National Institute for Health and Care Excellence

Draft for consultation

Atrial Fibrillation

Rate and rhythm control

NICE guideline

Intervention evidence review

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Draft for Consultation

Developed by the National Guideline Centre, hosted by the Royal College of Physicians

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Contents

1

1 Rate control

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

1.2 Introduction

In atrial fibrillation (AF) ventricular rate control is the one of the cornerstones of therapy and is usually sufficient to alleviate symptoms due to AF. AF with fast ventricular rates is a major contributing factor exercise limitation and disability. Unabated fast AF may lead to left ventricular dysfunction and heart failure.

The ventricular rate response to atrial fibrillation is dependent on atrio-ventricular (AV) node conduction and is influenced by autonomic tone. Alleviation of symptoms requires appropriate ventricular rate control both at rest and during exertion when rate response to AF may increase disproportionately. AV node conduction in response to AF varies considerably and some patients may not require rate control.

Non-ablative rate control in both the acute and non-acute settings is achieved by categories of drugs that slow AV node conduction including beta blockers, rate limiting calcium channel blockers, and digoxin. Amiodarone also slows AV node conduction and may be used in the acute phase particularly where there is evidence of haemodynamic instability or severely impaired left ventricular (LV) function. These drugs may be used alone but combinations are often required. Even so, rate control remains challenging particularly when choice is limited drug intolerance and patient factors (e.g. rate limiting calcium channel blockers are contraindicated in severe LV dysfunction). This evidence review aims to assess the effectiveness of these different AV node slowing drugs in the rate control of atrial fibrillation both in the acute and non-acute settings.

1.3 PICO table

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

Table 1: PICO characteristics of review question

Population	People aged over 18 with a diagnosis of non-valvular AF
Interventions	**Rate limiting Beta-blockers** (e.g.*. acebutolol, metoprolol, nadolol, pindolol, propranolol, esmalol) **Rate limiting Ca2+ channel blockers** (i.e.* diltiazem hydrochloride, verapamil) **Digoxin** **Amiodarone** Combinations of the above (i.e. Digoxin and Beta-blockers) drugs (licensed individually) are also included. UK licensed doses only Only UK licenced drugs (for any indication)

Comparisons	• To each other (BETWEEN the above 4 main CLASSES OF INTERVENTION ONLY - i.e. no comparisons between different types of beta-blockers or between different types of Ca2+ channel blockers will be undertaken) • Placebo • Usual Care / no treatment
Outcomes	Critical • health-related quality of life • mortality • hospitalisation • HF/exacerbation of heart failure. • Failure of non-ablative rate control
Study design	Randomised controlled trials and SRs of RCTs

1.4 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual.[101] Methods specific to this review question are described in the review protocol in Appendix A:.

Declarations of interest were recorded according to NICE's 2018 conflicts of interest policy.

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 rate control in non-valvular atrial fibrillation (NVAF), including beta-blockers, calcium channel blockers, digoxin, amiodarone and any combinations of these agents. Five studies (from six papers) were included in the review;[57, 71, 73, 132, 137, 148] these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 3).

Studies were included in this review only if the primary aim of the interventions was for rate control, and not for the restoration or control of sinus rhythm. The majority of the included studies employed intravenous administration of the drugs rather than oral doses and were set in secondary care, including over half in the emergency department for the treatment of acute AF. The included studies covered the following comparisons between the interventions listed in the protocol for this review:

- Four studies compared amiodarone with digoxin.[57, 132, 137, 148] Three of these used intravenous administration with one using oral administration.
- One study (two papers) compared beta-blockers (carvedilol) with digoxin[71, 73]. The study design was complex and involved two phases – one where carvedilol or placebo was initiated and a second where digoxin was either continued or discontinued to compare between a group receiving carvedilol alone and another group receiving digoxin alone at the end of the study. This study used oral administration of the drugs.

Not all of the studies explicitly stated that they covered a NVAF population; those with valvular disease as an exclusion criterion or those with no mention of concomitant valve disease within the population were included in the review, while studies where it was clear >10% of the population had experienced concomitant valve disease were excluded from the review.

It is also noted that studies that included intravenous use of diltiazem as one of the comparators were not included in the review, as this is not available for use in the UK in this form.

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

1.5.2 Excluded studies

See the excluded studies list in Appendix I.

