fibrillation: a systematic review and meta-analysis. International Journal of Cardiology. 2017; 227:284-291

41. Gun C, Bianco ACM, Freire RB, Ramos RF, Timernan A, Piegas LS. CD-ROM of abstracts from World Cardiology Congress: 1998. Beta-blocker effects on postoperative atrial fibrillation after coronary artery bypass surgery. Journal of American College of Cardiology 1998, Issue 3801.

42. Ha AC, Mazer CD, Verma S, Yanagawa B, Verma A. Management of postoperative atrial fibrillation after cardiac surgery. Current Opinion in Cardiology. 2016; 31(2):183-190

43. Habibollahi P, Jam SH, Vahdati SS, Baghi HM, Amiri H. Amiodaron in atrial fibrillation: post coronary artery bypass graft. World Journal of Emergency Medicine. 2016; 7(4):250-254

44. Han QQ, Lang XL, Han L, Lu FL, Zou LJ, Xu ZY. Ibutilide and amiodarone in management of new-onset atrial fibrillation after coronary artery bypass grafting: a comparison of safety and efficacy. Academic Journal of Second Military Medical University. 2010; 31(11):1169-1173

45. Helber U, Steinhilber B, Fenchel G, Hoffmeister HM. New occurance of post-operative atrial fibrillation after cardio-surgical operations: medical cardioversion verses placebo. Zeitschrift für Kardiologie. 1996; 85(Suppl 2):230

46. Hilleman DE, Hunter CB, Mohiuddin SM, Maciejewski S. Pharmacological management of atrial fibrillation following cardiac surgery. American Journal of Cardiovascular Drugs. 2005; 5(6):361-369

47. Hilleman DE, Spinler SA. Conversion of recent-onset atrial fibrillation with intravenous amiodarone: a meta-analysis of randomized controlled trials. Pharmacotherapy. 2002; 22(1):66-74

48. Hjelms E. Procainamide conversion of acute atrial fibrillation after open-heart surgery compared with digoxin treatment. Scandinavian Journal of Thoracic and Cardiovascular Surgery. 1992; 26(3):193-196

49. Hogue Jr CW, Hyder ML. Atrial fibrillation after cardiac operation: risks, mechanisms, and treatment. Annals of Thoracic Surgery. 2000; 69(1):300-306

50. Humphries JO. Unexpected instant death following successful coronary artery bypass graft surgery (and other clinical settings): atrial fibrillation, quinidine, procainamide, et cetera, and instant death. Clinical Cardiology. 1998; 21(10):711-718

51. Hwang MH, Danoviz J, Pacold I, Rad N, Loeb HS, Gunnar RM. Double-blind crossover randomized trial of intravenously administered verapamil. Its use for atrial fibrillation and flutter following open heart surgery. Archives of Internal Medicine. 1984; 144(3):491-494

52. Iliuta L, Rac-Albu M. Ivabradine versus beta-blockers in patients with conduction abnormalities or left ventricular dysfunction undergoing cardiac surgery. Cardiology and Therapy. 2013; 3(1-2):13-26

53. Iscan S, Eygi B, Besir Y, Yurekli I, Cakir H, Yilik L et al. Inflammation, atrial fibrillation and cardiac surgery: current medical and invasive approaches for the treatment of atrial fibrillation. Current Pharmaceutical Design. 2018; 24(3):310-322

54. Jannati M. Atrial fibrillation post coronary artery graft surgery: a review of literature. International Journal of General Medicine. 2019; 12:415-420

55. Ji Q, Mei Y, Wang X, Feng J, Wusha D, Cai J et al. Combination of irbesartan and amiodarone to maintain sinus rhythm in patients with persistent atrial fibrillation after rheumatic valve replacement. Circulation Journal. 2010; 74(9):1873-1879

56. Jie S, Yu C, Xiaohu L, Yanning Q, Zhengnian D, Xiaoyang T. The effect of amiodarone on cardiac rhythm after cardiopulmonary bypass in patients with atrial fibrillation. Journal of Heart Valve Disease. 2010; 19(6):786-788

57. Johnston BW, Hill R, Duarte R, Chean CS, McAuley DF, Blackwood B et al. Protocol for a systematic review and network meta-analysis of the management of new onset atrial fibrillation in critically unwell adult patients. Systematic Reviews. 2019; 8(1):242

58. Jung W, Meyerfeldt U, Birkemeyer R. Atrial arrhythmias after cardiac surgery in patients with diabetes mellitus. Clinical Research in Cardiology. 2006; 95 (Suppl 1):i88-i97

59. Kamali A, Sanatkar A, Sharifi M, Moshir E. Evaluation of amiodarone versus metoprolol in treating atrial fibrillation after coronary artery bypass grafting. Interventional Medicine and Applied Science. 2017; 9(2):51-55

60. Kleine P, Dzemali O, Moritz A. Internal cardioversion for treatment of postoperative atrial fibrillation. Surgical Technology International. 2003; 11:197-201

61. Kolokotroni SM, Toufektzian L, Harling L, Bille A. In patients undergoing lung resection is it safe to administer amiodarone either as prophylaxis or treatment of atrial fibrillation? Interactive Cardiovascular and Thoracic Surgery. 2017; 24(5):783-788

62. Koplan BA. Adrenergic blockade for management of atrial fibrillation after coronary artery bypass surgery: Is it important to go beyond the beta1-receptor? Heart Rhythm. 2007; 4(9):1175-1176

63. Kowey PR. Ibutilide for AF termination after cardiac surgery. American Heart Journal. 1997; 134(1):139

64. Kowey PR, Dorian P, Mitchell LB, Pratt CM, Roy D, Schwartz PJ et al. Vernakalant hydrochloride for the rapid conversion of atrial fibrillation after cardiac surgery: a randomized, double-blind, placebo-controlled trial. Circulation: Arrhythmia and Electrophysiology. 2009; 2(6):652-659

65. Landymore RW, Howell F. Recurrent atrial arrhythmias following treatment for postoperative atrial fibrillation after coronary bypass operations. European Journal of Cardio-Thoracic Surgery. 1991; 5(8):436-439

66. Larbuisson R, Venneman I, Stiels B. The efficacy and safety of intravenous propafenone versus intravenous amiodarone in the conversion of atrial fibrillation or flutter after cardiac surgery. Journal of Cardiothoracic and Vascular Anesthesia. 1996; 10(2):229-234

67. Lee JK, Klein GJ, Krahn AD, Yee R, Zarnke K, Simpson C et al. Rate-control versus conversion strategy in postoperative atrial fibrillation: trial design and pilot study results. Cardiac Electrophysiology Review. 2003; 7(2):178-184

68. Lee JK, Klein GJ, Krahn AD, Yee R, Zarnke K, Simpson C et al. Rate-control versus conversion strategy in postoperative atrial fibrillation: a prospective, randomized pilot study. American Heart Journal. 2000; 140(6):871-877

69. Liu TJ, Hsueh CW, Lee WL, Lai HC, Wang KY, Ting CT. Conversion of rheumatic atrial fibrillation by amiodarone after percutaneous balloon mitral commissurotomy. American Journal of Cardiology. 2003; 92(10):1244-1246

70. Ma W, Guo X, Wang Q, Sun G, Wang J. Systematic review and meta-analysis appraising efficacy and safety of vernakalant for cardioversion of recent-onset atrial fibrillation. Journal of Cardiovascular Pharmacology. 2020; 76(1):32-41

71. Mahrose R, Elsayed AM, Elshorbagy MS. Bisoprolol versus corticosteroid and bisoprolol combination for prevention of atrial fibrillation after on-pump coronary artery bypass graft surgery. Open Anesthesiology Journal. 2019; 13(1):18-24

72. Maisel WH, Rawn JD, Stevenson WG. Atrial fibrillation after cardiac surgery. Annals of Internal Medicine. 2001; 135(12):1061-1073

73. Mangin L, Vinet A, Page P, Glass L. Effects of antiarrhythmic drug therapy on atrioventricular nodal function during atrial fibrillation in humans. Europace: European Pacing, Arrhythmias, and Cardiac Electrophysiology. 2005; 7(Suppl 2):S71-S82

74. Mann CJ, Kendall S, Lip GYH. Acute management of atrial fibrillation with acute haemodynamic instability and in the postoperative setting. Heart. 2007; 93(1):45-47

75. Martinez EA, Bass EB, Zimetbaum P, American College of Chest P. Pharmacologic control of rhythm: American College of Chest Physicians guidelines for the prevention and management of postoperative atrial fibrillation after cardiac surgery. Chest. 2005; 128(Suppl 2):48S-55S

76. Martinez EA, Epstein AE, Bass EB, American College of Chest P. Pharmacologic control of ventricular rate: American College of Chest Physicians guidelines for the prevention and management of postoperative atrial fibrillation after cardiac surgery. Chest. 2005; 128(Suppl 2):56S-60S

77. McAlister HF, Luke RA, Smith WM. Amiodarone versus quinidine reversion of atrial fibrillation post-cardiac surgery. Australian and New Zealand Journal of Medicine. 1986; 16:588

78. McAlister HF, Luke RA, Whitlock RM, Smith WM. Intravenous amiodarone bolus versus oral quinidine for atrial flutter and fibrillation after cardiac operations. The Journal of thoracic and cardiovascular surgery. 1990; 99(5):911-918

79. McKeown PP, American College of Chest P. Introduction: American College of Chest Physicians guidelines for the prevention and management of postoperative atrial fibrillation after cardiac surgery. Chest. 2005; 128(Suppl 2):6S-8S

80. McMurry SA, Hogue Jr CW. Atrial fibrillation and cardiac surgery. Current Opinion in Anaesthesiology. 2004; 17(1):63-70

81. Mooss AN, Wurdeman RL, Mohiuddin SM, Reyes AP, Sugimoto JT, Scott W et al. Esmolol versus diltiazem in the treatment of postoperative atrial fibrillation/atrial flutter after open heart surgery. American Heart Journal. 2000; 140(1):176-180

82. Morttada A, Ramzy A, Ayoub A, Khaled S, Samir S, Zaki H. Effects of atrial fibrillation cardioversion after percutaneous mitral balloon valvuloplasty on echocardiographic left and right atrial functions. Journal of Atrial Fibrillation. 2016; 8(6):48-50

83. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual [Updated October 2018]. London. National Institute for Health and Care Excellence, 2014. Available from: https://www.nice.org.uk/process/pmg20/chapter/introduction-and-overview

84. Nemati MH, Astaneh B. Amiodarone versus propafenone to treat atrial fibrillation after coronary artery bypass grafting: a randomized double blind controlled trial. The Korean Journal of Thoracic and Cardiovascular Surgery. 2016; 49(3):177-184

85. O'Bryan LJ, Redfern OC, Bedford J, Petrinic T, Young JD, Watkinson PJ. Managing new-onset atrial fibrillation in critically ill patients: a systematic narrative review. BMJ Open. 2020; 10(3):e034774

86. Ozaydin M, Erdogan D, Yucel H, Peker O, Icli A, Akcay S et al. N-acetyl cysteine for the conversion of atrial fibrillation into sinus rhythm after cardiac surgery: a prospective, randomized, double-blind, placebo-controlled pilot study. International Journal of Cardiology. 2013; 165(3):580-583

87. Patel D, Gillinov MA, Natale A. Atrial fibrillation after cardiac surgery: where are we now? Indian Pacing and Electrophysiology Journal. 2008; 8(4):281-291

88. Plumb VJ, Karp RB, Kouchoukos NT, Zorn GL, Jr., James TN, Waldo AL. Verapamil therapy of atrial fibrillation and atrial flutter following cardiac operation. The Journal of thoracic and cardiovascular surgery. 1982; 83(4):590-596

89. Qian YJ, Xiao XJ, Yuan HS, Tang H, Shao HZ, Wei DM. Combination pharmacological cardioversion of permanent atrial fibrillation in post-prosthetic mitral valve replacement outpatients: a novel approach for the treatment of atrial fibrillation. Journal of International Medical Research. 2008; 36(3):537-543

90. Rho RW, Bridges CR, Kocovic D. Management of postoperative arrhythmias. Seminars in Thoracic and Cardiovascular Surgery. 2000; 12(4):349-361

91. Rosenberg K. Rate and rhythm control are equally effective in treating postoperative atrial fibrillation. American Journal of Nursing. 2016; 116(8):53-54

92. Sai C, Li J, Ruiyan M, Yingbin X. Atorvastatin prevents postoperative atrial fibrillation in patients undergoing cardiac surgery. Hellenic Journal of Cardiology. 2019; 60(1):40-47

93. Sakamoto A, Kitakaze M, Takamoto S, Namiki A, Kasanuki H, Hosoda S et al. Landiolol, an ultra-short-acting beta1-blocker, more effectively terminates atrial fibrillation than diltiazem after open heart surgery: prospective, multicenter, randomized, open-label study (JL-KNIGHT study). Circulation Journal. 2012; 76(5):1097-1101

94. Savelieva I, Graydon R, Camm AJ. Pharmacological cardioversion of atrial fibrillation with vernakalant: evidence in support of the ESC Guidelines. Europace: European Pacing, Arrhythmias, and Cardiac Electrophysiology. 2014; 16(2):162-173

95. Schleifer JW, Ramakrishna H. Perioperative atrial fibrillation: a systematic review of evolving therapeutic options in pharmacologic and procedural management. Annals of Cardiac Anaesthesia. 2015; 18(4):565-570

96. Schwartz M, Michelson EL, Sawin HS, MacVaugh H, 3rd. Esmolol: safety and efficacy in postoperative cardiothoracic patients with supraventricular tachyarrhythmias. Chest. 1988; 93(4):705-711

97. Selvaraj T, Kiran U, Das S, Chauhan S, Sahu B, Gharde P. Effect of single intraoperative dose of amiodarone in patients with rheumatic valvular heart disease and atrial fibrillation undergoing valve replacement surgery. Annals of Cardiac Anaesthesia. 2009; 12(1):10-16

98. Shantsila E, Watson T, Lip GYH. Atrial fibrillation post-cardiac surgery: changing perspectives. Current Medical Research and Opinion. 2006; 22(8):1437-1441

99. Shen SL, Zhao YC. A comparative study on the efficacy and safety of intravenous esmolol, amiodarone and diltiazem for controlling rapid ventricular rate of patients with atrial fibrillation during anesthesia period. Chinese Journal of Cardiovascular Diseases. 2010; 38(11):989-992

100. Simopoulos V, Hevas A, Hatziefthimiou A, Dipla K, Skoularigis I, Tsilimingas N et al. Amiodarone plus ranolazine for conversion of post-cardiac surgery atrial fibrillation: enhanced effectiveness in reduced versus preserved ejection fraction patients. Cardiovascular Drugs and Therapy. 2018; 32(6):559-565

101. Simopoulos V, Tagarakis GI, Daskalopoulou SS, Daskalopoulos ME, Lenos A, Chryssagis K et al. Ranolazine enhances the antiarrhythmic activity of amiodarone by accelerating conversion of new-onset atrial fibrillation after cardiac surgery. Angiology. 2014; 65(4):294-297

102. Somberg J, Molnar J. Sotalol versus amiodarone in treatment of atrial fibrillation. Journal of Atrial Fibrillation. 2016; 8(5):1359

103. Soucier R, Silverman D, Abordo M, Jaagosild P, Abiose A, Madhusoodanan KP et al. Propafenone versus ibutilide for post operative atrial fibrillation following cardiac surgery: neither strategy improves outcomes compared to rate control alone (the PIPAF study). Medical Science Monitor. 2003; 9(3):19-23

104. Stiell IG, Sivilotti MLA, Taljaard M, Birnie D, Vadeboncoeur A, Hohl CM et al. Electrical versus pharmacological cardioversion for emergency department patients with acute atrial fibrillation (RAFF2): a partial factorial randomised trial. Lancet. 2020; 395(10221):339-349

105. Szyszka A, Wachowiak-Baszyńska H, Paluszkiewicz L, Skorupski W, Brocki Z. Preventive pharmacological treatment after cardiac electroversion for atrial fibrillation following surgical treatment of heart defects. Kardiologia Polska. 1992; 37(8):74-78

106. Taenaka N, Kikawa S. The effectiveness and safety of landiolol hydrochloride, an ultra-short-acting beta1-blocker, in postoperative patients with supraventricular tachyarrhythmias: a multicenter, randomized, double-blind, placebo-controlled study. American Journal of Cardiovascular Drugs. 2013; 13(5):353-364

107. Tisdale JE, Padhi ID, Goldberg AD, Silverman NA, Webb CR, Higgins RS et al. A randomized, double-blind comparison of intravenous diltiazem and digoxin for atrial fibrillation after coronary artery bypass surgery. American Heart Journal. 1998; 135(5 Pt 1):739-747

108. Tsu LV, Lee S. Use of ranolazine in the prevention and treatment of postoperative atrial fibrillation in patients undergoing cardiac surgery. Annals of Pharmacotherapy. 2014; 48(5):633-637

109. VanderLugt JT, Mattioni T, Denker S, Torchiana D, Ahern T, Wakefield LK et al. Efficacy and safety of ibutilide fumarate for the conversion of atrial arrhythmias after cardiac surgery. Circulation. 1999; 100(4):369-375

110. Vilvanathan VK, Srinivas Prabhavathi Bhat BC, Nanjappa MC, Pandian B, Bagi V, Kasturi S et al. A randomized placebo-controlled trial with amiodarone for persistent atrial fibrillation in rheumatic mitral stenosis after successful balloon mitral valvuloplasty. Indian Heart Journal. 2016; 68(5):671-677

111. Wafa SS, Ward DE, Parker DJ, Camm AJ. Efficacy of flecainide acetate for atrial arrhythmias following coronary artery bypass grafting. American Journal of Cardiology. 1989; 63(15):1058-1064

112. White CM, Nguyen E. Novel use of ranolazine as an antiarrhythmic agent in atrial fibrillation. Annals of Pharmacotherapy. 2017; 51(3):245-252

113. Yilmaz AT, Demirkilic U, Arslan M, Kurulay E, Ozal E, Tatar H et al. Long-term prevention of atrial fibrillation after coronary artery bypass surgery: comparison of quinidine, verapamil, and amiodarone in maintaining sinus rhythm. Journal of Cardiac Surgery. 1996; 11(1):61-64

Appendices

Appendix A: Review protocols

Table 21: Review protocol: Treatment of atrial fibrillation after cardiothoracic surgery

ID	Field	Content
0.	PROSPERO registration number	CRD42019143365
1.	Review title	Clinical and cost-effectiveness of treatment strategies (rate or rhythm control or no treatment) for people with atrial fibrillation after cardiothoracic surgery
2.	Review question	What is the most clinical and cost effective treatment strategy (rate or rhythm control or no treatment) for people with atrial fibrillation after cardiothoracic surgery?
3.	Objective	To identify the most effective treatment strategy for treating AF after cardiothoracic surgery (CTS). Note that this differs from protocol 8, which was for prevention of AF using statins given pre-CTS
4.	Searches	The following databases will be searched: Cochrane Central Register of Controlled Trials (CENTRAL) Cochrane Database of Systematic Reviews (CDSR) Embase MEDLINE Epistemonikos Searches will be restricted by: English language Human studies Letters and comments are excluded. Other searches: Inclusion lists of relevant systematic reviews will be checked by the reviewer. The searches may be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion if relevant. The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Atrial Fibrillation
6.	Population	Inclusion: People aged over 18 who have had cardiothoracic surgery and who have post-operative AF. Exclusion:

ID	Field	Content
		Severe valve disease
7.	Intervention/Exposure/Test	Rate control strategies (lists below are not exhaustive) Beta blockers -for example, bisoprolol, acebutolol, metoprolol, nadolol, pindolol, betaspace, propranolol, esmalol Ca2+ channel blockers – for example, diltiazem hydrochloride, verapamil Digoxin Amiodarone* Rhythm control strategies (lists below are not exhaustive) Na+ channel blockers – such as procainamide, disopyramide, quinidine sulphate, flecainide, propafenone K+ channel blockers – such as amiodarone*, dronedarone, ibutilide, sotalol DC cardioversion *amiodarone may be used for rate or rhythm control.
8.	Comparator/Reference standard/Confounding factors	• Placebo • No treatment • To each other (between classes of intervention – i.e. beta blockers vs Ca channel blockers, or digoxin versus DC cardioversion). • RCTs where individuals in the intervention group may be prescribed different rate or rhythm drugs are allowed. No comparisons within classes will be included (i.e. bisoprolol versus pindolol, or procainamide versus flecainide)
9.	Types of study to be included	Systematic reviews RCTs (including those with a cross-over design). Non-randomised studies will be excluded.
10.	Other exclusion criteria	Non-English language studies. Abstracts will be excluded as it is expected there will be sufficient full text published studies available.
11.	Context	N/A
12.	Primary outcomes (critical outcomes)	health-related quality of life mortality stroke or thromboembolic complications Need for rescue DC cardioversion Rehospitalisation (all cause) Rehospitalisation for AF Achievement of sinus rhythm Adverse events Longest follow up point always used
13.	Secondary outcomes	freedom from anticoagulation freedom from AAD use Hospital length of stay

ID	Field	Content
	(important outcomes)	ICU length of stay Longest follow up point always used
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. Titles and/or abstracts of studies retrieved using the search strategy and those from additional sources will be screened for inclusion. The full text of potentially eligible studies will be retrieved and will be assessed for eligibility in line with the criteria outlined above. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. An in-house developed database; EviBase, will be used for data extraction. A standardised form is followed to extract data from studies (see Developing NICE guidelines: the manual[83]section 6.4) and for undertaking assessment of study quality. Summary evidence tables will be produced including information on: study setting; study population and participant demographics and baseline characteristics; details of the intervention and control interventions; study methodology' recruitment and missing data rates; outcomes and times of measurement; critical appraisal ratings. A second reviewer will quality assure the extracted data. Discrepancies will be identified and resolved through discussion (with a third reviewer where necessary).
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual.[83] For Intervention reviews the following checklist will be used according to study design being assessed: Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) Randomised Controlled Trial: Cochrane RoB(2.0) Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
16.	Strategy for data synthesis	Where possible, data will be meta-analysed. Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5) to combine the data given in all studies for each of the outcomes stated above. A fixed effect meta-analysis, with weighted mean differences for continuous outcomes and risk ratios for binary outcomes will be used, and 95% confidence intervals will be calculated for each outcome. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. We will consider anI^2 value greater than 50% indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented using random-effects.

ID	Field	Content		
		GRADE pro will be used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. Other bias will only be taken into consideration in the quality assessment if it is apparent. Where meta-analysis is not possible, data will be presented, and quality assessed individually per outcome. If sufficient data is available to make a network of treatments, WinBUGS will be used for network meta-analysis.		
17.	Analysis of sub-groups	Stratification • Pre-existing AF vs no pre-existing AF Sub-grouping If serious or very serious heterogeneity (I2>50%) is present within any stratum, sub-grouping will occur according to the following strategies: Type of cardiothoracic surgery (mitral valve surgery vs non mitral valve surgery) Type of AF (persistent <1 year vs persistent >1 year vs paroxysmal) Existence of HF (HF vs no HF) Concomitant perioperative prophylactic treatment (concomitant peri-operative beta-blockers or statins, etc. vs no concomitant prophylactic treatment)		
18.	Type and method of review	☒	Intervention	
		☐	Diagnostic	
		☐	Prognostic	
		☐	Qualitative	
		☐	Epidemiologic	
		☐	Service Delivery	
		☐	Other (please specify)	
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date			
22.	Anticipated completion date			
23.	Stage of review at time of this submission	Review stage	Started	Completed
		Preliminary searches	☐	☑
		Piloting of the study	☐	☑

ID	Field	Content		
		selection process		
		Formal screening of search results against eligibility criteria	☐	☑
		Data extraction	☐	☑
		Risk of bias (quality) assessment	☐	☑
		Data analysis	☐	☑
24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre		
25.	Review team members	From the National Guideline Centre: Sharon Swain Mark Perry Nicole Downes Sophia KemmisBetty Elizabeth Pearton		
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.		
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.		
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing		

ID	Field	Content	
		NICE guidelines: the manual.[83]Members of the guideline committee are available on the NICE website: [NICE guideline webpage].	
29.	Other registration details		
30.	Reference/URL for published protocol		
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: notifying registered stakeholders of publication publicising the guideline through NICE's newsletter and alerts issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Atrial Fibrillation, cardiothoracic surgery, antiarrhythmic drugs, rate limiting drugs	
33.	Details of existing review of same topic by same authors	N/A	
34.	Current review status	☒	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information	N/A	
36.	Details of final publication	www.nice.org.uk	

Table 22: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.

Search strategy	A healtheconomic study search will be undertaken using population-specific terms and a healtheconomic study filter – see appendix B below. For questions being updated from NICE guideline CG180, the search will be run from October 2013, which was the cut-off date for the searches. For questions being updated from the NICE guideline CG36 and for new questions, the search will be run from 2003.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2003, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Studies published after 2003 that were included in the previous guideline(s) will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix Hof Developing NICE guidelines: the manual.[83] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A healtheconomic evidence table will be completed, and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded, then a healtheconomic evidence table will not be completed, and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS(most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis(most applicable).

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

Appendix B: Literature search strategies

This literature search strategy was used for the following reviews:

- **What is the most clinical and cost-effective treatment strategy (rate or rhythm control or no treatment) for people with atrial fibrillation after cardiothoracic surgery?**

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[83]

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

B.1 Clinical search literature search strategy

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

Table 23: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 10 September 2020	Exclusions Randomised controlled trials Systematic review studies
Embase (OVID)	1974 – 10 September 2020	Exclusions Randomised controlled trials Systematic review studies
The Cochrane Library (Wiley)	Cochrane Reviews to 2020Issue 9of 12 CENTRAL to 2020Issue 9of 12	None
Epistemonikos (Epistemonikos Foundation)	Inception – 10 September 2020	Systematic review studies

Medline (Ovid) search terms

1.	exp atrial fibrillation/
2.	((atrial or atria or atrium or auricular) adj3 fibrillat*).ti,ab.
3.	AF.ti,ab.
4.	1 or 2 or 3
5.	exp Thoracic Surgery/
6.	exp cardiovascular surgical procedures/
7.	((heart or cardiac or aortic or thoracic or lung* or pulmonary or vascular) adj3 (surg* or operat* or procedure* or repair*)).ti,ab.
8.	((valve* or valvular) adj2 (surg* or operat* or procedure* or repair* or replac*)).ti,ab.
9.	(revascularis* or revasculariz*).ti,ab.
10.	(cardio-thoracic or cardiothoracic).ti,ab.

11.	((postcardiac or post-cardiac or postcardiothoracicor post-cardiothoracic or postthoracicor post-thoracic) adj3 (surg* or operat* or procedure*)).ti,ab.s
12.	(((coronary artery or cardio-pulmonary or cardiopulmonary) adj2 (surg* or operat* or graft*)) or CABG*).ti,ab.
13.	or/5-12
14.	4 and 13
15.	(POAF or NOAF).ti,ab.
16.	((postop* or post-op* or perioperative or peri-operative or intraoperative* or intra-operative* or intrasurg* or intra-surg* or peroperat* or per-operat* or perioperat* or peri-operat*) adj3 ((atrial or atria or atrium or auricular) adj3 fibrillat*)).ti,ab.
17.	((postop* or post-op* or perioperative or peri-operative or intraoperative* or intra-operative* or intrasurg* or intra-surg* or peroperat* or per-operat* or perioperat* or peri-operat*) adj3 AF).ti,ab.
18.	((post* or peri*) adj3 surg* adj3 ((atrial or atria or atrium or auricular) adj3 fibrillat*)).ti,ab.
19.	((post* or peri*) adj3 surg* adj3 AF).ti,ab.
20.	((during or duration or following or after) adj3 (surg* or operat* or anaesthes* or anesthes*) adj3 ((atrial or atria or atrium or auricular) adj3 fibrillat*)).ti,ab.
21.	((during or duration or following or after) adj3 (surg* or operat* or anaesthes* or anesthes*) adj3 AF).ti,ab.
22.	((sudden or recent or new) adjonset adj3 ((atrial or atria or atrium or auricular) adj3 fibrillat*)).ti,ab.
23.	((sudden or recent or new) adjonset adj3 AF).ti,ab.
24.	(acute adj3 ((atrial or atria or atrium or auricular) adj3 fibrillat*)).ti,ab.
25.	(acute adj3 AF).ti,ab.
26.	or/15-25
27.	14 or 26
28.	letter/
29.	editorial/
30.	news/
31.	exp historical article/
32.	Anecdotes as Topic/
33.	comment/
34.	case report/
35.	(letter or comment*).ti.
36.	or/28-35
37.	randomized controlled trial/ or random*.ti,ab.
38.	36 not 37
39.	animals/ not humans/
40.	exp Animals, Laboratory/
41.	exp Animal Experimentation/
42.	exp Models, Animal/
43.	exp Rodentia/
44.	(rat or rats or mouse or mice).ti.
45.	or/38-44

46.	27 not 45
47.	limit 46 to English language
48.	randomized controlled trial.pt.
49.	controlled clinical trial.pt.
50.	randomi#ed.ab.
51.	placebo.ab.
52.	randomly.ab.
53.	clinical trials as topic.sh.
54.	trial.ti.
55.	or/48-54
56.	Meta-Analysis/
57.	Meta-Analysis as Topic/
58.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
59.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
60.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
61.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
62.	(search* adj4 literature).ab.
63.	(medlineor pubmedor cochraneor embaseor psychlitor psyclitor psychinfoor psycinfoor cinahlor science citation index or bids or cancerlit).ab.
64.	cochrane.jw.
65.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
66.	or/56-65
67.	47 and (55 or 66)

Embase (Ovid) search terms

1.	exp atrial fibrillation/
2.	((atrial or atria or atrium or auricular) adj3 fibrillat*).ti,ab.
3.	AF.ti,ab.
4.	1 or 2 or 3
5.	exp *thorax surgery/
6.	exp *cardiovascular procedure/
7.	((heart or cardiac or aortic or thoracic or lung* or pulmonary or vascular) adj3 (surg* or operat* or procedure* or repair*)).ti,ab.
8.	((valve* or valvular) adj2 (surg* or operat* or procedure* or repair* or replac*)).ti,ab.
9.	(revascularis* or revascular iz*).ti,ab.
10.	(cardio-thoracic or cardiothoracic).ti,ab.
11.	((postcardiac or post-cardiac or postcardiothoracicor post-cardiothoracic or postthoracicor post-thoracic) adj3 (surg* or operat* or procedure*)).ti,ab.
12.	(((coronary artery or cardio-pulmonary or cardiopulmonary) adj2 (surg* or operat* or graft*)) or CABG*).ti,ab.
13.	or/5-12
14.	4 and 13

15.	(POAF or NOAF).ti,ab.
16.	((postop* or post-op* or perioperative or peri-operative or intraoperative* or intra-operative* or intrasurg* or intra-surg* or peroperat* or per-operat* or perioperat* or peri-operat*) adj3 ((atrial or atria or atrium or auricular) adj3 fibrillat*)).ti,ab.
17.	((postop* or post-op* or perioperative or peri-operative or intraoperative* or intra-operative* or intrasurg* or intra-surg* or peroperat* or per-operat* or perioperat* or peri-operat*) adj3 AF).ti,ab.
18.	((post* or peri*) adj3 surg* adj3 ((atrial or atria or atrium or auricular) adj3 fibrillat*)).ti,ab.
19.	((post* or peri*) adj3 surg* adj3 AF).ti,ab.
20.	((during or duration or following or after) adj3 (surg* or operat* or anaesthes* or anesthes*) adj3 ((atrial or atria or atrium or auricular) adj3 fibrillat*)).ti,ab.
21.	((during or duration or following or after) adj3 (surg* or operat* or anaesthes* or anesthes*) adj3 AF).ti,ab.
22.	((sudden or recent or new) adjonset adj3 ((atrial or atria or atrium or auricular) adj3 fibrillat*)).ti,ab.
23.	((sudden or recent or new) adjonset adj3 AF).ti,ab.
24.	(acute adj3 ((atrial or atria or atrium or auricular) adj3 fibrillat*)).ti,ab.
25.	(acute adj3 AF).ti,ab.
26.	or/15-25
27.	14 or 26
28.	letter.pt. or letter/
29.	note.pt.
30.	editorial.pt.
31.	case report/ or case study/
32.	(letter or comment*).ti.
33.	or/28-32
34.	randomized controlled trial/ or random*.ti,ab.
35.	33 not 34
36.	animal/ not human/
37.	nonhuman/
38.	exp Animal Experiment/
39.	exp Experimental Animal/
40.	animal model/
41.	exp Rodent/
42.	(rat or rats or mouse or mice).ti.
43.	or/35-42
44.	27 not 43
45.	limit 44 to English language
46.	random*.ti,ab.
47.	factorial*.ti,ab.
48.	(crossover* or cross over*).ti,ab.
49.	((doubl* or singl*) adjblind*).ti,ab.
50.	(assign* or allocat* or volunteer* or placebo*).ti,ab.

51.	crossover procedure/
52.	single blind procedure/
53.	randomized controlled trial/
54.	double blind procedure/
55.	or/46-54
56.	systematic review/
57.	Meta-Analysis/
58.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
59.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
60.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
61.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
62.	(search* adj4 literature).ab.
63.	(medlineor pubmedor cochraneor embaseor psychlitor psyclitor psychinfoor psycinfoor cinahlor science citation index or bids or cancerlit).ab.
64.	cochrane.jw.
65.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
66.	or/56-65
67.	45 and (55 or 66)

Cochrane Library (Wiley) search terms

#1.	MeSHdescriptor: [Atrial Fibrillation] explode all trees
#2.	((atrial or atria or atrium or auricular) near/3 fibrillat*):ti,ab
#3.	AF:ti,ab
#4.	#1 or #2 or #3
#5.	MeSHdescriptor: [Thoracic Surgery] explode all trees
#6.	MeSHdescriptor: [Cardiovascular Surgical Procedures] explode all trees
#7.	((heart or cardiac or aortic or thoracic or lung* or pulmonary or vascular) near/3 (surg* or operat* or procedure* or repair*)):ti,ab
#8.	((valve* or valvular) near/2 (surg* or operat* or procedure* or repair* or replac*)):ti,ab
#9.	(revascularis* or revascular iz*):ti,ab
#10.	(cardio-thoracic or cardiothoracic):ti,ab
#11.	((postcardiac or post-cardiac or postcardiothoracicor post-cardiothoracic or postthoracicor post-thoracic) near/3 (surg* or operat* or procedure*)):ti,ab
#12.	(((coronary artery or cardio-pulmonary or cardiopulmonary) near/2 (surg* or operat* or graft*)) or CABG*):ti,ab
#13.	(or #5-#12)
#14.	#4 and #13
#15.	(POAF or NOAF):ti,ab
#16.	((postop* or post-op* or perioperative or peri-operative or intraoperative* or intra-operative* or intrasurg* or intra-surg* or peroperat* or per-operat* or perioperat* or peri-operat*) near/3 ((atrial or atria or atrium or auricular) near/3 fibrillat*)):ti,ab

#17.	((postop* or post-op* or perioperative or peri-operative or intraoperative* or intra-operative* or intrasurg* or intra-surg* or peroperat* or per-operat* or perioperat* or peri-operat*) near/3 AF):ti,ab
#18.	((post* or peri*) near/3 surg* near/3 ((atrial or atria or atrium or auricular) near/3 fibrillat*)):ti,ab
#19.	((post* or peri*) near/3 surg* near/3 AF):ti,ab
#20.	((during or duration or following or after) near/3 (surg* or operat* or anaesthes* or anesthes*) near/3 ((atrial or atria or atrium or auricular) near/3 fibrillat*)):ti,ab
#21.	((during or duration or following or after) near/3 (surg* or operat* or anaesthes* or anesthes*) near/3 AF):ti,ab
#22.	((sudden or recent or new) next onset near/3 ((atrial or atria or atrium or auricular) near/3 fibrillat*)):ti,ab
#23.	((sudden or recent or new) next onset near/3 AF):ti,ab
#24.	(acute near/3 ((atrial or atria or atrium or auricular) near/3 fibrillat*)):ti,ab
#25.	(acute near/3 AF):ti,ab
#26.	(or #15-#25)
#27.	#14 or #26

Epistemonikossearch terms

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

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to the Atrial Fibrillation population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA- this ceased to be updated after March 2018). NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional health economics searches were run on Medline and Embase.

Table 24: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	2003– 10 September 2020	Exclusions Health economics studies
Embase	2003– 10 September 2020	Exclusions Health economics studies
Centre for Research and Dissemination (CRD)	NHSEED - 2003 to March 2015 HTA - 2003 –2003to 31 March2018	None

Medline (Ovid) search terms

1.	exp atrial fibrillation/
2.	((atrial or atria or atrium or auricular) adj3 fibrillat*).ti,ab.
3.	AF.ti,ab.
4.	1 or 2 or 3

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

Embase (Ovid) search terms

1.	exp atrial fibrillation/

2.	((atrial or atria or atrium or auricular) adj3 fibrillat*).ti,ab.
3.	AF.ti,ab.
4.	1 or 2 or 3
5.	letter.pt. or letter/
6.	note.pt.
7.	editorial.pt.
8.	case report/ or case study/
9.	(letter or comment*).ti.
10.	or/5-9
11.	randomized controlled trial/ or random*.ti,ab.
12.	10 not 11
13.	animal/ not human/
14.	nonhuman/
15.	exp Animal Experiment/
16.	exp Experimental Animal/
17.	animal model/
18.	exp Rodent/
19.	(rat or rats or mouse or mice).ti.
20.	or/12-19
21.	4 not 20
22.	limit 21 to English language
23.	health economics/
24.	exp economic evaluation/
25.	exp health care cost/
26.	exp fee/
27.	budget/
28.	funding/
29.	budget*.ti,ab.
30.	cost*.ti.
31.	(economic*or pharmaco?economic*).ti.
32.	(price*or pricing*).ti,ab.
33.	(cost*adj2 (effectiv*or utilit*or benefit*or minimi*or unit*or estimat*or variable*)).ab.
34.	(financ*or fee or fees).ti,ab.
35.	(value adj2 (money or monetary)).ti,ab.
36.	or/23-35
37.	22 and 36

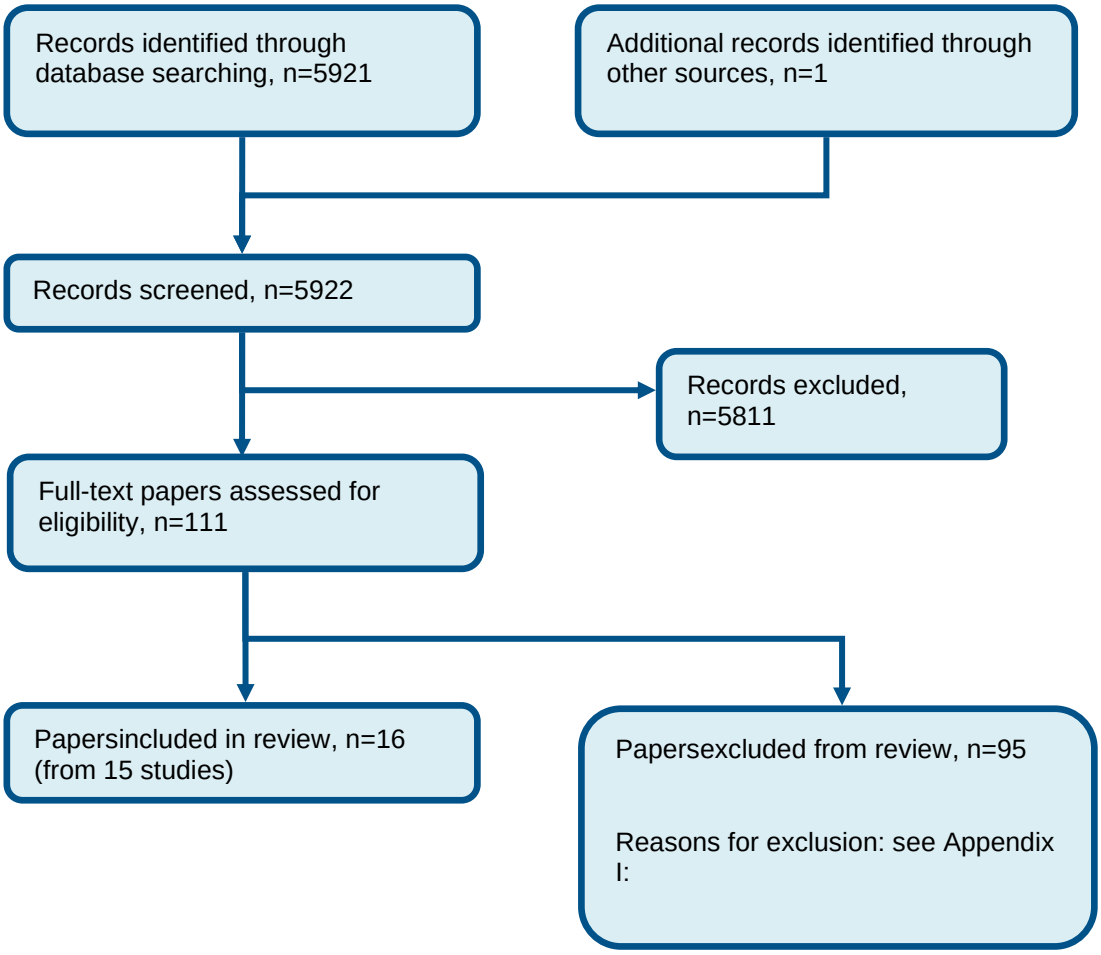
NHS EED and HTA (CRD) search terms

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

#4.	(#1 or #2 or #3)

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of treatment of atrial fibrillation after cardiothoracic surgery



Appendix D: Clinical evidence tables

Study	**Chen 2013[13]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=115)
Countries and setting	Conducted in China; Setting: Unclear - secondary care and outpatient setting?
Line of therapy	Unclear
Duration of study	Intervention + follow up: 3 months treatment in pharmacological group, ~5 weeks treatment in electrical cardioversion group. Longest follow-up was 34 months.
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: AF confirmed by two separate electrocardiographic examinations. 12-lead ECG performed before treatments.
Stratum	Pre-existing AF: Those with permanent AF prior to mitral valve replacement
Subgroup analysis within study	Not applicable:
Inclusion criteria	Age >18 years with permanent AF; undergone prosthetic mitral valve replacement with or without aortic valve replacement; cardiothoracic ratio ≤0.5 on cardiac anterioposterior X-radiography and a left atrial diameter ≤50 mm on Doppler ultrasound for ≥6 months post-surgery
Exclusion criteria	New York Heart Association heart failure class IV; history of sick sinus syndrome or second- or third-degree atrioventricular block; severe hepatic and/or renal dysfunction; hyperthyroidism; contraindications to treatment with amiodarone
Recruitment/selection of patients	Unclear

Age, gender and ethnicity	Age - Mean (SD): DC cardioversion, 52.8 (8) years; pharmacological cardioversion, 51.8 (10.9) years. Gender (M:F): DC cardioversion, 28/31; pharmacological cardioversion, 31/25. Ethnicity: Not reported
Further population details	1. Existence of heart failure: No heart failure (NYHA class IV excluded, LVEF >50% in both groups). 2. Type of AF: Persistent > 1 year (Duration of AF >50 months in both groups). 3. Type of cardiothoracic surgery: Mitral valve surgery (All had previous mitral valve replacement).
Extra comments	All patients received standard long-term anticoagulant therapy with warfarin and/or digoxin following surgery. Mean (SD) time since surgery: 10.3 (3.4) vs. 10.8 (2.9) months; mean (SD) duration of AF: 54.2 (25.9) vs. 53.5 (25.4) months; mean (SD) left atrial diameter: 45.2 (3.5) vs. 45.2 (3.6) mm; mean (SD) LVEF: 58.6 (6.5) vs. 58.2 (6.2) %; mean (SD) cardiothoracic ratio: 0.48 (0.02) vs. 0.48 (0.02)
Indirectness of population	No indirectness
Interventions	(n=59) Intervention 1: Rhythm control - DC cardioversion. Patients initially received 200mg amiodarone 3 times daily for 4 days. Digoxin treatment was stopped and warfarin dose was reduced to give an INR of 2–3. Electrical defibrillation was performed on 5th day. Patients received intravenous injection of 1 mg/kg propofol and were monitored continuously by 12-lead ECG. Once unconscious, patients received direct-current synchronized electrical cardioversion using an initial energy level of 200 J. If the first shock failed, two 300 J shocks were given. Electrical treatment was stopped if sinus rhythm was not restored within three shocks. After reversion to normal rhythm, 200 mg amiodarone was taken daily for 30 days. Patients were followed up once a month for 6 months and every 3–6 months thereafter. Duration ~5 weeks. Concurrent medication/care: All patients underwent 12-lead electrocardiography (ECG), cardiac anteroposterior X-ray, echocardiography, and measurement of haematological and biochemical parameters before treatment. Indirectness: No indirectness Further details: 1. Concomitant perioperative prophylactic treatment: Concomitant perioperative prophylactic treatment (e.g. with beta-blockers or statins) (n=56) Intervention 2: Rhythm control - K+ blockers. Oral amiodarone with captopril and simvastatin. 3 months combination therapy with oral amiodarone at a dose of 600 mg/day for 3 days, 400 mg/day for the following 3 days and then 200 mg/day, oral captopril at a dose of 12.5 mg twice daily before food and oral simvastatin at a dose of 15 mg/day at night. Patients were evaluated every 2 weeks by 12-lead ECG. Blood clotting was monitored, and the warfarin dose was adjusted to give an INRof 2-3. If there was no restoration of normal rhythm within 3 months, therapy was stopped. Patients were followed up every month for 6 months and then every 3-6 months thereafter. Duration 3 months. Concurrent medication/care: All patients underwent 12-lead electrocardiography (ECG), cardiac anteroposterior X-ray, echocardiography, and measurement of haematological and biochemical parameters before

	treatment. Indirectness: No indirectness Further details: 1. Concomitant perioperative prophylactic treatment: Not applicable
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DC CARDIOVERSION versus K+ BLOCKERS (AMIODARONE, WITH CAPTOPTRIL AND SIMVASTATIN)

Protocol outcome 1: Mortality at Define
- Actual outcome for Pre-existing AF: Mortality at Follow-up (range, 3-34 months); Group 1: 0/59, Group 2: 0/56
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Comparable for the variables reported (age, sex, valve replaced, time since surgery, duration of AF, left atrial diameter, LVEF, cardiothoracic ratio); Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Rehospitalisation for AF at Define
- Actual outcome for Pre-existing AF: Recurrence of AF at Follow-up (range, 3-34 months); Group 1: 2/58, Group 2: 1/15
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Comparable for the variables reported (age, sex, valve replaced, time since surgery, duration of AF, left atrial diameter, LVEF, cardiothoracic ratio); Group 1 Number missing: 1, Reason: 1 patient did not convert to sinus rhythm within treatment period so not included for this outcome (couldn't recur); Group 2 Number missing: 41, Reason: 41 patients did not convert to sinus rhythm within treatment period so not included for this outcome (couldn't recur)

Protocol outcome 3: Achievement of sinus rhythm at Define
- Actual outcome for Pre-existing AF: Conversion to sinus rhythm at end of treatment at End of treatment; Group 1: 58/59, Group 2: 15/56; Comments: Note treatment period longer in amiodarone group compared with DC cardioversion group
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Comparable for the variables reported (age, sex, valve replaced, time since surgery, duration of AF, left atrial diameter, LVEF, cardiothoracic ratio); Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Adverse events at Define
- Actual outcome for Pre-existing AF: Severe complications at Follow-up (range, 3-34 months); Group 1: 0/59, Group 2: 0/56
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Measurement bias: does not specify events that would be considered severe complications.; Indirectness of outcome: No indirectness ; Baseline details: Comparable for the variables reported (age, sex, valve replaced, time since surgery, duration of AF, left atrial diameter, LVEF, cardiothoracic ratio); Group 1 Number missing: ; Group 2 Number missing:

- Actual outcome for Pre-existing AF: Sinus bradycardia with heart rate of 43-52 beats/min at During treatment; Group 1: 2/59, Group 2: 0/56 Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Comparable for the variables reported (age, sex, valve replaced, time since surgery, duration of AF, left atrial diameter, LVEF, cardiothoracic ratio); Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for Pre-existing AF: Severe cough at During treatment; Group 1: 0/59, Group 2: 2/56; Comments: Severe cough resulted in withdrawal of captopril from the pharmacological cardioversion arm - only received amiodarone and simvastatin. Three others developed mild cough symptoms. Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Comparable for the variables reported (age, sex, valve replaced, time since surgery, duration of AF, left atrial diameter, LVEF, cardiothoracic ratio); Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Health-related quality of life at Define; Rehospitalisation (all-cause) at Define; Stroke or thromboembolic complications at Define; Need for rescue DC cardioversion at Define; Freedom from anticoagulation at Define; Freedom from antiarrhythmic drug use at Define; Intensive care unit length of stay at Define; Hospital length of stay at Define

Study	**Chen 2019[12]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=84)
Countries and setting	Conducted in China; Setting: Secondary care
Line of therapy	1st line
Duration of study	Intervention + follow up: Follow-up length unclear. Likely short term in-hospital
Method of assessment of guideline condition	Unclear method of assessment/diagnosis: Not reported
Stratum	No pre-existing AF
Subgroup analysis within study	Not applicable:

Inclusion criteria	Underwent elective valvular replacement; rheumatic heart disease with continuous atrial fibrillation; cardiac function no higher than grade III; satisfied application indication for amiodarone; normal electrolyte levels and acidity and alkalinity; heart rate <70 bpm
Exclusion criteria	Presence of other types of arrhythmia
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Amidoarone, 65.36 (10.77) years; routine care, 65.45 (10.82) years. Gender (M:F): Amiodarone, 22/20; routine care, 21/21. Ethnicity: Not reported
Further population details	1. Existence of heart failure: Heart failure (Mean NYHA score >II in each group). 2. Type of AF: Persistent > 1 year (Described as 'continuous' and present for mean of 30 months in each group). 3. Type of cardiothoracic surgery: Not stated / Unclear (Valve surgery but unclear if the mitral valve).
Extra comments	. Mean (SD) duration of atrial fibrillation, 30.96 (14.93) vs. 31.06 (15.02) months; mean (SD) left atrial diameter, 45.87 (3.95) vs. 47.06 (3.35) mm; mean (SD) left ventricular ejection fraction, 46.7 (4.32) vs. 47.5 (4.03)%; mean (SD) cardiothoracic ratio, 0.54 (0.07) vs. 0.56 (0.08); mean (SD) New York Heart Association score, 2.50 (0.51) vs. 2.58 (0.50)
Indirectness of population	No indirectness
Interventions	(n=42) Intervention 1: Rhythm control - K+ blockers .Received amiodarone in addition to routine treatment. On the day of the operation, a micro infusion pump was used to administer 600 mg amiodarone at a speed of 50 mg/h for 12 h. On postoperative day 1, amiodarone was taken orally following recovery of diet three time a day. A week later, patients took amiodarone twice per day. Another week later, the dose was reduced to once daily. Treatment course was 1 month. Routine treatment consisted of oral administration of drugs for diuresis, anticoagulation and routine application of antibiotics. Duration 1 month. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Concomitant perioperative prophylactic treatment: Not stated / Unclear (Not stated). (n=42) Intervention 2: No treatment. Routine care. Routine treatment consisted of oral administration of drugs for diuresis, anticoagulation and routine application of antibiotics. Duration 1 month. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Concomitant perioperative prophylactic treatment: Not stated / Unclear (Not stated).