1.5.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Hofmann 2006[57] RCT N=100 Conducted in Austria	**Amiodarone:** 450 mg IV amiodarone over 1 min followed by flush of 10 ml saline solution. If ventricular rate >100 bpm after 30 min, further IV dose of 300 mg amiodarone given **Digoxin:** 0.6 mg IV digoxin within 1 min. If ventricular rate >100 bpm after 30 min, second bolus of 0.4 mg digoxin given Rate control measured at 30 min post-initial dose	≥18 years old with atrial fibrillation and a mean ventricular rate >135 bpm measured in coronary care unit 12-lead ECG assessment	Mortality (in-hospital) Failure of non-ablative rate control	Some with a history of coronary bypass surgery and valve replacement but less than 10% Proportion were already taking beta-blockers (28% vs. 30%) or calcium channel blockers (12% vs. 8%) on admission
Khand 2003 and 2015[71, 73] RCT N=47 Conducted in UK	Study consisted of two phases for each of the two interventions. **Rate limiting beta-blockers – carvedilol:** **Phase I:** Open-label digoxin use prior to study continued + double-blind carvedilol randomly assigned at starting dose of 3.125 mg b.i.d. Dose increased at 2-week intervals until target dose of 25 mg b.i.d reached (2-month up titration	Patients with persistent AF (>1 month) and heart failure (appropriate symptoms for > 2 months and ECG evidence of cardiac dysfunction) that were receiving digoxin and diuretics Setting unclear – e.g. outpatients/secondary care 12-lead ECG assessment	Mortality Heart failure onset or exacerbation	Complex study design consisting of two phases was performed as withdrawal of digoxin at the same time as initiating and uptitrating beta-blockers could increase the risk of worsening HF. This design allowed the double-blinded initiation of carvedilol first, followed by double-blinded withdrawal of digoxin once maintenance doses of carvedilol had been achieved. At baseline proportion were using ACE inhibitors (71% vs. 71%)

Study	Intervention and comparison	Population	Outcomes	Comments
	period). Phase I lasted 4 months. **Phase II:** Open-label digoxin in phase I replaced with double-blind placebo + double-blind carvedilol use in phase I continued. Phase II lasted for duration of 2 months. **Digoxin:** **Phase I:** Open-label digoxin use prior to study continued + double-blind placebo randomly assigned instead of carvedilol. Phase I lasted 4 months. **Phase II:** Open-label digoxin in phase I replaced with double-blind digoxin + double-blind placebo use in phase I continued. Phase II lasted for duration of 2 months. Outcomes measured at 6 months post-randomisation (end of trial)			and/or anticoagulation (79% vs. 83%)
Shojaee 2017[132] RCT N=84 Conducted in Iran	**Amiodarone:** 150 mg IV amiodarone in 5% dextrose infused over 10 min. If no improvement, another 150 mg dose infused and all patients received maintenance dose of 50 mg/h during first 3 hours of treatment.	Patients between 18 and 80 years old presenting to emergency department with atrial fibrillation with rapid ventricular rate and relative contraindication for first line drugs (calcium channel blockers and beta-blockers)	Failure of non-ablative rate control	Valve disease not an exclusion criterion but no mention of any concomitant valve disease Amiodarone used a half the dose needed for rhythm conversion as using with the aim of rate control rather than rhythm control

Study	Intervention and comparison	Population	Outcomes	Comments
	Digoxin: 1 mg IV digoxin infused with initial injection of 0.5 mg followed by two 0.25 mg doses in second and fourth hour after intervention. Followed up for at least 12 hours post-first dose	12-lead ECG assessment		
Siu 2009[137] RCT N=150 Conducted in Hong Kong (China)	**Amiodarone:** Loading infusion of 300 mg IV amiodarone over first hour followed by 10 mg/kg over 24 h **Digoxin:** Initial bolus of 0.5 mg IV digoxin followed by 0.25 mg every 8 h (1.25 mg over 24 h).	Patients presenting to emergency department with symptomatic acute AF and rapid ventricular rate (>120 bpm) requiring hospitalisation ECG assessment method	Heart failure onset or exacerbation Failure of non-ablative rate control	Valve disease not an exclusion criterion but no mention of any concomitant valve disease Dose used for amiodarone was lower than maximum recommended dose for pharmacological conversion as aim of the study was to control rate not rhythm.
Tse 2001[148] RCT N=16 Conducted in Hong Kong (China)	**Amiodarone:** 600 mg daily for 1 week as loading dose followed by 100 mg daily for remaining 23 weeks **Digoxin:** 0.25 mg daily for 24 weeks. Lower dose used if body weight <50 kg or serum creatinine >200 mmol/L Outcomes measured at 24 weeks (end of treatment)	Patients with chronic AF. Setting unclear – outpatients? 12-lead ECG assessment and Holter monitoring	Health-related quality of life	All had failed a previous attempt at restoring and maintaining sinus rhythm All antiarrhythmic drugs discontinued for at least 2 weeks prior to beginning of study All patients received anticoagulation therapy with warfarin for prevention of thromboembolism