Funding	No funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: K+ BLOCKERS (AMIODARONE) versus NO TREATMENT (ROUTINE CARE) Protocol outcome 1: Achievement of sinus rhythm at Define - Actual outcome for No pre-existing AF: Maintenance of sinus rhythm at Unclear; Group 1: 20/42, Group 2: 14/42; Comments: Note, higher number in each group reported to convert from AF to sinus rhythm (32/42 vs. 24/32) but maintenance of sinus rhythm at later time point felt to be more useful. Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Hospital length of stay at Define - Actual outcome for No pre-existing AF: Hospitalisation time at In-hospital; Group 1: mean 10.24 days (SD 1.13); n=42, Group 2: mean 14.07 days (SD 1.17); n=42 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Intensive care unit length of stay at Define - Actual outcome for No pre-existing AF: ICU monitoring time at In-hospital; Group 1: mean 1.69 days (SD 0.91); n=42, Group 2: mean 2.83 days (SD 0.95); n=42 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Rehospitalisation (all-cause) at Define; Mortality at Define; Stroke or thromboembolic complications at Define; Need for rescue DC cardioversion at Define; Rehospitalisation for AF at Define; Adverse events at Define; Health-related quality of life at Define; Freedom from antiarrhythmic drug use at Define; Freedom from anticoagulation at Define

Study	**Cochrane 1994[15]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=30)
Countries and setting	Conducted in Australia; Setting: Secondary care
Line of therapy	1st line
Duration of study	Intervention time: First 24 h of treatment
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: 12-lead ECG performed in all patients at onset of arrhythmia
Stratum	No pre-existing AF: AF prior to surgery as an exclusion criterion
Subgroup analysis within study	Not applicable
Inclusion criteria	Development of AF which persisted for more than 20 min with systolic blood pressure of ≥85 mmHg without inotropic support, while recovering from open heart surgery
Exclusion criteria	AF prior to surgery; poor ventricular contractility on preoperative left venticulogram; postoperative administration of beta-blockers
Recruitment/selection of patients	Unclear - not reported
Age, gender and ethnicity	Age - Mean (SD): Amiodarone, 60.2 years; digoxin, 65.8 years. Gender (M:F): Amiodarone, 11/4; digoxin, 10/5. Ethnicity: Not reported
Further population details	1. Existence of heart failure: No heart failure (Population described as those without severe pre- or post-operative left ventricular dysfunction). 2. Type of AF: Not stated / Unclear (Not reported). 3. Type of cardiothoracic surgery: Non-mitral valve surgery (>75% non-mitral valve surgery (coronary artery bypass grafting or aortic valve replacement).).

Extra comments	Preoperative beta-blockade: amiodarone, 7/15; digoxin, 8/15. Type of operation: coronary artery bypass grafting (amiodarone, 11/15; digoxin, 10/15); aortic valve replacement (amiodarone, 3/15; digoxin, 3/15); mitral valvotomy (amiodarone, 1/15; digoxin, 0/15); combined procedures (amiodarone, 0/15; digoxin, 2/15).
Indirectness of population	No indirectness
Interventions	(n=15) Intervention 1: Rhythm control - K+ blockers .Intravenous amiodarone. Loading dose of 5 mg/kg (max. 400 mg) in 100 ml of 5% dextrose infused intravenously over 30 min. At 30 min after loading dose complete, infusion of 25 mg/h initiated. Infusion increased to 40 mg/h if ventricular rate still exceeded 120 beats/min after 6 h. Treatment continued for 24 h after reversion to sinus rhythm. If reversion had not occurred following 24 h of intravenous amiodarone infusion, digoxin was added at half the dose used in the digoxin treatment group. Duration 24 h. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Concomitant perioperative prophylactic treatment: Not stated / Unclear (n=15) Intervention 2: Rate control - Digoxin. Intravenous digoxin. Loading dose of 1 mg given intravenously over 9 h as follows: 0.5 mg over 30 min at start of treatment, followed by 0.25 mg after 2 h and 0.125 mg after 5 h and 9 h. Oral maintenance therapy started within 12 h at a dose suitable for body weight and renal function. Serum digoxin level measured between 6 and 12 h after completion of loading dose. All had therapeutic serum digoxin levels after loading dose. If reversion did not occur during 24 h treatment period amiodarone was added at dose described for amiodarone group and digoxin continued at half the previous dose. Duration 24 h. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Concomitant perioperative prophylactic treatment: Not stated / Unclear
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: K+ BLOCKERS (AMIODARONE) versus DIGOXIN

Protocol outcome 1: Need for rescue DC cardioversion at Define
- Actual outcome for No pre-existing AF: Direct current reversion at Post-24 h (time-point unclear); Group 1: 0/15, Group 2: 1/15; Comments: One patient in digoxin group required cardioversion having failed to revert to sinus rhythm despite therapy with both agents.
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Outcome reporting: time-point at which this measured unclear; Indirectness of outcome: Serious indirectness ; Baseline details: Age, male/female ratio, preoperative beta-blocker use and operation type similar between groups.; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Achievement of sinus rhythm at Define - Actual outcome for No pre-existing AF: Reversion to sinus rhythm at 24 h; Group 1: 14/15, Group 2: 12/15; Comments: Note: Amiodarone - 2/15 transient recurrences and 1/15 sustained recurrence following initial reversion in 15/15 patients; digoxin - 3/13 transient recurrences and 0/13 sustained recurrences following initial reversion in 13/15 patients, one of these transient recurrences was at 24 h so was included in results as no sinus rhythm at 24 h. Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Age, male/female ratio, preoperative beta-blocker use and operation type similar between groups.; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Adverse events at Define - Actual outcome for No pre-existing AF: Clinically significant hypotension or cardiac conduction abnormalities at 24 h; Group 1: 0/15, Group 2: 0/15; Comments: Not an outcome that was prespecified in the study and no definition of side effects interested in Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Outcome reporting: does not prespecify the adverse events interested in - may have only mentioned those that they did not observe; Indirectness of outcome: Serious indirectness ; Baseline details: Age, male/female ratio, preoperative beta-blocker use and operation type similar between groups.; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Health-related quality of life at Define; Rehospitalisation (all-cause) at Define; Mortality at Define; Stroke or thromboembolic complications at Define; Rehospitalisation for AF at Define; Freedom from anticoagulation at Define; Freedom from antiarrhythmic drug use at Define; Intensive care unit length of stay at Define; Hospital length of stay at Define

Study	Fitzgerald 2008[31]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=18)
Countries and setting	Conducted in Austria; Setting: Secondary care
Line of therapy	1st line
Duration of study	Intervention + follow up: Follow-up unclear
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Five-lead ECG used for monitoring following surgery
Stratum	No pre-existing AF: chronic atrial fibrillation and conduction disorders exclusion criteria
Subgroup analysis within study	Not applicable
Inclusion criteria	Those undergoing coronary artery bypass grafting or valve surgery; postoperative AF development
Exclusion criteria	chronic atrial fibrillation; conduction disorders; patients with pacemakers
Recruitment/selection of patients	Unclear
Age, gender and ethnicity	Age - Median (range): low-energy cardioversion, 75 (57-87) years; amiodarone, 72 (57-81) years. Gender (M:F): low-energy cardioversion, 6/3; amiodarone, 9/0. Ethnicity: Not reported
Further population details	1. Existence of heart failure: No heart failure (No mention of heart failure and LVEF >50% in both groups). 2. Type of AF: Not stated / Unclear (No details on type of AF). 3. Type of cardiothoracic surgery: Not stated / Unclear (Majority non-mitral valve surgery - 1/9 in each group had mitral valve operation. Also some with valve and CABG but type of valve operation not specified.).
Extra comments	ASA grade, median (range): 3 (2-4) vs. 3 (2-4) - for both groups, 0 in grade I, 1 in grade II, 4 in grade III, 4 in grade IV and 0 in grade V. NYHA class: I (11 vs. 11%), II (56 vs. 67%), III (22 vs. 11%) and IV (11 vs. 11%). Type of surgery: CABG (44 vs.

	56%), aortic valve (22 vs. 22%), mitral valve (11 vs. 11%), CABG + valve (22 vs. 11%). Median (range) ejection fraction, %: 53 (31-74) vs. 59 (36-68). Median (range) duration extracorporeal circulation, min: 113.5 (49-130) vs. 104.5 (74-129). .Median (range) duration aortic cross-clamping, min: 52 (36-88) vs. 61 (31-85)
Indirectness of population	No indirectness
Interventions	(n=9) Intervention 1: Rhythm control - DC cardioversion. ALERT catheter for intracardiac conversion. Sedation with midazolam (3-5 mg intravenously) and intracardiac cardioversion. ALERT system consists of multifunctional balloon-tipped 7.5 Fr catheter that is combined with a 12-lead ECG connected to a cardioverter. System provides temporary pacing, sensing and delivery of stimuli for internal cardioversion. Pressure readings and measurement of cardiac output is possible as with a standard pulmonary catheter. The catheter was introduced, and its placement controlled by pressure wave monitoring. Optimal positioning of catheter tip would be in left pulmonary artery but no X-ray control of position was done to minimise patient discomfort as recent data supplied by manufacturer has suggested placement in right artery is almost as effective. The first shock was delivered with 3 J. Following each shock, 12-lead ECG was obtained to assess sinus rhythm. If rhythm was not converted, shock energy was increased by increments of 3 J to a maximum of 15 J. If no response after 15 J shock, the patient was classified as being not responsive. When awake and haemodynamically stable patients were returned to the ward. Non-responders received treatment according to the preference of the doctor in charge and were excluded from further evaluation. Duration Unclear. Concurrent medication/care: Patients allowed treatment with intravenous digoxin if tachycardia led to haemodynamic instability at any time prior to the intervention. If this treatment was not successful in establishing stability and further treatment was required, patients were excluded from further evaluation. Indirectness: No indirectness Further details: 1. Concomitant perioperative prophylactic treatment: Not stated / Unclear (No details). (n=9) Intervention 2: Rhythm control - K+ blockers. Standard pulmonary artery catheter for delivery of intravenous amiodarone. Bolus dose of 250 mg followed by continuous infusion of 0.6 mg/kg/h. Duration Unclear. Concurrent medication/care: Prior to randomisation: All patients received multiport three-lumen central venous catheter including an introducer sheath for easy introduction of a pulmonary catheter at any time following operation during observation period. Anesthesia was administered after routine management: induction with midazolam, sufentanil, etomidate and pancuronium, while maintenance was by continuous infusion of sufentanil and propofol. No patient required a pulmonary artery catheter for the intraoperative or immediate postoperative periods. Surgery performed in standardised manner with cardiopulmonary bypass and cold blood cardioplegia. After surgery, patients transferred to intensive care unit and were rapidly weaned off ventilator. Following development of AF and randomisation: Patients allowed treatment with intravenous digoxin if tachycardia led to haemodynamic instability at any time prior to the intervention. If this treatment was not successful in establishing stability and further treatment was required, patients were excluded from further evaluation. Indirectness: No indirectness

	Further details: 1. Concomitant perioperative prophylactic treatment: Not stated / Unclear (No details).
Funding	Academic or government funding (Supported by a Grant of the Lord Major of the City of Vienna (project nr. 1850))
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DC CARDIOVERSION (LOW-ENERGY CARDIOVERSION; ALERT SYSTEM) versus K+ BLOCKERS (AMIODARONE) Protocol outcome 1: Need for rescue DC cardioversion at Define - Actual outcome for No pre-existing AF: Need for transthoracic cardioversion at Post-24 h; Group 1: 0/5, Group 2: 1/6 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Some differences in sex distribution, heart rate and mean arterial pressure ; Blinding details: Outcome subjective as could have been physician decision whether to perform transthoracic cardioversion or another approach; Group 1 Number missing: 4, Reason: Those that failed to convert at all using low-energy cardioversion were not evaluated further; Group 2 Number missing: 3, Reason: Study states event no. for those that had sinus rhythm after 24 h - 3 did not have sinus rhythm at 24 h Protocol outcome 2: Achievement of sinus rhythm at Define - Actual outcome for No pre-existing AF: Conversion to sinus rhythm at 24 h; Group 1: 2/9, Group 2: 6/9; Comments: In low-energy group, 5/9 converted but only 2/9 retained at 24 h. Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Some differences in sex distribution, heart rate and mean arterial pressure ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Health-related quality of life at Define; Rehospitalisation (all-cause) at Define; Mortality at Define; Stroke or thromboembolic complications at Define; Rehospitalisation for AF at Define; Adverse events at Define; Freedom from anticoagulation at Define; Freedom from antiarrhythmic drug use at Define; Intensive care unit length of stay at Define; Hospital length of stay at Define

Study	**Gillinov2016[35]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=523)
Countries and setting	Conducted in Canada, USA; Setting: Secondary care
Line of therapy	1st line
Duration of study	Intervention time: 60 days - drugs could be continued for 60 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Electrocardiography
Stratum	No pre-existing AF: History of AF was an exclusion criterion
Subgroup analysis within study	Not applicable
Inclusion criteria	Haemodynamically stable adults; undergone elective surgery to treat coronary artery disease or heart valve disease; postoperative atrial fibrillation persisting for >60 min or recurrent episodes of atrial fibrillation during index hospitalisation
Exclusion criteria	History of atrial fibrillation
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Rate control, 69.2(9.8) years; rhythm control, 68.4(8.4) years. Gender (M:F): Rate control, 197/65; rhythm control, 199/62. Ethnicity: Rate control: Hispanic, 3.8%; White, 92.4%. Rhythm control: Hispanic, 4.6%; White, 95.4%.
Further population details	1. Existence of heart failure: No heart failure (>75% without heart failure). 2. Type of AF: Not stated / Unclear (No details). 3. Type of cardiothoracic surgery: Not stated / Unclear (~60% had some form of valve intervention. Exact proportion with intervention on mitral valve not clear as valve type only given for replacement, not repair).

Extra comments	Median (IQR) body mass index: 27.6 (25.1-30.9) vs. 28.5 (25.4-31.9); diabetes: 31.3 vs. 30.3%; heart failure: 13.4 vs. 12.6%; hypertension: 73.7 vs. 75.9%; previous myocardial infarction: 19.1 vs. 18.4%; stroke: 6.5 vs. 5.7%; previous revascularisation: 17.6 vs. 15.7%; valve disease: 53.4 vs. 56.7%; ace inhibitor: 34 vs. 32.2%; ARB: 19.5 vs. 18%; beta-blocker: 61.8 vs. 55.6%; calcium channel blocker: 19.8 vs. 22.2%; diuretic: 30.2 vs. 31%; nitrate: 22.9 vs. 21.1%. . Index procedure - CABG only: 42.7 vs. 38.3%; valve repair only: 14.9 vs. 16.5%; CABG + valve repair: 3.8 vs. 2.7%; valve replacement only: 22.9 vs. 25.3%; CABG + valve replacement: 15.6 vs. 17.2%. Median (IQR) bypass time: 95 (73.5-127.5) vs. 94 (78-126) min; median (IQR) aortic cross-clamp time: 73.5 (53.5-96) vs. 73 (57.5-93.5) min.
Indirectness of population	No indirectness
Interventions	(n=262) Intervention 1: Rate control - Mixed. Received medications to slow heart rate with aim of achieving a resting heart rate <100 beats/min. Patients in whom sinus rhythm was not restored after rate control could be switched to rhythm control if provider thought necessary to improve haemodynamic status or alleviate symptoms. No further details on the interventions given. Duration 60 days. Concurrent medication/care: If patients remained in atrial fibrillation or had recurrent atrial fibrillation 48 hours after randomization, anticoagulation with warfarin (target international normalized ratio, 2 to 3) was recommended, and bridging with low-molecular-weight heparin was allowed. Anticoagulation was recommended to be continued for 60 days, unless complications occurred. Indirectness: Serious indirectness; Indirectness comment: Unclear which rate control drugs were used/recommended, and at which doses Further details: 1. Concomitant perioperative prophylactic treatment: Not stated / Unclear (No details). (n=261) Intervention 2: Rhythm control - Mixed. Amiodarone with or without rate-slowing agent. If atrial fibrillation persisted for 24-48 h after randomisation, direct current cardioversion was recommended. Recommended dose of amiodarone was 3 g of oral amiodarone before hospital discharge with a maintenance dose of 200 mg/day or less if direct current cardioversion was successful. It was recommended that the use of amiodarone be extended for 60 days, but discontinuation was allowed for amiodarone-related adverse events, such as bradycardia, corrected QT interval >480 msec or neuropathy. Duration 60 days. Concurrent medication/care: If patients remained in atrial fibrillation or had recurrent atrial fibrillation 48 hours after randomization, anticoagulation with warfarin (target international normalized ratio, 2 to 3) was recommended, and bridging with low-molecular-weight heparin was allowed. Anticoagulation was recommended to be continued for 60 days, unless complications occurred. Indirectness: No indirectness Further details: 1. Concomitant perioperative prophylactic treatment: Not stated / Unclear (No details).

Funding	Academic or government funding (Supported by cooperative agreement funded by the National Heart, Lung and Blood Institute and the National Institute of Neurological Disorders and Stroke of the National Institutes of Health, Bethesda, MD, and the Canadian Institutes of Health Research. Various authors report potential conflicts of interest with industry links.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MIXED (RATE CONTROL) versus MIXED (RHYTHM CONTROL)

Protocol outcome 1: Rehospitalisation (all-cause) at Define
- Actual outcome for No pre-existing AF: Readmission (any cause) at 60 days; Group 1: 79/262, Group 2: 80/261; Comments: Note that event rate includes some who may have had the event more than once. Study also gives as rate/100 patient months, which will use for analysis: rate control, 18.5 vs. rhythm control, 18.5 events/100 patient months. P=0.99. Rate ratio: 1.

Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Blinding: likely to be unblinded as different drug options could be selected for each patient. Incomplete outcome: results given as rate/100 patient-months from which rate ratio could be calculated. Unclear number that did not reach 60 days in each group.; Indirectness of outcome: No indirectness ; Group 1 Number missing: , Reason: Some may not have been followed-up for 60 days and therefore less time to experience the events to contribute to the rate/100 patient-months calculation; Group 2 Number missing: , Reason: Some may not have been followed-up for 60 days and therefore less time to experience the events to contribute to the rate/100 patient-months calculation

Protocol outcome 2: Mortality at Define
- Actual outcome for No pre-existing AF: Mortality at 60 days; Group 1: 3/262, Group 2: 2/261

Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Blinding: likely to be unblinded as different drug options could be selected for each patient.; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Stroke or thromboembolic complications at Define
- Actual outcome for No pre-existing AF: Serious and non-serious cerebrovascular (including stroke and TIA) and/or non-cerebral thromboembolism at 60 days; Group 1: 7/262, Group 2: 3/261; Comments: Note that event rate includes some who may have had the event more than once. Study also gives as rate/100 patient months, which will use for analysis: rate control, 1.4 vs. rhythm control, 0.6 events/100 patient months. Rate ratio: 2.33.

Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Blinding: likely to be unblinded as different drug options could be selected for each patient. Incomplete outcome: results given as rate/100 patient-months from which rate ratio could be calculated. Unclear number that did not reach 60 days in each group. ; Indirectness of outcome: No indirectness ; Group 1 Number missing: , Reason: Some may not have been followed-up for 60 days and therefore less time to experience the events to contribute to the rate/100 patient-months calculation; Group 2 Number missing: , Reason: Some may not have been followed-up for 60 days and therefore less time to experience the events to contribute to the rate/100 patient-months calculation

Protocol outcome 4: Need for rescue DC cardioversion at Define
- Actual outcome for No pre-existing AF: Direct current cardioversion at 60 days; Group 1: 24/262, Group 2: 36/261; Comments: DC cardioversion was recommended as part of the protocol in the rhythm control group if sinus rhythm not restored within 24-48 h, which may explain higher number.
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Blinding: likely to be unblinded as different drug options could be selected for each patient. Outcome reporting: DC cardioversion was part of the recommended strategy in rhythm control group if amiodarone did not restore sinus rhythm within 24-48 h, which may explain higher number in rhythm control group.; Indirectness of outcome: No indirectness ; Blinding details: Whether or not patient received direct current cardioversion based on decision by physicians; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 5: Rehospitalisation for AF at Define
- Actual outcome for No pre-existing AF: Readmission (treatment of atrial fibrillation) at 60 days; Group 1: 11/262, Group 2: 17/261; Comments: Note that event rate includes some who may have had the event more than once. Study also gives as rate/100 patient months, which will use for analysis: rate control, 2.6 vs. rhythm control, 3.9 events/100 patient months. P=0.27. Rate ratio: 0.67.
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Blinding: likely to be unblinded as different drug options could be selected for each patient. Incomplete outcome: results given as rate/100 patient-months from which rate ratio could be calculated. Unclear number that did not reach 60 days in each group. ; Indirectness of outcome: No indirectness ; Group 1 Number missing: , Reason: Some may not have been followed-up for 60 days and therefore less time to experience the events to contribute to the rate/100 patient-months calculation; Group 2 Number missing: , Reason: Some may not have been followed-up for 60 days and therefore less time to experience the events to contribute to the rate/100 patient-months calculation

Protocol outcome 6: Achievement of sinus rhythm at Define
- Actual outcome for No pre-existing AF: In sinus rhythm at hospital discharge; Group 1: 233/259, Group 2: 242/259
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Blinding: likely to be unblinded as different drug options could be selected for each patient. Outcome reporting: does not give number in each group analysed at later time-points so longer term results could not be extracted.; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 3 deaths; Group 2 Number missing: 2, Reason: 2 deaths

Protocol outcome 7: Adverse events at Define
- Actual outcome for No pre-existing AF: Serious and non-serious adverse events (other than cerebrovascular/non-cerebral thromboembolism) at 60 days; Group 1: 148/262, Group 2: 157/261; Comments: Note that event rate includes some who may have had the event more than once. Study also gives as rate/100 patient months, which will use for analysis: rate control, 30.1 vs. rhythm control, 31.4 events/100 patient months. Rate ratio: 0.96.
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Blinding: likely to be unblinded as different drug options could be selected for each patient. Incomplete outcome: results given as rate/100 patient-months from which rate ratio could be calculated. Unclear number that did not reach 60 days in each group. ; Indirectness of outcome: No indirectness ; Blinding details: Recording of certain adverse events could have been subjective based on individual clinician interpretation; Group 1 Number missing: ,

Reason: Some may not have been followed-up for 60 days and therefore less time to experience the events to contribute to the rate/100 patient-months calculation; Group 2 Number missing: , Reason: Some may not have been followed-up for 60 days and therefore less time to experience the events to contribute to the rate/100 patient-months calculation Protocol outcome 8: Hospital length of stay at Define - Actual outcome for No pre-existing AF: Hospital length of stay at 60 days; median (IQR) given instead of mean and SD – Group 1 (rate control): 5.1 (3.0-7.4) days (n=262), Group 2 (rhythm control): 5.0 (3.2-7.5) days (n=261) Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Blinding: likely to be unblinded as different drug options could be selected for each patient. ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 9: Freedom from anticoagulation at Define - Actual outcome for No pre-existing AF: No warfarin prescription at discharge at Discharge from hospital; Group 1: 150/262, Group 2: 148/261 Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Blinding: likely to be unblinded as different drug options could be selected for each patient. ; Indirectness of outcome: No indirectness ; Blinding details: Whether or not patient received warfarin anticoagulation likely to be based on physician decision; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Health-related quality of life at Define; Intensive care unit length of stay at Define; Freedom from antiarrhythmic drug use at Define

Study	Gray 1982[37]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=22)
Countries and setting	Conducted in USA; Setting: Secondary care
Line of therapy	1st line
Duration of study	Intervention + follow up: Follow-up up to 24 h following short intravenous interventions
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: 12-lead ECG and Holter monitoring used before treatments initiated
Stratum	Mixed/unclear: No details of whether pre-existing AF was an exclusion criterion - 18.1% had history of atrial tachyarrhythmias
Subgroup analysis within study	Not applicable:
Inclusion criteria	Development of supraventricular tachyarrhythmias (atrial fibrillation, atrial flutter or atrial tachycardias) following open heart surgery;
Exclusion criteria	Age >74 years or <21 years; evidence of renal or hepatic failure; received propanolol24 h previously
Recruitment/selection of patients	Not clear
Age, gender and ethnicity	Age - Mean (SD): 59.8 years (SD not reported). Gender (M:F): Not reported. Ethnicity: Not reported
Further population details	1. Existence of heart failure: Not stated / Unclear (No details regarding heart failure). 2. Type of AF: Not stated / Unclear (No details for AF type). 3. Type of cardiothoracic surgery: Non-mitral valve surgery (>75% coronary artery bypass grafting).
Extra comments	Type of surgery: coronary artery bypass grafting, 86.4%; double valve replacement (aortic and mitral), 9.09%; mitral commissurotomy and aortic valve replacement, 4.56%. Digoxin had been given in 20 patients (mean dose 0.5 mg)

	within the 24 h prior to administration of verapamil. With exception of 1 patient studied 90 days after surgery, all patients were studied between 1 and 6 days after operation (mean 3.2 days).
Indirectness of population	Serious indirectness: >10% with atrial flutter rather than atrial fibrillation
Interventions	(n=11) Intervention 1: Rate control - Calcium channel blockers. Intravenous verapamil. Low-dose verapamil (0.075 mg/kg body weight, up to maximum of 10 mg) administered as bolus intravenous injection over 1 min. A positive response was observed if the patient converted to sinus rhythm or the heart rate decreased below 100 bpm (120 bpm in digoxin-treated patients). If no positive response was seen within 10 min, a higher dose was administered consisting of 0.15 mg/kg verapamil. If no response was seen after 15 min, drug B (placebo) was administered first in low dose and then in high dose as described for the placebo intervention. Duration 30 min. Concurrent medication/care: Digoxin had been given in 20 patients (mean dose 0.5 mg) within the 24 h prior to administration of verapamil. Indirectness: Serious indirectness; Indirectness comment: Those that did not achieve positive response with first drug were switched over to the other drug, which may affect outcomes. Further details: 1. Concomitant perioperative prophylactic treatment: Concomitant perioperative prophylactic treatment (e.g. with beta-blockers or statins) (Digoxin had been given in 20 patients prior to verapamil administration.). (n=11) Intervention 2: Placebo. Intravenous placebo. Volume of placebo similar to that used in verapamil administration was administered as bolus intravenous injection over 1 min. A positive response was observed if the patient converted to sinus rhythm or the heart rate decreased below 100 bpm (120 bpm in digoxin-treated patients). If no positive response was seen within 10 min, a higher dose was administered consisting of a volume of placebo similar to that used for the higher dose of verapamil. If no response was seen after 15 min, drug B verapamil) was administered first in low dose and then in high dose as described for the verapamil intervention. Duration 30 min. Concurrent medication/care: Digoxin had been given in 20 patients (mean dose 0.5 mg) within the 24 h prior to administration of verapamil. Indirectness: Serious indirectness; Indirectness comment: Those that did not achieve positive response with first drug were switched over to the other drug, which may affect outcomes. Further details: 1. Concomitant perioperative prophylactic treatment: Concomitant perioperative prophylactic treatment (e.g. with beta-blockers or statins) (Digoxin had been given in 20 patients prior to verapamil administration.).
Funding	Study funded by industry (Financial support provided by Knoll Pharmaceutical Company, Whippany, NJ)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CALCIUM CHANNEL BLOCKERS (VERAPAMIL) versus PLACEBO Protocol outcome 1: Adverse events at Define - Actual outcome for Mixed/unclear: Adverse reaction or unusual haemodynamic response at 24 h; Group 1: 0/11, Group 2: 0/11 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Comments - Blinding/performance: very limited information about care patients received. Outcome could be subjective as types of reactions included not clear. Measurement: no details as to what would have been included as an adverse event. Crossover studies: only those that did not receive desired response crossed over, so represents parallel trial with switching option rather than true crossover trial; Indirectness of outcome: No indirectness ; Baseline details: Very limited information for the two intervention groups; Group 1 Number missing: , Reason: Some switched but amount unclear, as 0 events in both arms able to extract as randomised.; Group 2 Number missing: , Reason: Some switched but amount unclear, as 0 events in both arms able to extract as randomised.	
Protocol outcomes not reported by the study	Health-related quality of life at Define; Rehospitalisation (all-cause) at Define; Mortality at Define; Stroke or thromboembolic complications at Define; Need for rescue DC cardioversion at Define; Rehospitalisation for AF at Define; Achievement of sinus rhythm at Define; Freedom from anticoagulation at Define; Freedom from antiarrhythmic drug use at Define; Intensive care unit length of stay at Define; Hospital length of stay at Define

Study	Hwang 1984[51]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=14)
Countries and setting	Conducted in USA; Setting: Secondary care
Line of therapy	1st line
Duration of study	Intervention + follow up: Follow-up up to hospital discharge.
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: 12-lead ECG and continuous on-line single-lead ECG monitoring performed before treatments received
Stratum	No pre-existing AF: Inclusion criteria were being in normal sinus rhythm prior to and immediately after surgery
Subgroup analysis within study	Not applicable:
Inclusion criteria	Presence of sinus rhythm prior to and immediately following surgery; development of supraventricular tachycardia with a ventricular response >120 beats/min during postoperative period and persisting for at least 1 h
Exclusion criteria	Preoperative left ventricular ejection fraction <45% or clinical postoperative cardiac failure; hypotension (<systolic pressure below 90 mmHg); notable valvular heart disease; impaired atrioventricular conduction or evidence of depressed sinus node automaticity; impaired hepatic or renal function; administration of beta-blocking drugs or disopyramide within previous 48 h
Recruitment/selection of patients	Not clear
Age, gender and ethnicity	Age - Mean (range): 53 (39-64) years. Gender (M:F): 12/2. Ethnicity: Not reported
Further population details	1. Existence of heart failure: No heart failure (LVEF <45% preoperatively excluded. Clinical postoperative heart failure also exclusion criterion.). 2. Type of AF: Not stated / Unclear (No details about AF type). 3. Type of cardiothoracic surgery: Non-mitral valve surgery (All received non-valvular surgery).

Extra comments	Mean (range) weight: 85 (80-100) kg; mean (range) preoperative LVEF: 62 (49-74)%. Surgical procedures performed: aortocoronary bypass, 85.7%; aortocoronary bypass +thymectomy, 7.1%; atrial septal defect closure, 7.1%. Postoperative arrhythmia type: atrial fibrillation,78.6%; atrial flutter, 21.4%. Tachycardia occurred 1-8 days after operation and last for 1-5 h before initiation of the study. 6 patients receiving digoxin at the time of the study.
Indirectness of population	Serious indirectness: >10% with atrial flutter instead of atrial fibrillation
Interventions	(n=6) Intervention 1: Rate control - Calcium channel blockers. Intravenous verapamil. First dose of0.075 mg/kg given intravenously over 1 min. If therapeutic end point was not achieved after 15 min, administration of verapamil was repeated at a dose of 0.15 mg/kg, up to a maximum of 10 mg. After a further 30 min, if therapeutic end point not achieved, the second drug (placebo) was administered in a similar fashion. Duration 30 min. Concurrent medication/care: 6 patients were receiving digoxin at the time of the study. Indirectness: Serious indirectness; Indirectness comment: Those that did not achieve positive response with first drug were switched over to the other drug, which may affect outcomes. Further details: 1. Concomitant perioperative prophylactic treatment: Concomitant perioperative prophylactic treatment (e.g. with beta-blockers or statins) (6 patients receiving digoxin at time of study). (n=8) Intervention 2: Placebo. Intravenous placebo. First dose of 0.075 mg/kg placebo given intravenously over 1 min. If therapeutic end point was not achieved after 15 min, administration of placebo was repeated at a dose of 0.15 mg/kg, up to a maximum of 10 mg. After a further 30 min, if therapeutic end point not achieved, the second drug (verapamil) was administered in a similar fashion. Duration 30 min. Concurrent medication/care: 6 patients were receiving digoxin at the time of the study. Indirectness: Serious indirectness Further details: 1. Concomitant perioperative prophylactic treatment: Concomitant perioperative prophylactic treatment (e.g. with beta-blockers or statins) (6 patients receiving digoxin at time of study).
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CALCIUM CHANNEL BLOCKERS (VERAPAMIL) versus PLACEBO

Protocol outcome 1: Achievement of sinus rhythm at Define
- Actual outcome for No pre-existing AF: In sinus rhythm at end of hospital stay at In-hospital; At end of study, all patients had received verapamil, as those in placebo arm did not convert to sinus rhythm and were therefore switched to verapamil. Of all the patients receiving verapamil, at end of study 3/14 remained in sinus rhythm at the end of their hospital stay. Of these, 2 had been receiving oral doses of digoxin or propanololhydrochloride, but none maintained on oral doses of verapamil.;

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Incomplete outcome: results given in terms of which group they were in at the end of the study - all patients in placebo switched to receive verapamil so no results given separately for the placebo group. Crossover studies: only those that did not receive desired response crossed over, so represents parallel trial with switching option rather than true crossover trial; Indirectness of outcome: No indirectness ; Baseline details: Limited factors described so difficult to compare groups; Group 1 Number missing: , Reason: Switching between groups occurred but extent within each unclear, all those that received at least one dose of verapamil (including those switching from placebo if no response) analysed in verapamil group; Group 2 Number missing: , Reason: Switching between groups occurred but extent within each unclear, all those that received at least one dose of verapamil (including those switching from placebo if no response) analysed in verapamil group Protocol outcome 2: Adverse events at Define - Actual outcome for No pre-existing AF: Adverse events requiring premature termination of study (such as hypotension or bradycardia) at In-hospital; Group 1: 0/6, Group 2: 0/8 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Blinding/performance: Outcome could be subjective as types of reactions included not clear. Measurement: no details as to what would have been included as an adverse event. Crossover studies: only those that did not receive desired response crossed over, so represents parallel trial with switching option rather than true crossover trial; Indirectness of outcome: No indirectness ; Baseline details: Limited factors described so difficult to compare groups; Blinding details: Outcome not very well described and likely to be subjective; Group 1 Number missing: , Reason: Switching between groups occurred but extent within each unclear, as 0 events in each arm could extract as randomised; Group 2 Number missing: , Reason: Switching between groups occurred but extent within each unclear, as 0 events in each arm could extract as randomised	
Protocol outcomes not reported by the study	Health-related quality of life at Define; Rehospitalisation (all-cause) at Define; Mortality at Define; Stroke or thromboembolic complications at Define; Need for rescue DC cardioversion at Define; Rehospitalisation for AF at Define; Freedom from anticoagulation at Define; Freedom from antiarrhythmic drug use at Define; Intensive care unit length of stay at Define; Hospital length of stay at Define

Study	**Kowey2009[64]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=190)
Countries and setting	Conducted in Argentina, Canada, Denmark, India, Italy, Poland, USA; Setting: Secondary care

Line of therapy	1st line
Duration of study	Intervention + follow up: Follow-up up to 30 days post-dosing
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ECG, telemetry and Holter monitoring mentioned
Stratum	No pre-existing AF: Documented sinus rhythm before and immediately following surgery was an inclusion criterion
Subgroup analysis within study	Not applicable
Inclusion criteria	≥18 years old; sustained atrial fibrillation or atrial flutter (lasting 3-72 h) occurring between 24 h and 7 days following CABG, valvular surgery or both; haemodynamically stable (systolicblood pressure >90 mmHg and <160 mmHg, diastolic blood pressure <95 mmHg); weight between 45 and 136 kg; documented sinus rhythm before and after surgery; using effective form of birth control if premenopausal
Exclusion criteria	Pregnancy or nursing; uncorrected QT interval >500 ms; a ventricular response rate to AF <45 bpm; aQRS interval >140 ms without a pacemaker; second- or third-degree atrioventricular block; a history of torsadesde pointes; unstable class IV congestive heart failure; serious hepatic or renal disease; end-stage disease states; reversible cause of AF such as hyperthyroidism or pulmonary embolism; uncorrected electrolyte imbalance; digoxin toxicity; received another investigational drug or intravenous vernakalant in the 30 days prior to enrolment; oral amiodarone use within previous 3 months; administration of amiodarone with previous 24 h; class I or III antiarrhythmic drugs administered following cardiac surgery
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Vernakalant, 67.8 (6.4) years; placebo, 68.3 (7.7) years. Gender (M:F): Define. Ethnicity: White: vernakalant, 94.4%; placebo, 92.6%

Further population details	1. Existence of heart failure: No heart failure (<40% in each group had heart failure at baseline). 2. Type of AF: Not stated / Unclear (Not reported). 3. Type of cardiothoracic surgery: Non-mitral valve surgery (Majority following CABG surgery - some with valve intervention but unclear if mitral valve).
Extra comments	Surgery type: CABG (66.4 vs. 68.5%), valvular (26.2 vs. 18.5%) or both (7.5 vs. 13.0%); mean (SD) left atrial diastolic dimension, 42.0 (6.6) vs. 42.9 (6.8) mm; LVEF <50%, 36 vs. 30.8%; hypertension, 67.3 vs. 74.1%; ischaemic heart disease, 78.5 vs. 83.3%; heart failure, 33.6 vs. 27.8%. Concomitant therapy: any rate control (66.4 vs. 70.4%); beta-blockers (59.8 vs. 70.4%); calcium channel blockers (6.5 vs. 5.6%); digitalis glycosides (8.4 vs. 5.6%); class I antiarrhythmics (0 vs. 0%); class III antiarrhythmics (3.7 vs. 5.6%)
Indirectness of population	No indirectness: Includes some with atrial flutter instead of atrial fibrillation but this was <10% in both groups: atrial fibrillation, 93.5 vs. 92.6%; atrial flutter, 5.6 vs. 7.4%.
Interventions	(n=127) Intervention 1: Rhythm control - K+ blockers .10 min infusion of 3.0 mg/kg vernakalant followed by a 15 min observation period. If the patient did not demonstrate conversion to sinus rhythm, a second 10 min infusion of 2.0 mg/kg vernakalant was administered. The infusion was discontinued if any of the following were observed: uncorrected QT interval ≥550 msor prolongation of the uncorrected QT interval >25%, HR <45 bpm lasting ≥30 seconds with symptoms or <40 bpm lasting ≥30 seconds with or without symptoms, systolic blood pressure >190 mmHg or <85 mmHg or new requirement for inotropic support, new bundle-branch block or QRS interval prolongation of ≥50%, any polymorphic ventricular tachycardia, sinus pause of ≥5 seconds, change in cardiac rhythm or AV conduction that compromised patient safety, or any intolerable side effects. . Duration 1 or 2 x 10 min infusions. Concurrent medication/care: Electric cardioversion and the administration of any additional antiarrhythmic medication were withheld for at least 2 h after dosing. Indirectness: No indirectness Further details: 1. Concomitant perioperative prophylactic treatment: Not stated / Unclear (Unclear whether perioperative drugs given prophylactically or only after AF developed). (n=63) Intervention 2: Placebo. 10 min infusion of 3.0 mg/kg placebo (normal saline solution) followed by a 15 min observation period. If the patient did not demonstrate conversion to sinus rhythm, a second 10 min infusion of 2.0 mg/kg placebo was administered. The infusion was discontinued if any of the following were observed: uncorrected QT interval ≥550 msor prolongation of the uncorrected QT interval >25%, HR <45 bpm lasting ≥30 seconds with symptoms or <40 bpm lasting ≥30 seconds with or without symptoms, systolic

	blood pressure >190 mmHg or <85 mmHg or new requirement for inotropic support, new bundle-branch block or QRS interval prolongation of ≥50%, any polymorphic ventricular tachycardia, sinus pause of ≥5 seconds, change in cardiac rhythm or AV conduction that compromised patient safety, or any intolerable side effects. . Duration 1 or 2 x 10 min infusions. Concurrent medication/care: Electric cardioversion and the administration of any additional antiarrhythmic medication were withheld for at least 2 h after dosing. Indirectness: No indirectness Further details: 1. Concomitant perioperative prophylactic treatment: Not stated / Unclear (Unclear whether perioperative drugs given prophylactically or only after AF developed).
Funding	Study funded by industry (Study sponsored by Astellas Pharma US, Inc (Deerfield, Ill) and CardiomePharma Corp (Vancouver, British Columbia, Canada))

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: K+ BLOCKERS (VERNAKALANT) versus PLACEBO

Protocol outcome 1: Mortality at Define
- Actual outcome for No pre-existing AF: Deaths at 30 days; Group 1: 0/106, Group 2: 0/54
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 20, Reason: Not treated due to spontaneous SR conversion (n=17), withdrawn consent (n=2) or required use of prohibited medication (n=1); Group 2 Number missing: 9, Reason: Not treated due to spontaneous SR conversion (n=7), investigator decision (n=1) or being ineligible for the study (n=1)

Protocol outcome 2: Achievement of sinus rhythm at Define
- Actual outcome for No pre-existing AF: Conversion to sinus rhythm within 90 min of first infusion (duration at least 1 min) at 90 min; Group 1: 48/107, Group 2: 8/54
Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 20, Reason: Not treated due to spontaneous SR conversion (n=17), withdrawn consent (n=2) or required use of prohibited medication (n=1); Group 2 Number missing: 9, Reason: Not treated due to spontaneous SR conversion (n=7), investigator decision (n=1) or being ineligible for the study (n=1)

Protocol outcome 3: Adverse events at Define
- Actual outcome for No pre-existing AF: Serious adverse events at 30 days; Group 1: 10/107, Group 2: 6/54

Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 20, Reason: Not treated due to spontaneous SR conversion (n=17), withdrawn consent (n=2) or required use of prohibited medication (n=1); Group 2 Number missing: 9, Reason: Not treated due to spontaneous SR conversion (n=7), investigator decision (n=1) or being ineligible for the study (n=1) - Actual outcome for No pre-existing AF: Treatment-emergent adverse events at 24 h; Group 1: 41/107, Group 2: 17/54 Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 20, Reason: Not treated due to spontaneous SR conversion (n=17), withdrawn consent (n=2) or required use of prohibited medication (n=1); Group 2 Number missing: 9, Reason: Not treated due to spontaneous SR conversion (n=7), investigator decision (n=1) or being ineligible for the study (n=1)	
Protocol outcomes not reported by the study	Health-related quality of life at Define; Rehospitalisation (all-cause) at Define; Stroke or thromboembolic complications at Define; Need for rescue DC cardioversion at Define; Rehospitalisation for AF at Define; Freedom from anticoagulation at Define; Freedom from antiarrhythmic drug use at Define; Intensive care unit length of stay at Define; Hospital length of stay at Define

Study (subsidiary papers)	**Lee 2000[68](Lee 2003[67])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=50)
Countries and setting	Conducted in Canada; Setting: Secondary care
Line of therapy	1st line
Duration of study	Intervention + follow up: Follow-up 8 weeks post-hospital discharge
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: 12-lead ECG
Stratum	No pre-existing AF: Those with history of paroxysmal AF excluded
Subgroup analysis within study	Not applicable
Inclusion criteria	Development of atrial fibrillation lasting at least 1 h following heart surgery; ability to give informed consent; 18 years of age or above
Exclusion criteria	History of paroxysmal atrial fibrillation; received antiarrhythmic therapy within 5 half-livesof the time of randomisation; had beta-blockers withdrawn after surgery; were in cardiogenic shock; had a creatinine level of >200 µg/mmol; had serum aspartate aminotransferase or alanine aminotransferase concentrations 4 times the upper limit of normal; had conduction disturbances before randomisation; contraindications to anticoagulation
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Conversion, 67 (7) years; rate control, 70 (5) years. Gender (M:F): Conversion, 21/6; rate control, 18/5.. Ethnicity: Not reported
Further population details	1. Existence of heart failure: Not stated / Unclear (LVEF 49% and 47% respectively). 2. Type of AF: Not stated / Unclear (Type of AF unclear). 3. Type of cardiothoracic surgery: Non-mitral valve surgery (30% valvular surgery in both arms - not clear if mitral valve in all cases).

Extra comments	Mean (SD) LVEF: 49 (1)% vs. 47(11)%; preoperative beta-blockers: 63 vs. 61%; valvular surgery: 30 vs. 30%; smokers: 67 vs. 56%; mean (SD)ventricular response at randomisation: 131 (35) vs. 123 (32); diabetes: 19 vs. 23%; mean (SD) postoperative timing of AF: 3(1) vs. 3(1) days; mean (SD) bypass pump time: 91 (29) vs. 84 (21) min; COPD: 15 vs. 13%; hypertension: 48 vs. 52%; preoperative calcium channel blockers: 63 vs. 36%
Indirectness of population	No indirectness
Interventions	(n=27) Intervention 1: Rhythm control - Mixed. Conversion group. Antiarrhythmic drug therapy with or without electrical cardioversion. Aimed at restoration of sinus rhythm within 48 h. Preferred initial treatment was with sotalol or propafenone, taking into consideration left ventricular function, history of coronary artery disease and contraindications to beta-blockers. Sotalol prescribed at dose of 120-360 mg/day; amiodarone at 200 mg/day after a loading dose of 1200-1600 mg for 4-5 days; and propafenone at dose of 300-900 mg/day. Procainamide given as intravenous load of 500-1000 mg followed by continuous infusion of 1-4 mg/h or 2-3 g/day in divided oral doses. If sinus rhythm was not achieved within 48 h, patients were electrically cardioverted. Duration 8 weeks post-hospital discharge. Concurrent medication/care: Rate control therapy used in rate control group were permitted if clinically indicated (i.e., ventricular rates ≥110 per min) and in patients who received propafenone because of potential for 1:1 AV conduction during atrial fibrillation. Intravenous heparin and oral warfarin started within 24 h after randomisation. Intravenous heparin delayed for 24 h if postoperative chest tube removal was delayed. Dose of heparin was titrated to maintain a partial thromboplastin time between 80 and 100 seconds. Warfarin doses adjusted to obtain an INR between 2 and 3. Anticoagulation continued until end of study (2 months).Indirectness: Serious indirectness; Indirectness comment: Includes some interventions not available in UK, such as procainamide - <10% used this in study. Further details: 1. Concomitant perioperative prophylactic treatment: Not stated / Unclear (No details of beta-blocker or other drug use perioperatively). (n=23) Intervention 2: Rate control - Mixed. Rate control drugs. Preferred initial treatment was intravenous diltiazem for those requiring intravenous agent on basis of symptom severity and beta-blockers in those treated with oral agents. Intravenous diltiazem administered as initial bolus of 5-20 mg followed by continuous infusion of 5-15 mg/h. Oral diltiazem given at 120-360 mg/day and verapamil given orally in similar fashion. Metoprolol given at dose of 25-100 mg/day in 2 divided doses, atenolol given at dose of 25-100 mg/day, propanolol given at a dose of 30-120 mg in 3 divided doses and esmolol given at 0.05 mg/kg per minute intravenous loading followed by maintenance dose of 0.05-0.2 mg/kg per minute. Digoxin loading administered either intravenously or orally - oral loading dose of 0.25-0.5 mg digoxin was given followed by 0.25 mg every 4-6 hours until a loading dose of 1 mg had been given. Intravenous digoxin administered in similar fashion. Daily maintenance dose of 0.25 mg was administered thereafter for digoxin. Duration 8 weeks post-hospital discharge. Concurrent medication/care: Intravenous heparin and oral warfarin started within 24 h after randomisation. Intravenous heparin delayed for 24 h if postoperative chest tube removal was delayed. Dose of

	heparin was titrated to maintain a partial thromboplastin time between 80 and 100 seconds. Warfarin doses adjusted to obtain an INR between 2 and 3. Anticoagulation continued until end of study (2 months). Indirectness: Serious indirectness; Indirectness comment: Includes some interventions not available in UK, such IV administration of diltiazem - proportion that received this unclear Further details: 1. Concomitant perioperative prophylactic treatment: Not stated / Unclear (No details of beta-blocker or other drug use perioperatively).
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MIXED (ANTIARRYTHMIC DRUGS WITH/WITHOUT ELECTRICAL CARDIOVERSION) versus MIXED (RATE CONTROL DRUGS)

Protocol outcome 1: Mortality at Define
- Actual outcome for No pre-existing AF: Mortality at 8 weeks post-discharge from hospital; Group 1: 2/27, Group 2: 0/23
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Outcome reporting: 8 week time-point too short for measuring mortality?; Indirectness of outcome: No indirectness ; Baseline details: Differences in ventricular response and proportion using preoperative calcium blockers; Group 1 Number missing: 0; Group 2 Number missing: 5, Reason: 5 switched from rate control to conversion group but mortality stated as randomised

Protocol outcome 2: Achievement of sinus rhythm at Define
- Actual outcome for No pre-existing AF: Conversion to sinus rhythm at 8 weeks post-discharge from hospital; Group 1: 26/27, Group 2: 21/23; Comments: In sinus rhythm at end of 8 weeks following discharge from hospital
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Differences in ventricular response and proportion using preoperative calcium blockers; Group 1 Number missing: 0; Group 2 Number missing: 5, Reason: 5 switched from rate control to conversion group but outcome reported as randomised

Protocol outcome 3: Hospital length of stay at Define
- Actual outcome for No pre-existing AF: Hospital stay (from surgery to discharge) at In-hospital; Group 1: mean 7.4 Days (SD 0.3); n=27, Group 2: mean 9.7 Days (SD 1); n=23; Comments: P<0.01
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Differences in ventricular response and proportion using preoperative calcium blockers; Group 1 Number missing: 0; Group 2 Number missing: 5, Reason: 5 switched from rate control to conversion group but outcome reported

as randomised	
Protocol outcomes not reported by the study	Rehospitalisation (all-cause) at Define; Stroke or thromboembolic complications at Define; Need for rescue DC cardioversion at Define; Rehospitalisation for AF at Define; Adverse events at Define; Health-related quality of life at Define; Freedom from antiarrhythmic drug use at Define; Intensive care unit length of stay at Define; Freedom from anticoagulation at Define

Study	Nemati 2016[84]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=122)
Countries and setting	Conducted in Iran; Setting: Secondary care
Line of therapy	1st line
Duration of study	Intervention time: Unclear duration
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Continuous ECG monitoring for at least 96 h
Stratum	No pre-existing AF: History of AF within previous 6 months an exclusion criterion. <10% with history of AF before this period
Subgroup analysis within study	Not applicable:
Inclusion criteria	Development of postoperative atrial fibrillation (continuous AF for at least 30 min or AF requiring treatment for symptoms or hemodynamic compromise) following elective coronary artery bypass grafting
Exclusion criteria	Patients that underwent concomitant cardiac operations, such as valve procedures, at same time as coronary artery bypass grafting; patients with bradycardia (<50 beats/min in resting position); patients with > type I second-degree heart block; those with symptomatic sick sinus syndrome without a pacemaker; those taking class I or III antiarrhythmic medications; those with a history of AF within past 6 months; those with sensitivity to propafenone; cardiogenic shock; ejection fraction <30%; marked hypotension (systolic blood pressure <90 mmHg); electrolyte imbalances
Recruitment/selection of patients	Unclear
Age, gender and ethnicity	Age - Mean (SD): Propafenone, 66.7 (8.7) years; amiodarone, 68.1 (9.9) years. Gender (M:F): Not reported. Ethnicity: Not reported

Further population details	1. Existence of heart failure: No heart failure (<10% with congestive heart failure). 2. Type of AF: Not stated / Unclear (No details). 3. Type of cardiothoracic surgery: Non-mitral valve surgery (All received coronary artery bypass grafting. Those with concomitant valve procedures not included).
Extra comments	Hypertension: 70.9 vs. 77.6%; hyperlipidaemia: 69.1 vs. 67.2%; diabetes mellitus: 50.9 vs. 49.3%; congestive heart failure: 0 vs. 3.1%; chronic obstructive pulmonary disease: 16.4 vs. 31.8%; right atrium enlargement: 0 vs. 1.6%; intra-aortic balloon pump: 9.1 vs. 9.1%; previous atrial fibrillation: 9.1 vs. 3.2%. Drugs - beta-blocker: 87.3 vs. 80.6%; calcium channel blocker: 9.1 vs. 12.5%; ACE inhibitor: 34.5 vs. 25.8%. Mean (SD) preoperative K+: 4.21 (0.51) vs. 4.23 (0.71) meq/L
Indirectness of population	No indirectness
Interventions	(n=55) Intervention 1: Rhythm control - Na+ blockers. Oral propafenone. 600 mg loading dose and 150 mg every 8 h for 10 days after onset of atrial fibrillation. If AF did not resolve after this first dosing strategy, it could be repeated or switched to amiodarone. Duration 10 days. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Concomitant perioperative prophylactic treatment: Not stated / Unclear (Rate control drugs mentioned but unclear if used perioperatively). (n=67) Intervention 2: Rhythm control - K+ blockers .Intravenous amiodarone. 300 mg intravenous loading dose followed by continuous intravenous infusion of 600 mg over 12-24 h after the onset of atrial fibrillation. If AF did not resolve after this first dosing strategy, it could be repeated or switched to propafenone. Duration 24 h. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Concomitant perioperative prophylactic treatment: Not stated / Unclear (Rate control drugs mentioned but unclear if used perioperatively).
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NA+ BLOCKERS (PROPAFENONE) versus K+ BLOCKERS (AMIODARONE)

Protocol outcome 1: Need for rescue DC cardioversion at Define
- Actual outcome for No pre-existing AF: Cardioversion at End of study; Group 1: 2/55, Group 2: 3/67
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low,

Subgroups - Low, Other 1 - Low, Comments - Measurement: not clear if referring to DC cardioversion.; Indirectness of outcome: No indirectness ; Blinding details: Whether or not received cardioversion likely based on subjective decision by physicians; Group 1 Number missing: , Reason: Number switching to receive amiodarone if propafenone failed multiple doses not clear - could influence results substantially; Group 2 Number missing: , Reason: Number switching to receive propafenone if amiodarone failed multiple doses not clear - could influence results substantially Protocol outcome 2: Achievement of sinus rhythm at Define - Actual outcome for No pre-existing AF: Sinus rhythm obtained without electrical cardioversion at End of study; Group 1: 53/55, Group 2: 64/67 Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Outcome reporting: reporting of those in sinus rhythm at various points in study is very unclear.; Indirectness of outcome: No indirectness ; Group 1 Number missing: , Reason: Number switching to receive amiodarone if propafenone failed multiple doses not clear - could influence results substantially; Group 2 Number missing: , Reason: Number switching to receive propafenone if amiodarone failed multiple doses not clear - could influence results substantially - Actual outcome for No pre-existing AF: Sinus rhythm obtained after first dose (without repeating dose or switching drug) at After first dose; Group 1: 38/55, Group 2: 44/67 Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Outcome reporting: reporting of those in sinus rhythm at various points in study is very unclear. Measurement: not clear if referring to DC cardioversion.; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Adverse events at Define - Actual outcome for No pre-existing AF: Significant side effects at End of study; Group 1: 0/55, Group 2: 0/67 Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Measurement: not clear if referring to DC cardioversion.; Indirectness of outcome: No indirectness ; Blinding details: Significant side effects could be very subjective and not defined; Group 1 Number missing: , Reason: Number switching to receive amiodarone if propafenone failed multiple doses not clear - could influence results substantially; Group 2 Number missing: , Reason: Number switching to receive propafenone if amiodarone failed multiple doses not clear - could influence results substantially	
Protocol outcomes not reported by the study	Health-related quality of life at Define; Rehospitalisation (all-cause) at Define; Mortality at Define; Stroke or thromboembolic complications at Define; Rehospitalisation for AF at Define; Freedom from anticoagulation at Define; Freedom from antiarrhythmic drug use at Define; Intensive care unit length of stay at Define; Hospital length of stay at Define

Study	**Qian 2008[89]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=99)
Countries and setting	Conducted in China; Setting: Outpatient
Line of therapy	Unclear
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Two separate ECG confirmations of AF used to confirm diagnosis of permanent AF
Stratum	Pre-existing AF: Duration of AF substantially longer than time since operation, indicating present prior to operation
Subgroup analysis within study	Not applicable:
Inclusion criteria	>18 years of age; permanent atrial fibrillation for at least 6 months following prosthetic mitral valve replacement;
Exclusion criteria	moderate or severe tricuspid regurgitation; New York Heart Association heart failure class IV; history of sick sinus syndrome; history of second- or third-degree atrioventricular block; significant thyroid, pulmonary or hepatic disease; contraindications to treatment with amiodarone; significant impairment of renal function; pregnancy or females shortly intending to become pregnant; any other medical condition that in the opinion of the investigators could make the patient inappropriate for the study
Recruitment/selection of patients	Unclear
Age, gender and ethnicity	Age - Mean (SD): Rate control, 44.7 (13.1) years; pharmacological cardioversion, 45.4 (14.0) years. Gender (M:F): Rate control, 24/26; pharmacological conversion, 22/27. Ethnicity: Not reported

Further population details	1. Existence of heart failure: Not stated / Unclear (Class IV on New York Heart Association heart failure scale excluded but unclear as to less severe heart failure. LVEF <50% in both groups could suggest heart failure?). 2. Type of AF: Persistent > 1 year (Duration of AF >35 months in both groups). 3. Type of cardiothoracic surgery: Mitral valve surgery (All received mitral valve surgery).
Extra comments	Mean (SD) postoperative duration: 10.8 (4.0) vs. 11.2 (5.0) months; mean (SD) duration of AF: 35.7 (16.1) vs. 36.3 (17.5) months; mean (SD) left atrial dimension: 52.8 (6.9) vs. 53.1 (7.8) mm; mean (SD) left ventricular ejection fraction: 46.0 (13.1) vs. 45.7 (12.1) %.
Indirectness of population	No indirectness
Interventions	(n=50) Intervention 1: Rate control - Mixed. Control of ventricular rate using digoxin and diltiazem, either alone or in combination. Doses of drugs not stated. Appears to be oral dosing based on length of the study but not explicitly stated. Duration 12 months. Concurrent medication/care: INR was monitored, and warfarin dose adjusted accordingly. Indirectness: No indirectness Further details: 1. Concomitant perioperative prophylactic treatment: Not stated / Unclear (No details for this intervention arm). (n=49) Intervention 2: Rhythm control - Mixed. Pharmacological cardioversion with low-dose oral amiodarone (2 mg/kg), captopril (0.25 mg/kg) and simvastatin (0.3 mg/kg) administered daily. Heart rate was maintained at 60-80 beats/min under quiescent conditions. If needed, digoxin and/or diltiazem were also administered in these patients. Duration 12 months. Concurrent medication/care: INR was monitored, and warfarin dose adjusted accordingly. Indirectness: No indirectness Further details: 1. Concomitant perioperative prophylactic treatment: Concomitant perioperative prophylactic treatment (e.g. with beta-blockers or statins) (Captopril and simvastatin received alongside the amiodarone treatment).
Funding	Academic or government funding (Supported by a grant from the Science and Technology Bureau of Sichuan Province, People's Republic of China (No. 05SG022-014-4))

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MIXED (RATE CONTROL - DIGOXIN AND/OR DILTIAZEM) versus MIXED (PHARMACOLOGICAL CARDIOVERSION - AMIODARONE WITH CAPTOPRIL AND SIMVASTATIN)

Protocol outcome 1: Achievement of sinus rhythm at Define - Actual outcome for Pre-existing AF: Sinus rhythm conversion at 12 months at 12 months (mean, SD: 12, 1.3 months); Group 1: 3/50, Group 2: 19/49 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Blinding/performance: unclear if blinded, selection of rate control drug and whether or not rate control drugs given as well in the pharmacological conversion group may have been influenced by knowledge of patient characteristics and may affect results; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Adverse events at Define - Actual outcome for Pre-existing AF: Adverse events requiring discontinuation of one or more study drugs (treatment-related adverse events) at 12 months (mean, SD: 12, 1.3 months); Group 1: 0/50, Group 2: 7/48; Comments: 6 patients discontinued captopril after developing cough but remaining drugs in combination therapy were continued. Event leading to discontinuation of treatment completely was severe pruritus. Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Blinding/performance: unclear if blinded, selection of rate control drug and whether or not rate control drugs given as well in the pharmacological conversion group may have been influenced by knowledge of patient characteristics and may affect results; Indirectness of outcome: No indirectness ; Blinding details: Subjective as need to discontinue may have differed depending on physician interpretation; Group 1 Number missing: 0; Group 2 Number missing: 1, Reason: 1 withdrew from study as did not want to continue drug therapy - not available for follow-up to 12 months	
Protocol outcomes not reported by the study	Health-related quality of life at Define; Rehospitalisation (all-cause) at Define; Mortality at Define; Stroke or thromboembolic complications at Define; Need for rescue DC cardioversion at Define; Rehospitalisation for AF at Define; Freedom from anticoagulation at Define; Freedom from antiarrhythmic drug use at Define; Intensive care unit length of stay at Define; Hospital length of stay at Define

Study	**Simopoulos2014[101]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=41)
Countries and setting	Conducted in Greece; Setting: Secondary care
Line of therapy	1st line
Duration of study	Intervention time: Unclear - 2 weeks?
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ECG or Holter monitoring
Stratum	No pre-existing AF: History of AF an exclusion criterion
Subgroup analysis within study	Not applicable
Inclusion criteria	Development of postoperative atrial fibrillation following elective on-pump coronary artery bypass grafting
Exclusion criteria	History of AF; prior antiarrhythmic therapy
Recruitment/selection of patients	Consecutive
Age, gender and ethnicity	Age - Mean (SD): Amiodarone, 69(7) years; amiodarone + ranolazine, 67(8) years. Gender (M:F): Amidarone, 14/6; amiodarone + ranolazine, 14/7. Ethnicity: Not reported
Further population details	1. Existence of heart failure: No heart failure (LVEF >50% both groups). 2. Type of AF: Not stated / Unclear (Type of AF unclear). 3. Type of cardiothoracic surgery: Non-mitral valve surgery (coronary artery bypass grafting in all patients).
Extra comments	Mean (SD) LVEF: 52.6 (8.6) vs. 53.8 (9.4)%; mean (SD) left atrial diameter: 34.9 (3.4) vs. 33.8 (2.7) mm; diabetes: 40 vs. 38%; renal insufficiency: 15 vs. 14.28%; mean (SD) aortic cross clamp time: 52.2 (11.7) vs. 54.8 (10.1) min; mean (SD) serum potassium: 4.7 (0.2) vs. 4.7 (0.2) mEq/L

Indirectness of population	No indirectness
Interventions	(n=21) Intervention 1: Rhythm control - K+ blockers .Intravenous amiodarone. 300 mg in 30 min followed by 750 mg in 24 h. After conversion to sinus rhythm the amiodarone infusion was stopped but received amiodarone orally at a dose of 200 mg twice daily for a week and 200 mg once daily for the second week, or according to their cardiologist's advice following discharge. Duration 2 weeks? Concurrent medication/care: All patients after extubation and until discharge received a standard drug regimen that included acetylsalicylic acid (100 mg daily), atorvastatin (20-40 mg daily), the beta-blocker metoprolol (50-100 mg daily), and the angiotensin-converting enzyme inhibitor perindopril (5-10 mg daily), in addition to each patient's individual treatment based on his or her personal medical history. Indirectness: No indirectness Further details: 1. Concomitant perioperative prophylactic treatment: Concomitant perioperative prophylactic treatment (e.g. with beta-blockers or statins) (All received metoprolol and other drugs after surgery and before discharge). (n=20) Intervention 2: Rhythm control - Other. Intravenous amiodarone + oral ranolazine. Intravenous amiodarone at 300 mg in 30 min followed by 750 mg in 24 h. Oral ranolazine regimen consisted of 500 mg loading dose followed by 375 mg 6 hours later and then 375 mg twice daily. After conversion to sinus rhythm the amiodarone infusion was stopped but received amiodarone orally at a dose of 200 mg twice daily for a week and 200 mg once daily for the second week, or according to their cardiologist's advice following discharge. Ranolazine 375 mg twice daily was also continued. oral amiodarone scheme. Duration 2 weeks? Concurrent medication/care: All patients after extubation and until discharge received a standard drug regimen that included acetylsalicylic acid (100 mg daily), atorvastatin (20-40 mg daily), the beta-blocker metoprolol (50-100 mg daily), and the angiotensin-converting enzyme inhibitor perindopril (5-10 mg daily), in addition to each patient's individual treatment based on his or her personal medical history. Indirectness: No indirectness Further details: 1. Concomitant perioperative prophylactic treatment: Concomitant perioperative prophylactic treatment (e.g. with beta-blockers or statins) (All received metoprolol and other drugs after surgery and before discharge).
Funding	No funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: K+ BLOCKERS (AMIODARONE) versus OTHER (AMIODARONE + RANOLAZINE)	

Protocol outcome 1: Achievement of sinus rhythm at Define - Actual outcome for No pre-existing AF: Conversion to sinus rhythm at Unclear; Group 1: 20/21, Group 2: 20/20; Comments: Doesn't explicitly state numbers achieving sinus rhythm but does not mention that any failed and only mentions one recurrence in amiodarone only group. Have extracted those in sinus rhythm at end of study/discharge. Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Health-related quality of life at Define; Rehospitalisation (all-cause) at Define; Mortality at Define; Stroke or thromboembolic complications at Define; Need for rescue DC cardioversion at Define; Rehospitalisation for AF at Define; Adverse events at Define; Freedom from anticoagulation at Define; Freedom from antiarrhythmic drug use at Define; Intensive care unit length of stay at Define; Hospital length of stay at Define

Study	Simopoulos2018[100]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=812)
Countries and setting	Conducted in Greece; Setting: Secondary care
Line of therapy	1st line
Duration of study	Intervention time: 24-36 h
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: 12-lead ECG mentioned for outcome measurement, not clear whether this also used for diagnosis
Stratum	No pre-existing AF: Those with previously documented persistent or permanent AF in last 6 months prior to operation excluded
Subgroup analysis within study	Stratified then randomised: Gives results separately for those with heart failure with or without preserved ejection fraction
Inclusion criteria	Those that underwent coronary artery bypass grafting; development of atrial fibrillation 2-3 days following operation
Exclusion criteria	Previously documented persistent of permanent AF in last 6 months prior to surgery; receiving CYP3A inhibitors or inducers; history of hepatic or renal failure
Recruitment/selection of patients	Consecutive matching inclusion criteria
Age, gender and ethnicity	Age - Mean (SD): Amiodarone, 65.94 (9.51) years; amiodarone + ranolazine, 65.15 (10.08) years. Gender (M:F): Amiodarone, 352/53; amiodarone + ranolazine, 350/57. Ethnicity: Not reported.
Further population details	1. Existence of heart failure: Heart failure (Includes those with concomitant heart failure with reduced or preserved ejection fraction). 2. Type of AF: Not stated / Unclear (Type of AF not clear). 3. Type of cardiothoracic surgery: Non-mitral valve surgery (All underwent coronary artery bypass grafting).

Extra comments	Mean (SD) LVEF: 42.65 (8.98) vs. 43.24 (9.70); mean (SD) left atrial diameter: 43.26 (7.11) vs. 43.46 (6.63) mm; prior myocardial infarction: 53.8 vs. 59.0%; type II diabetes mellitus: 54.6 vs. 53.8%; hypertension: 58.5 vs. 54.3%; mean (SD) cardiopulmonary bypass time: 91.14 (19.28) vs. 93.02 (19.55) min; mean (SD) cross-clamp time: 57.3 (12.92) vs. 56.81 (12.05) min. Medications: beta-blockers (84.0 vs. 81.8%), digoxin (0.2 vs. 0%), spironolactone (19.3 vs. 17.0%), eplerenone (36.0 vs. 40.0%), ACE inhibitors/ARBs (65.9 vs. 66.8%), statins (58.3 vs. 68.6%), sulphonylure as (18.5 vs. 20.1%), metformin (25.7 vs. 25.1%), dihydropyridines (24.7 vs. 32.9%), anti-diabetics (14.3 vs. 16.6%)
Indirectness of population	No indirectness
Interventions	(n=405) Intervention 1: Rhythm control - K+ blockers .Intravenous amiodarone. Loading dose of 300 mg in 30 min followed by 750 mg in 24 h. If arrhythmia was sustained after 24 h, further 375 mg given in 12 h. Maximum recording period of 36 h. After conversion to sinus rhythm amiodarone infusion was discontinued and treatment with amiodarone 200 mg t.i.dwas continued until hospital discharge. Duration 24-36 h. Concurrent medication/care: Those taking coumarin anticoagulants or other newer generation anticoagulants and anti-platelet therapy were switched to LMWH for 5 days prior to surgery and until night before operation. Beta-blockers continued until day of surgery unless new-onset marked bradycardia or hypotension occurred. Treatment with LMWH on day of surgery was dependent on coagulation assays. On first postoperative day, all given LMWH and acetylsalicylic acid 100 mg once daily, which continued during the AF and conversion to sinus rhythm. Where sinus rhythm was not restored with 36 h, anticoagulation was changed to acenocoumarol4 mg and adjusted according to INR. Indirectness: No indirectness Further details: 1. Concomitant perioperative prophylactic treatment: Concomitant perioperative prophylactic treatment (e.g. with beta-blockers or statins) (Beta-blockers continued until day of surgery unless new-onset bradycardia or hypotension occurred. >80% using beta-blockers in patient characteristics table). (n=407) Intervention 2: Rhythm control - Other. Intravenous amiodarone + oral ranolazine. Amiodarone loading dose of 300 mg in 30 min followed by 750 mg in 24 h. If arrhythmia was sustained after 24 h, further 375 mg given in 12 h. Maximum recording period of 36 h. 500 mg ranolazine was administered once at time of randomisation, followed by 375 mg 6 h later and subsequently 375 mg twice daily. After conversion to sinus rhythm amiodarone infusion was discontinued and treatment with amiodarone 200 mg t.i.d and 375 mg b.i.dranolazine was continued until hospital discharge. Duration 24-36 h. Concurrent medication/care: Those taking coumarin anticoagulants or other newer generation anticoagulants and anti-platelet therapy were switched to LMWH for 5 days prior to surgery and until night before operation. Beta-blockers continued until day of surgery unless new-onset marked bradycardia or hypotension occurred. Treatment with LMWH on day of surgery was dependent on coagulation assays. On first postoperative day, all given LMWH and acetylsalicylic acid 100 mg once daily, which continued during the AF and conversion to sinus rhythm. Where sinus rhythm was not restored with 36 h, anticoagulation was changed to acenocoumarol4 mg and adjusted according to INR. Indirectness: No indirectness

	Further details: 1. Concomitant perioperative prophylactic treatment: Concomitant perioperative prophylactic treatment (e.g. with beta-blockers or statins) (Beta-blockers continued until day of surgery unless new-onset bradycardia or hypotension occurred. >80% using beta-blockers in patient characteristics table).
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: K+ BLOCKERS (AMIODARONE) versus OTHER (AMIODARONE + RANOLAZINE) Protocol outcome 1: Achievement of sinus rhythm at Define - Actual outcome for No pre-existing AF: Conversion to sinus rhythm at 36 h; Group 1: 405/405, Group 2: 407/407; Comments: Note they also give time-point at ≤24 h but extracting longest time-point from each study Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Some differences in the proportions taking different drug types prior to surgery; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Health-related quality of life at Define; Rehospitalisation (all-cause) at Define; Mortality at Define; Stroke or thromboembolic complications at Define; Need for rescue DC cardioversion at Define; Rehospitalisation for AF at Define; Adverse events at Define; Freedom from anticoagulation at Define; Freedom from antiarrhythmic drug use at Define; Intensive care unit length of stay at Define; Hospital length of stay at Define

Study	**Vilvanathan2016[110]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=89)
Countries and setting	Conducted in India; Setting: Secondary care followed by outpatient
Line of therapy	Unclear
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ECG evidence of permanent AF
Stratum	Pre-existing AF: All patients had permanent AF for at least 3 months prior to successful balloon mitral valvuloplasty
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged >18 years; underwent successful balloon mitral valvuloplasty; ECG evidence of atrial fibrillation for >3 months
Exclusion criteria	Prior history of cardioversion; significant mitral, tricuspid or aortic regurgitation; significant tricuspid or aortic stenosis; left atrial thrombus (detected by transoesophageal echocardiography); left atrial diameter ≥6 cm; inability to comply with 12 months follow-up period; contraindications to anticoagulation or amiodarone.
Recruitment/selection of patients	Not clear
Age, gender and ethnicity	Age - Mean (SD): Amiodarone + DC cardioversion, 38.80 (8.426) years; placebo + DC cardioversion, 37.62 (9.260) years. Gender (M:F): Amiodarone + DC cardioversion, 9/35; placebo + DC cardioversion, 15/30. Ethnicity: Not reported
Further population details	1. Existence of heart failure: Heart failure (Majority with NYHA class >II in each group). 2. Type of AF: Persistent < 1 year (Mean duration of AF in each group ~10 months). 3. Type of cardiothoracic surgery: Mitral valve surgery (All received balloon mitral valvulotomy).