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: Amiodarone 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 Amiodarone (95% CI)
SF-36 physical functioning domain (24 weeks) Scale from: 0 to 100.	15 (1 study)	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision		The mean sf-36 physical functioning domain (24 weeks) in the control groups was 78	The mean sf-36 physical functioning domain (24 weeks) in the intervention groups was 14 higher (0.27 to 27.73 higher) Note: MID was deemed to be 8 (based on 0.5 x median sd [16.0] in digoxin group)
SF-36 physical role functioning domain (24 weeks) Scale from: 0 to 100.	15 (1 study)	⨁⊖⊖⊖ VERY LOW[a,c] due to risk of bias, imprecision		The mean sf-36 physical role functioning domain (24 weeks) in the control groups was 92	The mean sf-36 physical role functioning domain (24 weeks) in the intervention groups was 9 lower (34.83 lower to 16.83 higher) Note: MID was deemed to be 6 (based on 0.5 x median sd [12.0] in digoxin group)
SF-36 bodily pain domain (24 weeks) Scale from: 0 to 100.	15 (1 study)	⨁⊖⊖⊖ VERY LOW[a,d] due to risk of bias, imprecision		The mean sf-36 bodily pain domain (24 weeks) in the control groups was 77	The mean sf-36 bodily pain domain (24 weeks) in the intervention groups was 6 lower (34.18 lower to 22.18 higher) Note: MID was deemed to be 15 (based on 0.5 x median sd [30.0] in digoxin group)

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 Amiodarone (95% CI)
SF-36 general health domain (24 weeks) Scale from: 0 to 100.	15 (1 study)	⨁⊖⊖⊖ VERY LOW[a,e] due to risk of bias, imprecision		The mean sf-36 general health domain (24 weeks) in the control groups was 57	The mean sf-36 general health domain (24 weeks) in the intervention groups was 1 higher (19.95 lower to 21.95 higher) Note: MID was deemed to be 11 (based on 0.5 x median sd [22.0] in digoxin group)
SF-36 vitality domain (24 weeks) Scale from: 0 to 100.	15 (1 study)	⨁⊖⊖⊖ VERY LOW[a,f] due to risk of bias, imprecision		The mean sf-36 vitality domain (24 weeks) in the control groups was 58	The mean sf-36 vitality domain (24 weeks) in the intervention groups was 9 higher (12.76 lower to 30.76 higher) Note: MID was deemed to be 10 (based on 0.5 x median sd [20.0] in digoxin group)
SF-36 social functioning domain (24 weeks) Scale from: 0 to 100.	15 (1 study)	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision		The mean sf-36 social functioning domain (24 weeks) in the control groups was 84	The mean sf-36 social functioning domain (24 weeks) in the intervention groups was 6 higher (7.73 lower to 19.73 higher) Note: MID was deemed to be 8 (based on 0.5 x median sd [16.0] in digoxin group)
SF-36 emotional role functioning domain (24 weeks) Scale from: 0 to 100.	15 (1 study)	⨁⊖⊖⊖ VERY LOW[a,g] due to risk of bias, imprecision		The mean sf-36 emotional role functioning domain (24 weeks) in the control groups was 86	The mean sf-36 emotional role functioning domain (24 weeks) in the intervention groups was 5 lower (35.43 lower to 25.43 higher)

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 Amiodarone (95% CI)
					Note: MID was deemed to be 13 (based on 0.5 x median sd [26.0] in digoxin group)
SF-36 mental health domain (24 weeks) Scale from: 0 to 100.	15 (1 study)	⨁⊖⊖⊖ VERY LOW[a,h] due to risk of bias, imprecision		The mean sf-36 mental health domain (24 weeks) in the control groups was 58	The mean sf-36 mental health domain (24 weeks) in the intervention groups was 10 higher (15.31 lower to 35.31 higher) Note: MID was deemed to be 11.5 (based on 0.5 x median sd [23.0] in digoxin group)
Mortality (in-hospital)	100 (1 study)	⨁⊖⊖⊖ VERY LOW[a,i] due to risk of bias, imprecision	RR 0.5 (0.05 to 5.34)	Moderate	
				40 per 1000	20 fewer per 1000 (from 38 fewer to 174 more)
Heart failure onset or exacerbation (new-onset congestive heart failure)	100 (1 study)	⨁⊖⊖⊖ VERY LOW[a,k] due to risk of bias, imprecision	RD 0 (-0.04 to 0.04)	Moderate	
				0 per 1000	0 fewer per 1000 (from 40 fewer to 40 more)[j]
Failure of non-ablative rate control	284 (3 studies) 0.5-24 hours	⨁⊖⊖⊖ VERY LOW[a,i,l] due to risk of bias, inconsistency, imprecision	RR 0.64 (0.39 to 1.04)	Moderate	
				595 per 1000	214 fewer per 1000 (from 363 fewer to 24 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]Downgraded by 1 increment as the confidence intervals crossed the upper MID of 8
[c]Downgraded by 2 increments as the confidence intervals crossed the upper and lower MIDs of 6 and -6
[d]Downgraded by 2 increments as the confidence intervals crossed the upper and lower MIDs of 15 and -15