Extra comments	Mean (SD) duration of AF: 10.05 (5.718) vs. 10.27 (5.495) months. Other valve disease: mild aortic regurgitation (AR), 13.6 vs. 13.3%; moderate AR, 11.4 vs. 15.6%; mild aortic stenosis (AS), 18.2 vs. 15.6%; moderate AS, 2.3 vs. 8.9%; mild AR and AS, 0 vs. 2.2%; none, 54.5 vs. 44.4%. Other medical illness: none, 86.4 vs. 86.7%; hypertension, 4.5 vs. 6.7%; diabetes, 4.5 vs. 2.2%; hypertension and diabetes, 2.3 vs. 4.4%; diabetes and coronary heart disease, 2.3 vs. 0%.NYHA class: I, 20.5 vs. 4.4%; II, 63.6 vs. 75.6%; III, 11.4 vs. 13.3%; IV, 4.5 vs. 6.7%. Concomitant drugs: beta-blockers, 48.9 vs. 43.2%; calcium channel blockers, 24.4 vs. 22.7%; digoxin, 64.4 vs. 68.2%
Indirectness of population	No indirectness
Interventions	(n=44) Intervention 1: Rhythm control - Other. Amiodarone + DC cardioversion. DC cardioversion was performed 48 h after balloon mitral valvuloplasty. All patients were fasted throughout the night before they underwent cardioversion. Prior to DC cardioversion, patients administered intravenous midazolam or diazepam for sedation and meperidine for analgesia. Synchronised DC cardioversion was given using biphasic defibrillators using the following protocol: 100J, 200J, 300J and 360 J. Unsuccessful DC cardioversion was considered to include those who did not revert with 360J. Amiodarone was given as an intravenous bolus of 150 mg followed by a 1 g intravenous infusion for 12 h prior to DC cardioversion. Following cardioversion, oral amiodarone was started initially 200 mg three times a day for 2 weeks, followed by 200 mg twice daily for 2 weeks and subsequently 200 mg once daily for 12 months. Duration 12 months. Concurrent medication/care: Patients were anticoagulated with warfarin and INR was required to be between 2 and 3 for at least 1 month prior to DC cardioversion. Concomitant medications at baseline: beta-blockers, 48.9%; calcium channel blockers, 24.4%; digoxin, 64.4% - unclear if receiving during study period as well. Indirectness: No indirectness Further details: 1. Concomitant perioperative prophylactic treatment: Concomitant perioperative prophylactic treatment (e.g. with beta-blockers or statins) (>60% in both groups on concomitant digoxin alone, also large proportions with concomitant beta-blockers or calcium channel blockers. Unclear if used during perioperative period). (n=45) Intervention 2: Rhythm control - Other. Placebo + DC cardioversion. DC cardioversion was performed 48 h after balloon mitral valvuloplasty. All patients were fasted throughout the night before they underwent cardioversion. Prior to DC cardioversion, patients administered intravenous midazolam or diazepam for sedation and meperidine for analgesia. Synchronised DC cardioversion was given using biphasic defibrillators using the following protocol: 100J, 200J, 300J and 360 J. Unsuccessful DC cardioversion was considered to include those who did not revert with 360J. DC cardioversion alone performed without preloading amiodarone. Following DC cardioversion, patients received placebo for 12 months. Duration 12 months. Concurrent medication/care: Patients were anticoagulated with warfarin and INR was required to be between 2 and 3 for at least 1 month prior to DC cardioversion. Concomitant medications at baseline: beta-blockers, 43.2%; calcium channel blockers, 22.7%; digoxin, 68.2% - unclear if receiving during study period as well. Indirectness: No indirectness Further details: 1. Concomitant perioperative prophylactic treatment: Concomitant perioperative prophylactic

	treatment (e.g. with beta-blockers or statins) (>60% in both groups on concomitant digoxin alone, also large proportions with concomitant beta-blockers or calcium channel blockers. Unclear if used during perioperative period).
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: K+ BLOCKERS + DC CARDIOVERSION (AMIODARONE + DC CARDIOVERSION) versus OTHER (PLACEBO + DC CARDIOVERSION)

Protocol outcome 1: Health-related quality of life at Define
- Actual outcome for Pre-existing AF: Physical component score SF-8 questionnaire at 12 months; Group 1: mean 49.79 (SD 6.794); n=36, Group 2: mean 46.62 (SD 5.917); n=37; SF-8 0-100 Top=High is good outcome; Comments: Baseline values: Amiodarone + DC cardioversion, 48.03 (5.005, n=44); placebo + DC cardioversion, 46.46 (4.628, n=45)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Blinding/performance: outcome is subjective rated by patients, results could have been affected if assignment was known; Indirectness of outcome: No indirectness ; Baseline details: Comparable for most of the parameters reported, but substantially higher proportion with NYHA class I in amiodarone group.; Blinding details: Subjective outcome rated by patients, could have been affected if aware of drug assignment; Group 1 Number missing: 8, Reason: Missing as either did not convert at all by cardioversion or lost to follow-up, proportion of each unclear; Group 2 Number missing: 8, Reason: Missing as either did not convert at all by cardioversion or lost to follow-up, proportion of each unclear
- Actual outcome for Pre-existing AF: Mental component score SF-8 questionnaire at 12 months; Group 1: mean 53.89 (SD 6.244); n=36, Group 2: mean 50.15 (SD 5.216); n=37; SF-8 0-100 Top=High is good outcome; Comments: Baseline values: amiodarone + DC cardioversion, 45.08 (4.928, n=44); placebo + cardioversion, 43.94 (5.276, n=45).
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Blinding/performance: outcome is subjective rated by patients, results could have been affected if assignment was known; Indirectness of outcome: No indirectness ; Baseline details: Comparable for most of the parameters reported, but substantially higher proportion with NYHA class I in amiodarone group.; Blinding details: Subjective outcome rated by patients, could have been affected if aware of drug assignment; Group 1 Number missing: 8, Reason: Missing as either did not convert at all by cardioversion or lost to follow-up, proportion of each unclear; Group 2 Number missing: 8, Reason: Missing as either did not convert at all by cardioversion or lost to follow-up, proportion of each unclear

Protocol outcome 2: Achievement of sinus rhythm at Define
- Actual outcome for Pre-existing AF: Sinus rhythm at 12 months at 12 months; Group 1: 22/36, Group 2: 7/37; Comments: Does not include 8 that were lost to follow-up and 8 that did not convert following cardioversion, proportions of each in each group unclear
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Incomplete outcome: proportion within each intervention group that were missing as they did not convert originally by cardioversion is unclear and could affect estimate if this was the reason for missing data in more people within one of the groups.; Indirectness of outcome: No

indirectness ; Baseline details: Comparable for most of the parameters reported, but substantially higher proportion with NYHA class I in amiodarone group.; Group 1 Number missing: 8, Reason: Missing as either did not convert at all by cardioversion or lost to follow-up, proportion of each unclear; Group 2 Number missing: 8, Reason: Missing as either did not convert at all by cardioversion or lost to follow-up, proportion of each unclear Protocol outcome 3: Adverse events at Define - Actual outcome for Pre-existing AF: Dose reduction due to adverse events at 12 months; Group 1: 9/44, Group 2: 0/45; Comments: 9 patients required dose reduction in amiodarone group due to sinus bradycardia (n=3), abnormal liver function test (n=2), clinical or subclinical hypothyroidism (n=3) and QT prolongation (n=1). Nothing reported for the placebo group. Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Blinding/performance: decision to reduce dose due to adverse events quite subjective and could have been affected if drug assignment was known. Outcome reporting: study states fact that study follow-up was only 12 months means longer term effects of amiodarone may not be captured within this short time period.; Indirectness of outcome: No indirectness ; Baseline details: Comparable for most of the parameters reported, but substantially higher proportion with NYHA class I in amiodarone group.; Blinding details: Could be subjective as to whether dose needs to be reduced; Group 1 Number missing: 8, Reason: Missing as either did not convert at all by cardioversion or lost to follow-up, proportion of each unclear; Group 2 Number missing: 8, Reason: Missing as either did not convert at all by cardioversion or lost to follow-up, proportion of each unclear	
Protocol outcomes not reported by the study	Rehospitalisation (all-cause) at Define; Mortality at Define; Stroke or thromboembolic complications at Define; Need for rescue DC cardioversion at Define; Rehospitalisation for AF at Define; Freedom from anticoagulation at Define; Freedom from antiarrhythmic drug use at Define; Intensive care unit length of stay at Define; Hospital length of stay at Define

Study	**Wafa1989[111]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=29)
Countries and setting	Conducted in United Kingdom; Setting: Secondary care
Line of therapy	1st line
Duration of study	Intervention time: 24 h
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: 12-lead ECG on entry to study and continuous ECG tape monitoring used throughout study
Stratum	No pre-existing AF: Preoperative atrial arrhythmias an exclusion criterion
Subgroup analysis within study	Not applicable
Inclusion criteria	18-80 years of age; had undergone coronary artery bypass grafting, which was complicated within 96 hours after surgery by atrial tachyarrhythmias (atrial fibrillation, atrial flutter or atrial tachycardia) lasting at least 15 min with a ventricular rate >120 beats/min
Exclusion criteria	Preoperative atrial arrhythmia; second- or third-degree atrioventricular block; presence or history of bifascicular block or bundle branch block with any degree of atrioventricular block; known sinus node dysfunction in the absence of a pacing wire; impaired left ventricular dysfunction (as detected clinically and angiographically); treatment with other antiarrhythmics (including verapamil) during anaesthesia or since return to intensive care unit; treatment with digoxin or beta-blockers in the 24 h before entry into the study; serious renal or hepatic disease; receipt of any investigational drug during the 4-weeks prior to the study; receipt of any antiarrhythmic agents within 3 elimination half-lives of the date of inclusion in the study
Recruitment/selection of patients	Not reported

Age, gender and ethnicity	Age - Mean (SD): Flecainide, 61 (8) years; digoxin, 66 (5) years. Gender (M:F): Flecainide, 15/0; digoxin, 11/3. Ethnicity: Not reported
Further population details	1. Existence of heart failure: No heart failure (Impaired left ventricular function an exclusion criterion). 2. Type of AF: Not stated / Unclear (Type of AF not reported). 3. Type of cardiothoracic surgery: Non-mitral valve surgery (All underwent coronary artery bypass grafting).
Extra comments	Arrhythmia type: atrial fibrillation, 100 vs. 85.7%; atrial flutter, 0 vs. 14.3%. Type of operation: CABG alone (93.3% vs. 92.9%); CABG + aortic valve replacement (6.7 vs. 7.1%). Coronary artery disease: 100 vs. 100%. Aortic valve disease: 6.7 vs. 7.1%.
Indirectness of population	No indirectness: <10% with atrial flutter instead of atrial fibrillation
Interventions	(n=15) Intervention 1: Rhythm control - Na+ blockers. Intravenous flecainide. Bolus of 1 mg/kg body weight over 10 min followed by an infusion of 1.5 mg/kg/h for 1 h and another infusion of 0.25 mg/kg/h for the rest of the 24 h study period. Duration 24 h. Concurrent medication/care: A single dose of verapamil (10 mg intravenously) was given over a 5 min period if after 45 min reversion to sinus rhythm and adequate ventricular rate control (<100 beats/min) had not been achieved. Every reasonable effort was made to correct plasma potassium and arterial oxygen saturation if these were thought to be unsatisfactory. Indirectness: No indirectness Further details: 1. Concomitant perioperative prophylactic treatment: Not stated / Unclear (No details). (n=14) Intervention 2: Rate control - Digoxin. Intravenous digoxin. Bolus of 0.5 mg over 10 min followed after 6 and 12 h by bolus doses of 0.25 mg over 10 min. Duration 24 h. Concurrent medication/care: A single dose of verapamil (10 mg intravenously) was given over a 5 min period if after 45 min reversion to sinus rhythm and adequate ventricular rate control (<100 beats/min) had not been achieved. Every reasonable effort was made to correct plasma potassium and arterial oxygen saturation if these were thought to be unsatisfactory. Indirectness: No indirectness Further details: 1. Concomitant perioperative prophylactic treatment: Not stated / Unclear (No details).
Funding	Study funded by industry (Study supported by a grant from Riker Laboratories, Loughborough, England)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NA+ BLOCKERS (FLECAINIDE) versus DIGOXIN	

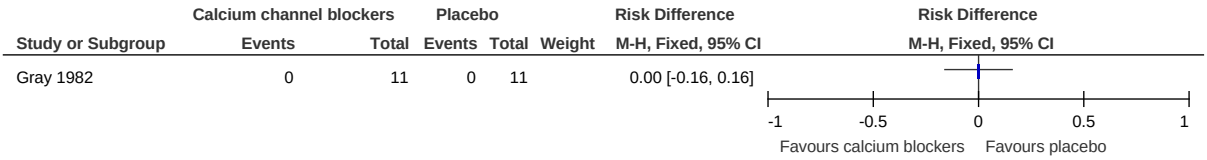
Protocol outcome 1: Achievement of sinus rhythm at Define - Actual outcome for No pre-existing AF: Reversion to sinus rhythm at 24 h at 24 h; Group 1: 14/15, Group 2: 10/14; Comments: Flecainide: 9 with flecainide alone; digoxin: 0 with digoxin alone. Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: 100% vs. 78% men in flecainide and digoxin groups, respectively. Also 2 cases were atrial flutter in the digoxin group with 0 cases of atrial flutter in the flecainide group. Mean age similar.; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Adverse events at Define - Actual outcome for No pre-existing AF: Adverse reactions at 24 h; Group 1: 3/15, Group 2: 0/14; Comments: Adverse reactions: 1 patient hypotensive following addition of verapamil, sweating and dizziness - withdrew from study; 1 patient had dizziness, headache and blurred vision associated with hypotension during flecainide infusion; 1 patient experienced some nausea after intravenous verapamil. Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Outcome reporting: list of adverse events most interested in not prespecified; Indirectness of outcome: No indirectness ; Baseline details: 100% vs. 78% men in flecainide and digoxin groups, respectively. Also 2 cases were atrial flutter in the digoxin group with 0 cases of atrial flutter in the flecainide group. Mean age similar.; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Health-related quality of life at Define; Rehospitalisation (all-cause) at Define; Mortality at Define; Stroke or thromboembolic complications at Define; Need for rescue DC cardioversion at Define; Rehospitalisation for AF at Define; Freedom from anticoagulation at Define; Freedom from antiarrhythmic drug use at Define; Intensive care unit length of stay at Define; Hospital length of stay at Define

Appendix E: Forest plots

E.1 Mixed/unclear stratum

E.1.1 Calcium channel blockers vs. placebo

Figure 2: Adverse events (adverse reaction or unusual haemodynamic response at 24 h)



E.2 No pre-existing AF stratum

E.2.1 DC cardioversion vs. K+ blockers

Figure 3: Achievement of sinus rhythm (sinus rhythm at 24 h)

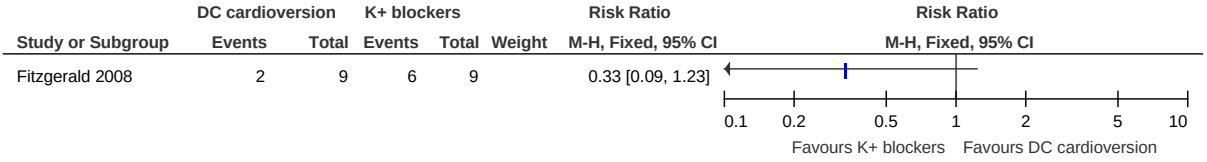


Figure 4: Need for rescue DC cardioversion (need for transthoracic cardioversion post-24 h)

E.2.2 K+ blockers vs. digoxin

Figure 5: Achievement of sinus rhythm (reversion to sinus rhythm at 24 h)

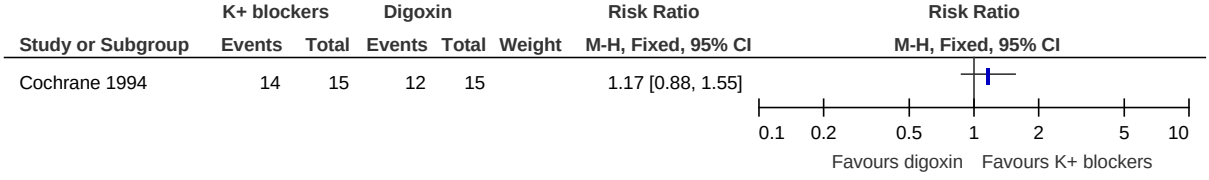


Figure 6: Adverse events (clinically significant hypotension or cardiac conduction abnormalities at 24 h)

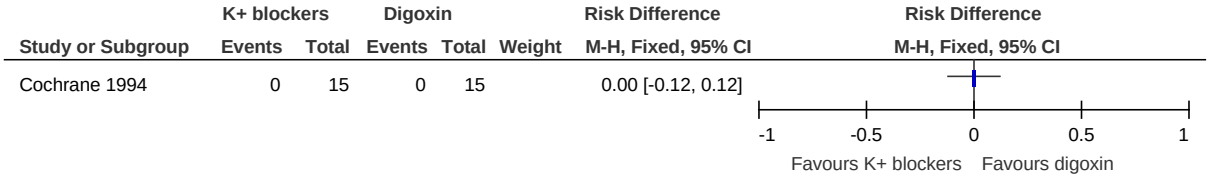
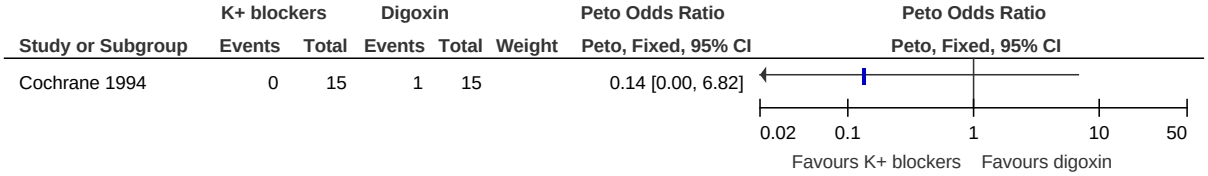
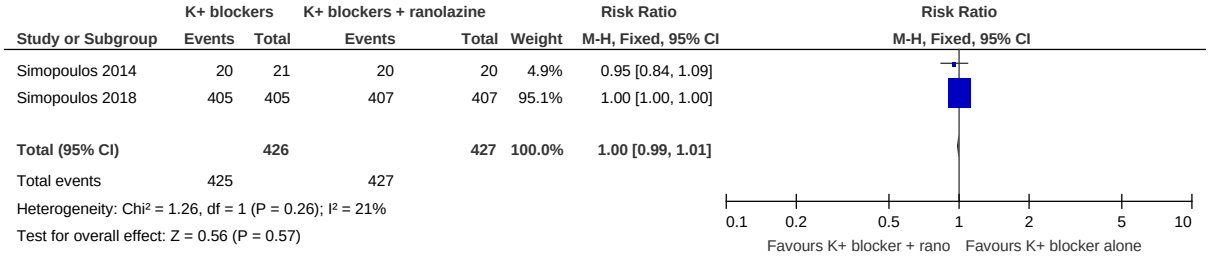


Figure 7: Need for rescue DC cardioversion (direct current reversion post-24 h)



E.2.3 K+ blockers vs. K+ blockers + ranolazine

Figure 8: Achievement of sinus rhythm (sinus rhythm at 36 h/unclear time-point)



E.2.4 Mixed rate control vs. K+ blocker with/without rate control agent

Figure 9: Achievement of sinus rhythm (sinus rhythm at hospital discharge)

Figure 10: Adverse events (serious and non-serious adverse events, other than cerebrovascular/non-cerebrovascular thromboembolism, at 60 days) – rate ratio for events per 100 patient months

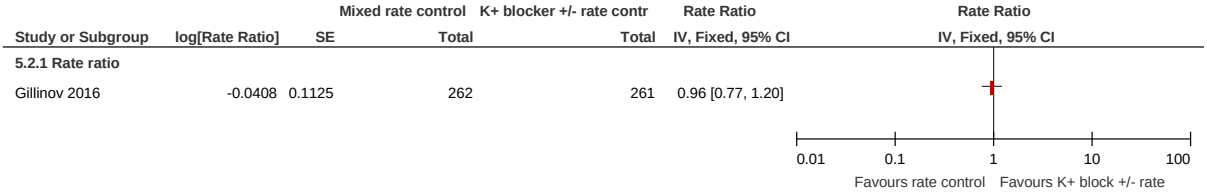


Figure 11: Freedom from anticoagulation (no warfarin prescription at hospital discharge)

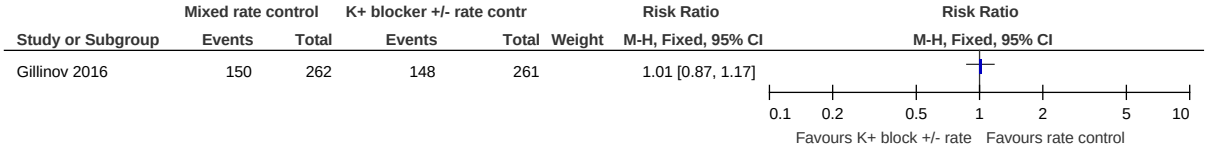


Figure 12: Mortality (mortality at 60 days)

Figure 13: Need for rescue DC cardioversion (direct current cardioversion at 60 days)

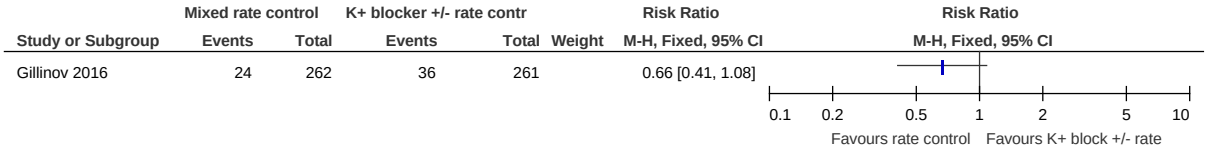


Figure 14: Rehospitalisation, all-cause (readmission due to any cause at 60 days) – rate ratio for events per 100 patient months

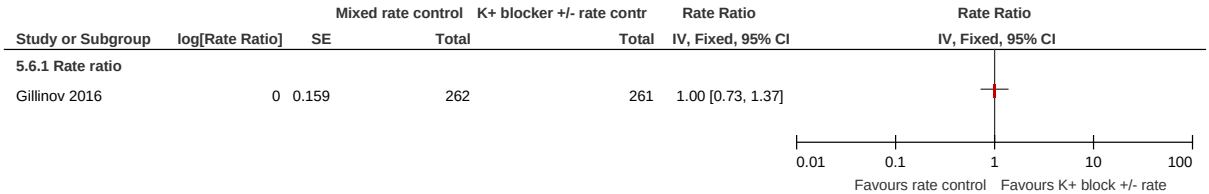


Figure 15: Rehospitalisation for AF (readmission due to treatment of AF at 60 days) – rate ratio for events per 100 patient months

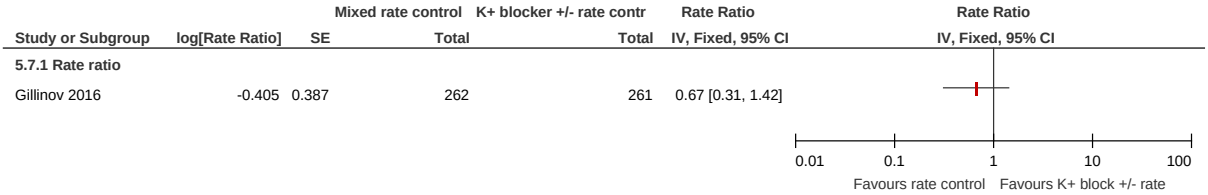
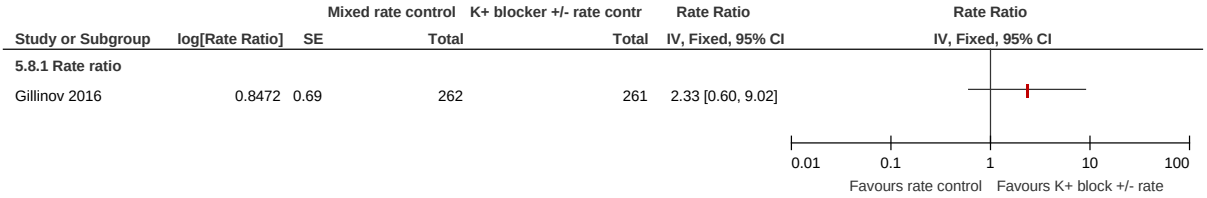


Figure 16: Stroke or thromboembolic complications (serious and non-serious cerebrovascular, and/or non-cerebral thromboembolism at 60 days) – rate ratio for events per 100 patient months



E.2.5 Mixed rhythm control with/without electrical cardioversion vs. mixed rate control

Figure 17: Achievement of sinus rhythm (conversion to sinus rhythm at 8 weeks post-hospital discharge)

Figure 18: Mortality (mortality at 8 weeks post-hospital discharge)

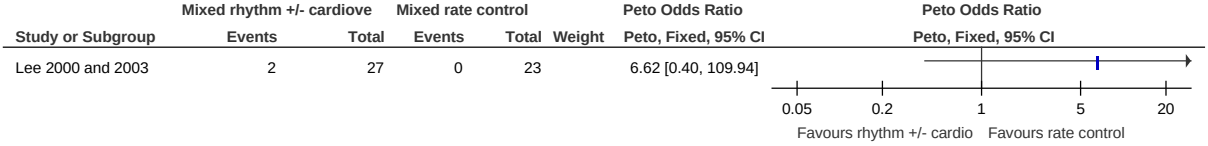
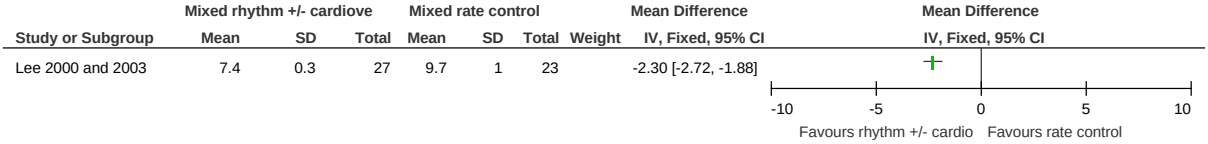


Figure 19: Hospital length of stay (from surgery to discharge)



E.2.6 Na+ blockers vs. digoxin

Figure 20: Achievement of sinus rhythm (reversion to sinus rhythm at 24 h)

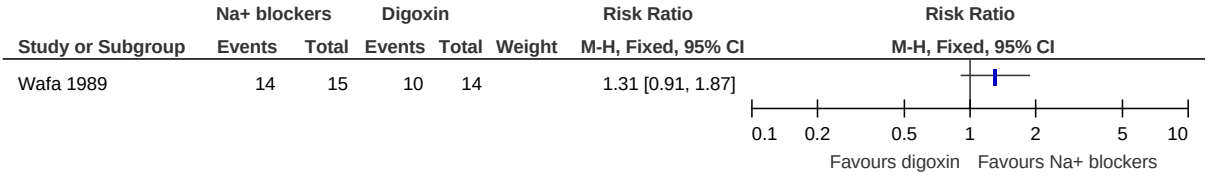
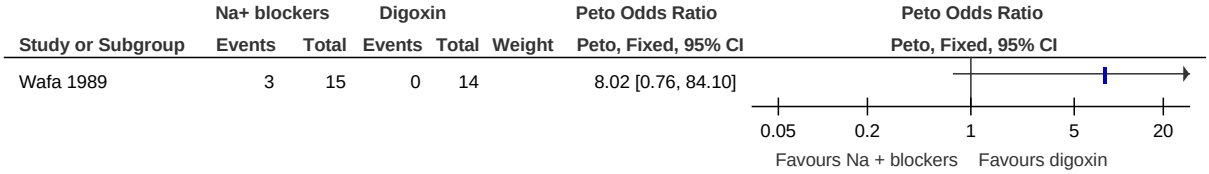


Figure 21: Adverse events (adverse reactions at 24 h)



E.2.7 Na+ blockers vs. K+ blockers

Figure 22: Achievement of sinus rhythm (without electrical cardioversion at end of study – includes those switching groups if no response)

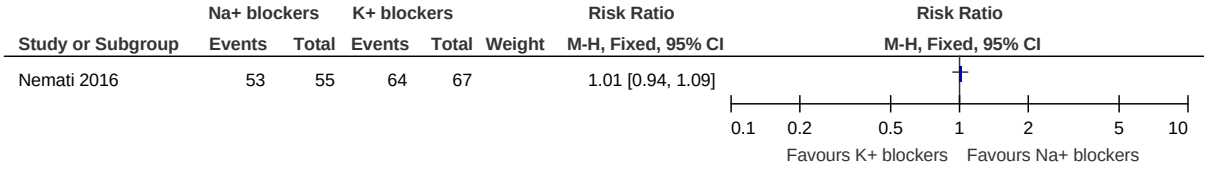


Figure 23: Adverse events (significant side effects at end of study)

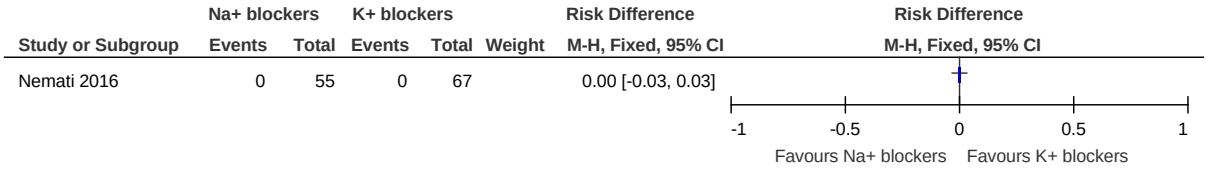
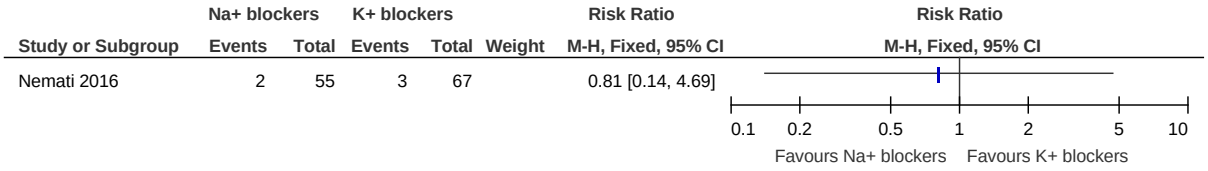
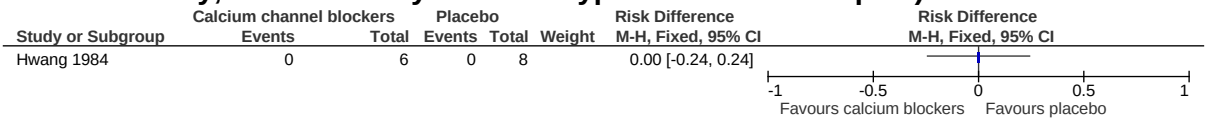


Figure 24: Need for rescue DC cardioversion (cardioversion at end of study)



E.2.8 Calcium channel blockers vs. placebo

Figure 25: Adverse events (adverse events requiring premature termination of study, such as bradycardia or hypotension – in-hospital)



E.2.9 K+ blockers (vernakalant) vs. placebo

Figure 26: Mortality (30 days)

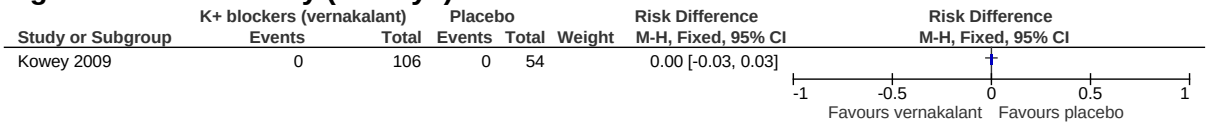


Figure 27: Achievement of sinus rhythm (90 min after initial infusion)

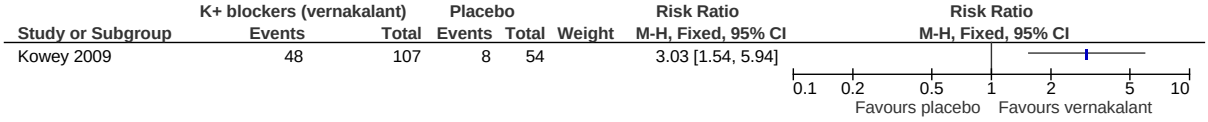


Figure 28: Serious adverse events (30 days)

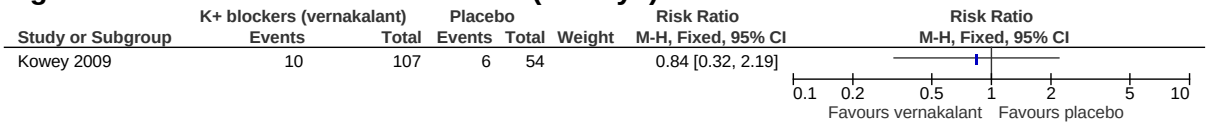
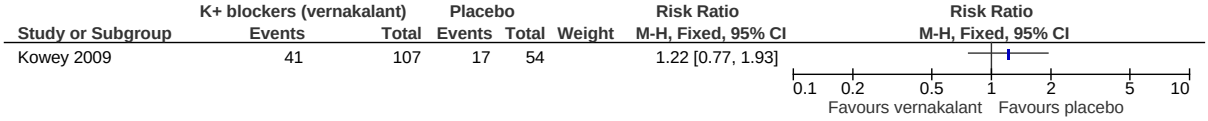


Figure 29: Treatment-emergent adverse events (24 h)



E.2.10 K+ blockers (amiodarone) vs. routine medical treatment alone

Figure 30: Achievement of sinus rhythm

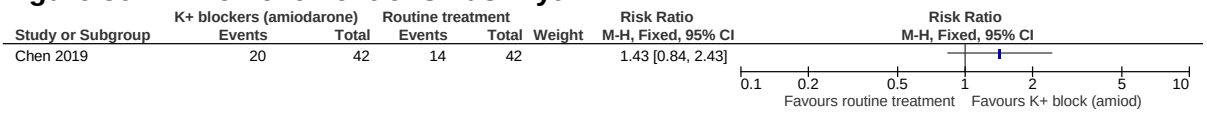


Figure 31: Hospital length of stay

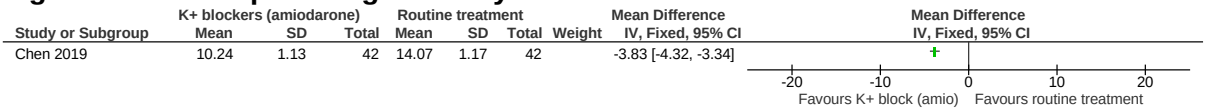
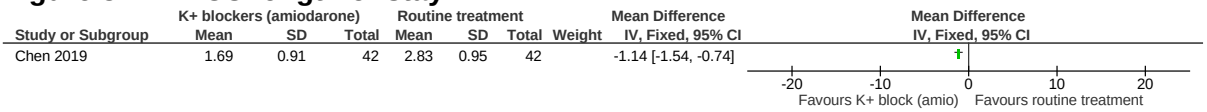


Figure 32: ICU length of stay



E.3 Pre-existing AF stratum

E.3.1 DC cardioversion vs. K+ blockers+ captopril + simvastatin

Figure 33: Achievement of sinus rhythm (conversion to sinus rhythm at end of treatment)

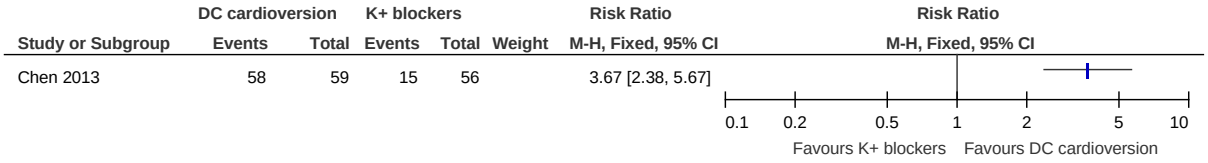


Figure 34: Adverse events (severe complications at follow-up, range 3-34 months)

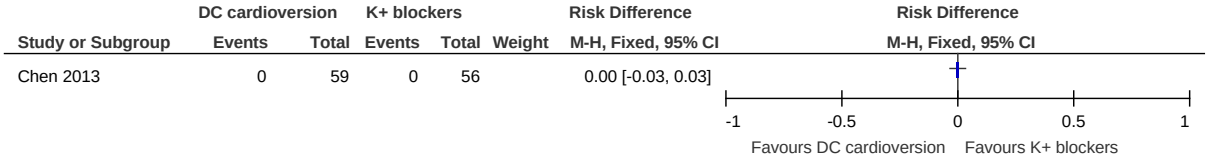


Figure 35: Adverse events (severe cough during treatment)

Figure 36: Adverse events (sinus bradycardia with heart rate of 43-52 bpm during treatment)

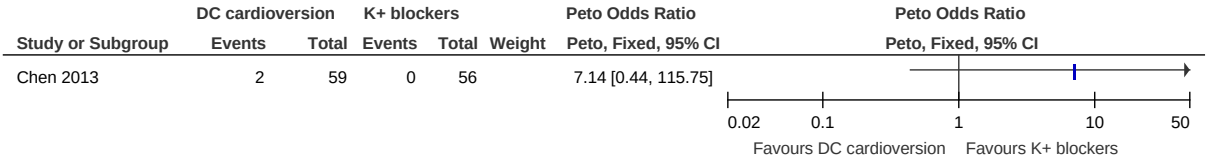


Figure 37: Mortality (mortality at follow-up, range 3-34 months)

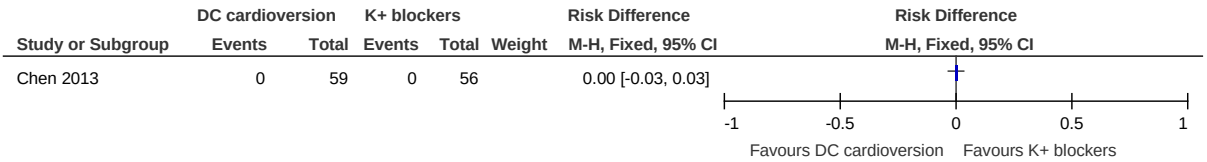
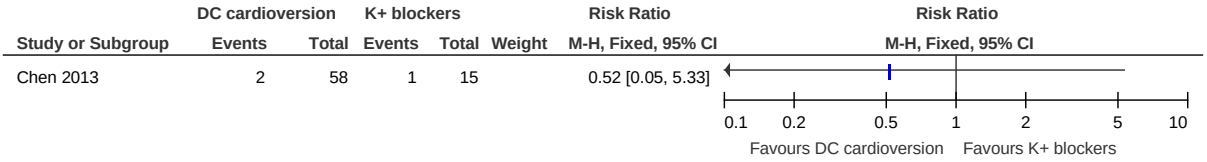


Figure 38: Rehospitalisation for AF (recurrence of AF at follow-up, range 3-34 months)



E.3.2 Mixed rate control vs. K+ blockers +captopril +simvastatin

Figure 39: Achievement of sinus rhythm (sinus rhythm conversion at 12 months)

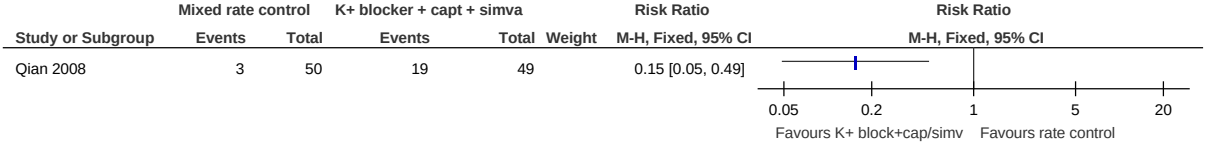
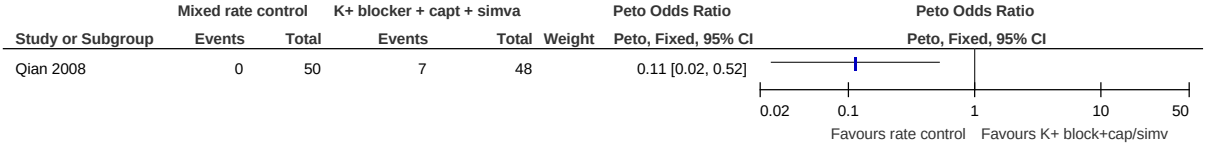


Figure 40: Adverse events (adverse events requiring discontinuation of one or more study drugs at 12 months)



E.3.3 K+ blockers + DC cardioversion vs. placebo + DC cardioversion

Figure 41: Achievement of sinus rhythm (sinus rhythm at 12 months)

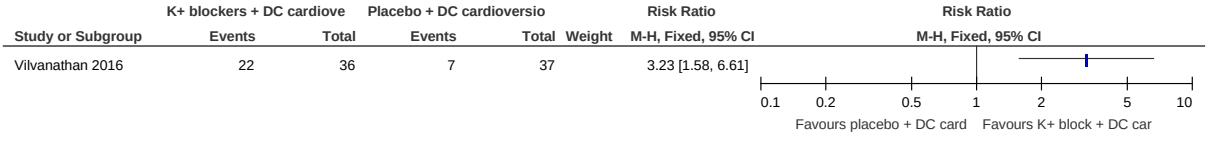


Figure 42: Adverse events (dose reduction due to adverse events at 12 months)

Figure 43: Health-related quality of life (mental component score SF-8 at 12 months)

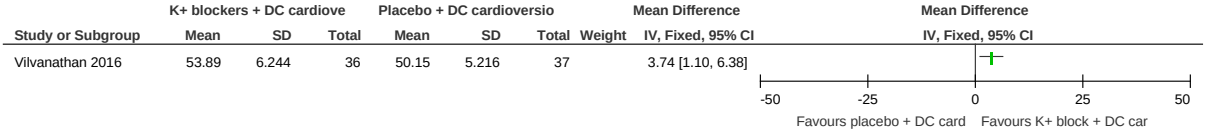
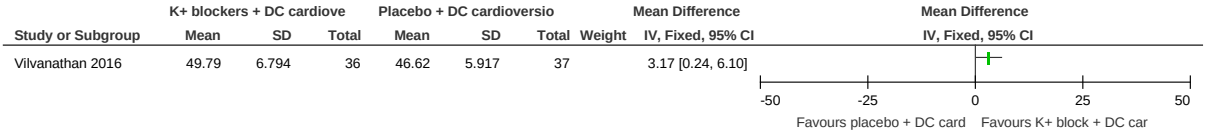


Figure 44: Health-related quality of life (physical component score SF-8 at 12 months)



Appendix F:GRADE tables

Table 25: Clinical evidence profile: Mixed/unclear stratum – calcium channel blockers vs. placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Calcium channel blockers	placebo	Relative (95% CI)	Absolute		
Adverse events (adverse reaction or unusual haemodynamic response) (follow-up mean 24 hours)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	0/11 (0%)	0%	RD 0 (-0.16 to 0.16)	0 fewer per 1000 (from 160 fewer to 160 more)[4]	⊕OOO VERY LOW	CRITICAL

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2]>10% with atrial flutter rather than atrial fibrillation
[3]Imprecision assessed using sample size as zero events in both arms of the study. Sample size <70 so very serious imprecision.
[4]Absolute effect calculated manually using risk difference as zero events in both arms of the study.

Table 26: Clinical evidence profile: No pre-existing AF stratum – DC cardioversion vs. K+ blockers

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DC cardioversion	K+ blockers	Relative (95% CI)	Absolute		
Achievement of sinus rhythm (sinus rhythm at 24 h) (follow-up mean 24 hours)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	2/9 (22.2%)	66.7%	RR 0.33 (0.09 to 1.23)	447 fewer per 1000 (from 607 fewer to 153 more)	⊕OOO VERY LOW	CRITICAL

Need for rescue DC cardioversion (need for transthoracic cardioversion post-24 h - follow-up unclear)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/5 (0%)	16.7%	OR 0.16 (0 to 8.19)	167 fewer per 1000 (from 543 fewer to 209 more)[3]	⊕OOO VERY LOW	CRITICAL

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2]Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3]Absolute effect calculated manually using risk difference as zero events in one arm of single study.

Table 27: Clinical evidence profile: No pre-existing AF stratum – K+ blockers vs. digoxin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**K+ blockers**	**Digoxin**	**Relative (95% CI)**	**Absolute**		
Achievement of sinus rhythm (sinus rhythm at 24 h) (follow-up mean 24 hours)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	14/15 (93.3%)	80%	RR 1.17 (0.88 to 1.55)	136 more per 1000 (from 96 fewer to 440 more)	⊕OOO VERY LOW	CRITICAL
Adverse events (clinically significant hypotension or cardiac conduction abnormalities) (follow-up mean 24 hours)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/15 (0%)	0%	RD 0 (-0.12 to 0.12)	0 fewer per 1000 (from 120 fewer to 120 more)[4]	⊕OOO VERY LOW	CRITICAL
Need for rescue DC cardioversion (direct current reversion post-24 h - follow-up unclear)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/15 (0%)	6.7%	OR 0.14 (0 to 6.82)	67 fewer per 1000 (from 233 fewer to 100 more)[5]	⊕OOO VERY LOW	CRITICAL

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2]Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3]Imprecision assessed using sample size as zero events in both arms of the study. Sample size <70 so very serious imprecision.

[4]Absolute effect calculated manually using risk difference as zero events in both arms of the study.
[5]Absolute effect calculated manually using risk difference as zero events in one arm of the study.

Table 28: Clinical evidence profile: No pre-existing AF stratum – K+ blockers vs. K+ blockers + ranolazine

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	K+ blockers	K+ blocker + ranolazine	Relative (95% CI)	Absolute		
Achievement of sinus rhythm (sinus rhythm at 36 h/unclear)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	425/426 (99.8%)	100%	RR 1 (0.99 to 1.01)	0 fewer per 1000 (from 10 fewer to 10 more)	⊕⊕OO LOW	CRITICAL[2]

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2]Follow-up unclear for one of the studies.

Table 29: Clinical evidence profile: No pre-existing AF stratum – mixed rate control vs. K+ blockers with/without rate control agent

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	mixed rate control	K+ blocker with/without rate control agent	Relative (95% CI)	Absolute		
Achievement of sinus rhythm (sinus rhythm at hospital discharge)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	233/259 (90%)	93.4%	RR 0.96 (0.91 to 1.01)	37 fewer per 1000 (from 84 fewer to 9 more)	⊕OOO VERY LOW	CRITICAL
Adverse events (serious and non-serious adverse events, other than cerebrovascular/non-cerebral thromboembolism) (follow-up mean 60 days)												

1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	Patients could have more than one event included in rate count. Event rate per 100 patient-months: 30.1	Patients could have more than one event included in rate count. Event rate per 100 patient-months: 31.4	Rate ratio 0.96 (0.77 to 1.2)	1.3 fewer per 100 patient-months (from 8.22 fewer to 5.58 more)[4,5]	⊕OOO VERY LOW	CRITICAL
Freedom from anticoagulation (no warfarin prescription at hospital discharge)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	150/262 (57.3%)	56.7%	RR 1.01 (0.87 to 1.17)	6 more per 1000 (from 74 fewer to 96 more)	⊕OOO VERY LOW	IMPORTANT
Mortality (mortality at 60 days) (follow-up mean 60 days)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	3/262 (1.1%)	0.8%	OR 1.49 (0.26 to 8.66)	4 more per 1000 (from 6 fewer to 57 more)	⊕OOO VERY LOW	CRITICAL
Need for rescue DC cardioversion (direct current cardioversion at 60 days) (follow-up mean 60 days)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	24/262 (9.2%)	13.8%	RR 0.66 (0.41 to 1.08)	47 fewer per 1000 (from 81 fewer to 11 more)	⊕OOO VERY LOW	CRITICAL
Rehospitalisation, all-cause (readmission due to any cause at 60 days) (follow-up mean 60 days)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	Patients could have more than one event included in rate count. Event rate per 100 patient-months: 18.5	Patients could have more than one event included in rate count. Event rate per 100 patient-months: 18.5	Rate ratio 1.0 (0.73 to 1.37)	0 fewer per 100-patient-months (from 5.77 fewer to 5.74 more)[4,5]	⊕OOO VERY LOW	CRITICAL
Rehospitalisation for AF (readmission due to treatment of AF at 60 days) (follow-up mean 60 days)												

1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	Patients could have more than one event included in rate count. Event rate per 100 patient-months: 2.6	Patients could have more than one event included in rate count. Event rate per 100 patient-months: 3.9	Rate ratio 0.67 (0.31 to 1.42)	1.3 fewer per 100 patient-months (from 3.71 fewer to 1.12 more)[4,5]	⊕OOO VERY LOW	CRITICAL
Stroke or thromboembolic complications (serious and non-serious cerebrovascular, inc, stroke and TIA, and/or non-cerebral thromboembolism at 60 days) (follow-up mean 60 days)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	Patients could have more than one event included in rate count. Event rate per 100 patient-months: 1.4	Patients could have more than one event included in rate count. Event rate per 100 patient-months: 0.6	Rate ratio 2.33 (0.6 to 9.02)	0.8 more per 100 patient-months (from 0.44 fewer to 2.04 more)[4,5]	⊕OOO VERY LOW	CRITICAL

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2]Unclear which rate control agents were included - could include some not listed in our protocol
[3]Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[4]Per 100 patient-months.
[5]Absolute effect calculated manually using difference in rates per 100 patient months

Table 30: Clinical evidence profile: No pre-existing AF stratum – mixed rhythm control +/- electrical cardioversion vs. mixed rate control

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**mixed rhythm control +/- electrical cardioversion**	**mixed rate control**	**Relative (95% CI)**	**Absolute**		
Achievement of sinus rhythm (sinus rhythm at 8 weeks post-hospital discharge) (follow-up mean 8 weeks post-hospital discharge)												

1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	26/27 (96.3%)	91.3%	RR 1.05 (0.91 to 1.22)	46 more per 1000 (from 82 fewer to 201 more)	⊕OOO VERY LOW	CRITICAL
Mortality (mortality at 8 weeks post-hospital discharge) (follow-up mean 8 weeks post-hospital discharge)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	2/27 (7.4%)	0%	OR 6.62 (0.4 to 109.94)	74 more per 1000 (from 46 fewer to 194 more)[4]	⊕OOO VERY LOW	CRITICAL
Hospital length of stay (from surgery to discharge) (Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	27	23	-	MD 2.3 lower (2.72 to 1.88 lower)	⊕OOO VERY LOW	IMPORTANT

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2]Serious indirectness as some in the mixed rate control arm could have received intravenous diltiazem - not available in UK in this form. Proportion unclear.
[3]Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[4]Absolute effect calculated manually using risk difference as zero events in control group

Table 31: Clinical evidence profile: No pre-existing AF stratum – Na+ blockers vs. digoxin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Na+ blockers**	**digoxin**	**Relative (95% CI)**	**Absolute**		
Achievement of sinus rhythm (sinus rhythm at 24 h) (follow-up mean 24 hours)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	14/15 (93.3%)	71.4%	RR 1.31 (0.91 to 1.87)	221 more per 1000 (from 64 fewer to 621 more)	⊕OOO VERY LOW	CRITICAL
Adverse events (adverse reactions at 24 h) (follow-up mean 24 hours)												

1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/15 (20%)	0%	OR 8.02 (0.76 to 84.1)	200 more per 1000 (from 22 fewer to 422 more)[3]	⊕OOO VERY LOW	CRITICAL

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2]Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3]Absolute effect calculated manually using risk difference as zero events in control group

Table 32: Clinical evidence profile: No pre-existing AF stratum – Na+ blockers vs. K+ blockers

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**No pre-existing AF stratum: Na+ blockers**	**K+ blockers**	**Relative (95% CI)**	**Absolute**		
Achievement of sinus rhythm (without electrical cardioversion at end of study - includes those switching drug)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	53/55 (96.4%)	95.5%	RR 1.01 (0.94 to 1.09)	10 more per 1000 (from 57 fewer to 86 more)	⊕⊕OO LOW	CRITICAL
Adverse events (significant side effects at end of study)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/55 (0%)	0%	RD 0 (-0.03 to 0.03)	0 fewer per 1000 (from 30 fewer to 30 more)[3]	⊕OOO VERY LOW	CRITICAL
Need for rescue DC cardioversion (cardioversion at end of study)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	2/55 (3.6%)	4.5%	RR 0.81 (0.14 to 4.69)	9 fewer per 1000 (from 39 fewer to 166 more)	⊕OOO VERY LOW	CRITICAL

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2]Imprecision assessed using sample size as zero events in both arms of the study. Sample size >70 and <350 so serious imprecision.
[3]Absolute effect calculated manually using risk difference as zero events in both arms of the study.
[4]Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 33: Clinical evidence profile: No pre-existing AF stratum – Calcium channel blockers vs. placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No pre-existing AF stratum: calcium channel blockers	placebo	Relative (95% CI)	Absolute		
Adverse events (adverse events requiring premature termination of study, such as hypotension or bradycardia - in-hospital)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	0/6 (0%)	0%	RD 0 (-0.24 to 0.24)	0 fewer per 1000 (from 240 fewer to 240 more)[4]	⊕OOO VERY LOW	CRITICAL

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2]>10% with atrial flutter rather than atrial fibrillation
[3]Imprecision assessed using sample size as zero events in both arms of the study. Sample size <70 so very serious imprecision.
[4]Absolute effect calculated manually using risk difference as zero events in both arms of the study.

Table 34: Clinical evidence profile: No pre-existing AF stratum – K+ blockers (vernakalant)vs. placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No pre-existing AF stratum: K+ blockers (vernakalant)	placebo	Relative (95% CI)	Absolute		
Mortality (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/106 (0%)	0%	RD 0 (-0.03 to 0.03)	0 fewer per 1000 (from 30 fewer to 30 more)[3]	⊕⊕OO LOW	CRITICAL
Achievement of sinus rhythm (follow-up 90 min)												

1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	48/107 (44.9%)	14.8%	RR 3.03 (1.54 to 5.94)	300 more per 1000 (from 80 more to 731 more)	⊕⊕OO LOW	CRITICAL
Serious adverse events (follow-up 30 days)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	10/107 (9.3%)	11.1%	RR 0.84 (0.32 to 2.19)	18 fewer per 1000 (from 75 fewer to 132 more)	⊕OOO VERY LOW	CRITICAL
Treatment-emergent adverse events (follow-up 24 h)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	41/107 (38.3%)	31.5%	RR 1.22 (0.77 to 1.93)	69 more per 1000 (from 72 fewer to 293 more)	⊕OOO VERY LOW	CRITICAL

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2]Imprecision assessed using sample size as zero events in both arms of the study. Sample size >70 and <350 so serious imprecision.
[3]Absolute risk calculated manually using risk difference as zero events in both arms of the study
[4]Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 35:Clinical evidence profile: No pre-existing AF stratum – K+ blockers (amiodarone) vs. routine medical treatment alone

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**No pre-existing AF stratum: K+ blockers (amiodarone)**	**routine treatment**	**Relative (95% CI)**	**Absolute**		
Achievement of sinus rhythm (follow-up unclear)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	20/42 (47.6%)	33.3%	RR 1.43 (0.84 to 2.43)	143 more per 1000 (from 53 fewer to 476 more)	⊕OOO VERY LOW	CRITICAL
Hospital length of stay (Better indicated by lower values)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	42	42	-	MD 3.83 lower (4.32 to 3.34 lower)	⊕⊕⊕O MODERATE	IMPORTANT
ICU length of stay (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	42	42	-	MD 1.14 lower (1.54 to 0.74 lower)	⊕⊕⊕O MODERATE	IMPORTANT

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2]Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 36: Clinical evidence profile: Pre-existing AF stratum – DC cardioversion vs. K+ blockers + captopril + simvastatin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**DC cardioversion**	**K+ blockers + captopril + simvastatin**	**Relative (95% CI)**	**Absolute**		
Achievement of sinus rhythm (sinus rhythm at end of treatment)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	58/59 (98.3%)	26.8%	RR 3.67 (2.38 to 5.67)	716 more per 1000 (from 370 more to 1000 more)	⊕⊕⊕O MODERATE	CRITICAL
Adverse events (severe complications at follow-up) (follow-up 3-34 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/59 (0%)	0%	RD 0 (-0.03 to 0.03)	0 fewer per 1000 (from 30 fewer to 30 more)[3]	⊕OOO VERY LOW	CRITICAL
Adverse events (severe cough during treatment)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	0/59 (0%)	3.6%	OR 0.13 (0.01 to 2.04)	36 fewer per 1000 (from 94 fewer to 22 more)[5]	⊕OOO VERY LOW	CRITICAL
Adverse events (sinus bradycardia with heart rate of 43-52 bpm during treatment)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	2/59 (3.4%)	0%	OR 7.14 (0.44 to 115.75)	34 more per 1000 (from 22 fewer to 90 more)[6]	⊕OOO VERY LOW	CRITICAL
Mortality (mortality at follow-up) (follow-up 3-34 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/59 (0%)	0%	RD 0 (-0.03 to 0.03)	0 fewer per 1000 (from 30 fewer to 30 more)[3]	⊕⊕OO LOW	CRITICAL
Rehospitalisation for AF (recurrence of AF at follow-up) (follow-up 3-34 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	2/58 (3.4%)	6.7%	RR 0.52 (0.05 to 5.33)	32 fewer per 1000 (from 64 fewer to 290 more)	⊕OOO VERY LOW	CRITICAL

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2]Imprecision assessed using sample size as zero events in both arms. Sample size >70 and <350 so serious imprecision.
[3]Absolute effect calculated manually using risk difference as zero events in both arms of the study
[4]Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[5]Absolute effect calculated manually using risk difference as zero events in one arm of single study
[6]Absolute effect calculated manually using risk difference as zero events in the control group

Table 37: Clinical evidence profile: Pre-existing AF stratum – Mixed rate control vs. K+ blockers + captopril + simvastatin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**mixed rate control**	**K+ blocker + captopril + simvastatin**	**Relative (95% CI)**	**Absolute**		
Achievement of sinus rhythm (sinus rhythm conversion at 12 months) (follow-up mean 12 months)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	3/50 (6%)	38.8%	RR 0.15 (0.05 to 0.49)	330 fewer per 1000 (from 198 fewer to 369 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Adverse events (adverse events requiring discontinuation of one or more study drugs at 12 months) (follow-up mean 12 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/50 (0%)	14.6%	OR 0.11 (0.02 to 0.52)	146 fewer per 1000 (from 250 fewer to 42 more)[2]	⊕⊕OO LOW	CRITICAL

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2]Absolute effect calculated manually using risk difference as zero events in one arm of the study

Table 38: Clinical evidence profile: Pre-existing AF stratum – K+ blockers + DC cardioversion vs. placebo + DC cardioversion

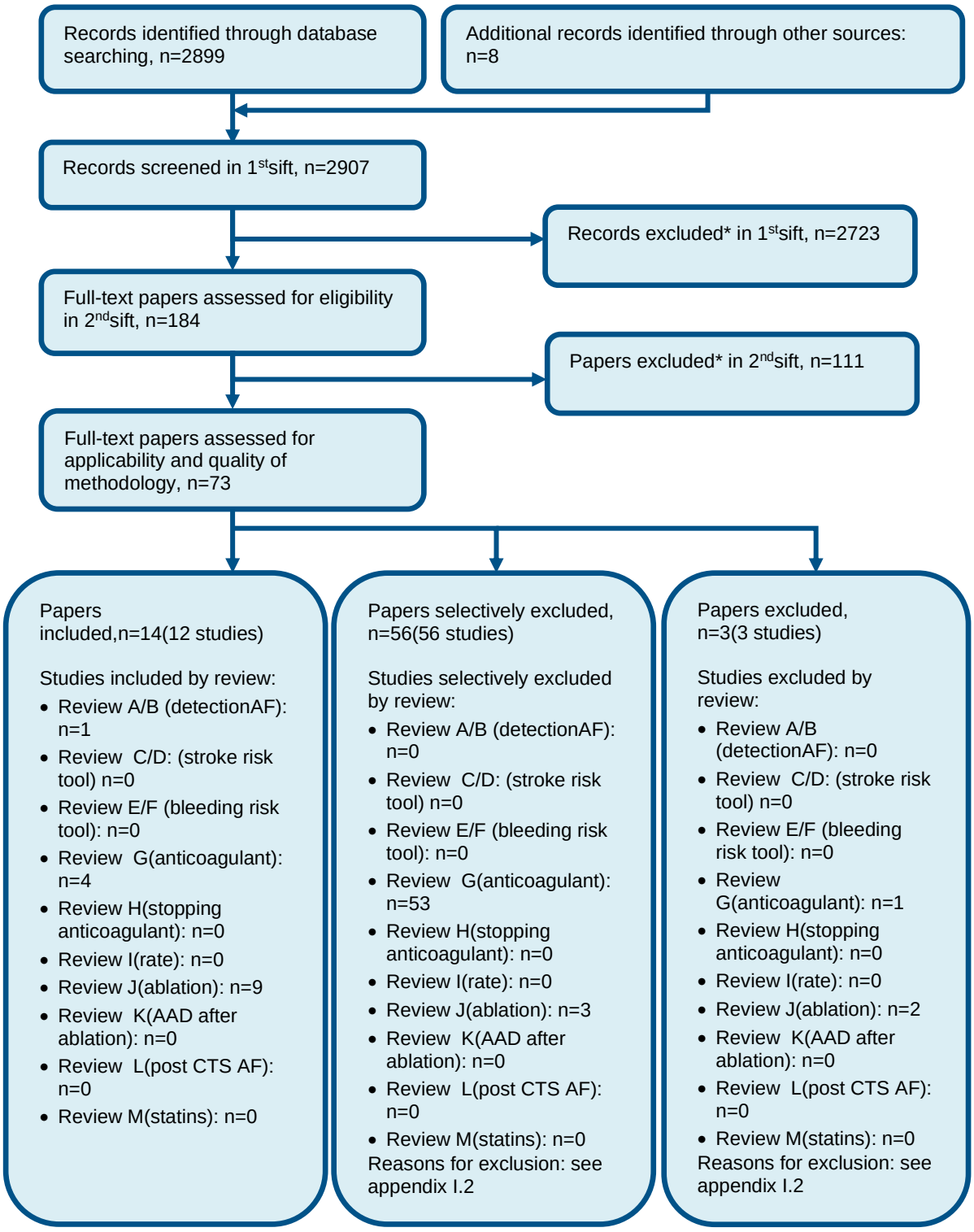
Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**K+ blockers + DC cardioversion**	**placebo + DC cardioversion**	**Relative (95% CI)**	**Absolute**		
Achievement of sinus rhythm (sinus rhythm at 12 months) (follow-up mean 12 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	22/36 (61.1%)	18.9%	RR 3.23 (1.58 to 6.61)	421 more per 1000 (from 110 more to 1000 more)	⊕⊕OO LOW	CRITICAL
Adverse events (dose reduction due to adverse events at 12 months) (follow-up mean 12 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	9/44 (20.5%)	0%	OR 9.25 (2.35 to 36.43)	205 more per 1000 (from 82 more to 328 more)[2]	⊕⊕OO LOW	CRITICAL
Health-related quality of life (mental component score SF-8 at 12 months) (follow-up mean 12 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	36	37	-	MD 3.74 higher (1.1 to 6.38 higher)	⊕OOO VERY LOW	CRITICAL
Health-related quality of life (physical component score SF-8 at 12 months) (follow-up mean 12 months; range of scores: 0-100; Better indicated by higher values)												

1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	36	37	-	MD 3.17 higher (0.24 to 6.1 higher)	⊕OOO VERY LOW	CRITICAL

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2]Absolute effect calculated manually using risk difference as zero events in control group of study
[3]Downgraded by 1 increment as the confidence intervals crossed the upper MID of 2.61
[4]Downgraded by 1 increment as the confidence intervals crossed the upper MID of 2.96

Appendix G: Health economic evidence selection

Figure 45: Flow chart of health economic study selection for the guideline



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

Appendix H: Health economic evidence tables

None.

Appendix I: Excluded studies

I.1 Excluded clinical studies

Table 39: Studies excluded from the clinical review

Study	Exclusion reason
Anonymous 2006[1]	Literature review/editorial
Balser1998[2]	Not review population
Banach 2005[3]	Not available - not in English
Bechtel 2003[4]	Incorrect study design
Bernard 2003[5]	Incorrect interventions - ibutilidenot licensed in UK
Blessberger2019[6]	Not review population
Bockeria2020[8]	Not review population
Burke 2003[9]	Literature review
Campbell 1980[11]	Incorrect interventions - disopyramide not available in IV form in UK
Campbell 1985[10]	Incorrect interventions - IV form of sotalol not available in UK
Cheng 2008[14]	Literature review
Connolly 1987[16]	Incorrect interventions - IV form of propafenone not available in UK
Conte 2019[17]	Systematic review: methods are not adequate/unclear
Crystal 2003[18]	Not review population
Dagres2014[19]	Systematic review is not relevant to review question or unclear PICO
Daoud 2004[20]	Literature review
De vecchis2018[21]	Systematic review is not relevant to review question or unclear PICO
Desouza2020[23]	Not review population
Desouza2020[24]	Systematic review is not relevant to review question or unclear PICO
Di biasi1995[25]	Incorrect interventions - IV form of propafenone not available in UK
Ding 2009[26]	Not available - not in English
Duggan 2011[27]	Literature review
Dunning 2004[28]	Systematic review: methods are not adequate/unclear
Effert1967[29]	Not available - not in English
Fellahi2018[30]	Systematic review: methods are not adequate/unclear. Systematic review: study designs inappropriate
Frost 1997[32]	Incorrect interventions – dofetilide not licensed in UK
Gao 2019[33]	Incorrect interventions. Not review population
Gavaghan 1988[34]	Incorrect interventions - IV form of disopyramide not available in UK
Gong 2017[36]	Systematic review is not relevant to review question or unclear PICO
Greenberg 2017[38]	Literature review
Gudbjartsson2019[39]	Literature review
Guerra 2017[40]	Systematic review is not relevant to review question or unclear PICO
Gun 1998[41]	Abstract only

Study	Exclusion reason
Ha 2016[42]	Literature review
Habibollahi2016[43]	Literature review
Han 2010[44]	Not in English
Helber1996[45]	Not available - not in English
Hilleman 2002[47]	Systematic review is not relevant to review question or unclear PICO. Systematic review: methods are not adequate/unclear
Hilleman 2005[46]	Literature review
Hjelms1992[48]	Incorrect interventions - procainamide not licensed in UK
Hogue jr2000[49]	Literature review
Humphries 1998[50]	Literature review
Iliuta2013[52]	Not review population
Iscan2018[53]	Literature review
Jannati2019[54]	Literature review
Ji 2010[55]	Incorrect interventions
Jie2010[56]	Incorrect interventions - given during surgery
Johnston 2019[57]	Not review population
Jung 2006[58]	Literature review
Kamali2017[59]	Incorrect interventions
Kleine2003[60]	Literature review
Kolokotroni2017[61]	Systematic review: study designs inappropriate. Systematic review: methods are not adequate/unclear
Koplan2007[62]	Editorial
Kowey1997[63]	Abstract only
Landymore1991[65]	Inappropriate comparison. Incorrect interventions
Larbuisson1996[66]	Incorrect interventions - IV form of propafenone not available in UK
Liu 2003[69]	Incorrect interventions
Ma 2020[70]	Not review population
Mahrose2019[71]	Not review population
Maisel 2001[72]	Systematic review: methods are not adequate/unclear
Mangin2005[73]	Non-randomised study
Mann 2007[74]	Literature review
Martinez 2005[75]	Systematic review: methods are not adequate/unclear
Martinez 2005[76]	Systematic review: methods are not adequate/unclear
Mcalister1986[77]	Abstract only
Mcalister1990[78]	Incorrect interventions - quinidine not licensed in UK
Mckeown2005[79]	Editorial/introduction to guideline
Mcmurry2004[80]	Literature review
Mooss2000[81]	Incorrect interventions - IV form of diltiazem not available in UK
Morttada2016[82]	No relevant outcomes
O'bryan2020[85]	Not review population
Ozaydin2013[86]	Incorrect interventions
Patel 2008[87]	Literature review
Plumb 1982[88]	Outcomes - insufficient information to extract
Rho 2000[90]	Literature review
Rosenberg 2016[91]	Abstract only
Sai 2019[92]	Not review population. Incorrect interventions

Study	Exclusion reason
Sakamoto 2012[93]	Incorrect interventions – landiolol not licensed in UK
Savelieva2014[94]	Systematic review is not relevant to review question or unclear PICO
Schleifer 2015[95]	Systematic review is not relevant to review question or unclear PICO
Schwartz 1988[96]	Case series
Selvaraj 2009[97]	Incorrect interventions - given during operation
Shantsila2006[98]	Editorial
Shen 2010[99]	Not available - not in English
Somberg2016[102]	Systematic review is not relevant to review question or unclear PICO
Soucier 2003[103]	Incorrect interventions – ibutilide not licensed in UK
Stiell2020[104]	Not review population
Szyszka1992[105]	Not available - not in English
Taenaka2013[106]	Not review population
Tisdale 1998[107]	Incorrect interventions – IV form of diltiazem not available in UK
Tsu2014[108]	Literature review
Vanderlugt1999[109]	Incorrect interventions – ibutilide not licensed in UK
White 2017[112]	Literature review
Yilmaz 1996[113]	Not review population

I.2 Excluded health economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2003or later and not from non-OECD country) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

Table 40: Studies excluded from the health economic review

Reference	Reason for exclusion
None	