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 Amiodarone (95% CI)

[e]Downgraded by 2 increments as the confidence intervals crossed the upper and lower MIDs of 11 and -11
[f]Downgraded by 2 increments as the confidence intervals crossed the upper and lower MIDs of 10 and -10
[g]Downgraded by 2 increments as the confidence intervals crossed the upper and lower MIDs of 13 and -13
[h]Downgraded by 2 increments as the confidence intervals crossed the upper and lower MIDs of 11.5 and -11.5
[i]Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[j]Absolute effect calculated manually using risk difference as zero events in both arms
[k]Serious imprecision as sample size >70 and <350
[l]Serious inconsistency as I2 >50% and some variation in point estimates on Forest plot. Switched to random effects and rated down for inconsistency.

Table 4: Clinical evidence summary: Beta-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 Beta-blockers (95% CI)
Mortality (phase I - carvedilol + digoxin vs. placebo + digoxin)	43 (1 study)	⨁⊖⊖⊖ VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 1.05 (0.07 to 15.69)	Moderate	
				46 per 1000	2 more per 1000 (from 43 fewer to 676 more)
Mortality (phase II - carvedilol + placebo vs. placebo + digoxin)	37 (1 study)	⨁⊖⊖⊖ VERY LOW[a,c] due to risk of bias, imprecision	Peto OR 8.82 (0.17 to 450.05)	Moderate	
				0 per 1000	60 more per 1000 (from 80 fewer to 200 more)[d]

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 Beta-blockers (95% CI)
Heart failure onset or exacerbation (worsening heart failure symptoms during phase II - carvedilol + placebo vs. placebo + digoxin)	40 (1 study)	⨁⊖⊖⊖ VERY LOW[a,c] due to risk of bias, imprecision	RR 3.32 (0.38 to 29.23)	Moderate	
				48 per 1000	111 more per 1000 (from 30 fewer to 1000 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]Indirectness for the intervention as during phase I of this study patients receiving carvedilol + digoxin or placebo + digoxin rather than carvedilol or digoxin only, which was initiated in phase II of the study.
[c]Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[d]Absolute effect calculated manually from risk difference as zero events in one arm of the only included study

See Appendix F: for full GRADE tables.

1.6 Economic evidence

1.6.1 Included studies

No health economic studies were included.

1.6.2 Excluded studies

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

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

1.6.3 Unit costs

Relevant drug unit costs are provided in Table 5 to aid consideration of cost effectiveness.

Table 5: Drug unit costs

Class	Drug (preparation)	Dose range	Cost range per day	Cost range per year
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 (a)	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 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
Class IV (calcium channel blocker)	Diltiazem hydrochloride	120mg to 360mg daily	£0.13 to £0.38	£46.60 to £139.81
Class IV (calcium channel blocker)	Verapamil hydrochloride (tablet)	40mg to 120 mg tid	£0.06 to £0.14	£20.34 to £52.40
Class IV (calcium channel blocker)	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) BNF dose states: 50–200 micrograms/kg/minute, consult product literature for details of dose titration and doses during peri-operative period. Topic advisor noted that it would be used (rarely) to control rate in an emergency pending definitive treatment. In this scenario costing a 2.5g/250ml infusion bag would adequately reflect current practice. This would provide 4-6 hours of infusion depending on weight.

(b) Brevibloc premixed 2.5mg/250ml infusion bags

Source of cost and dose: BNF[15], last accessed January 2020. With exception of diltiazem hydrochloride as this is an unlicensed indication. Dose based on Topic advisor clinical experience.

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

1.7 The committee's discussion of the evidence

1.7.1 Interpreting the evidence

1.7.1.1 The outcomes that matter most

All outcomes listed in the protocol for this review, which comprised health-related quality of life, mortality, hospitalisation, heart failure/exacerbation of heart failure and failure of non-ablative rate control, were considered by the committee to be critical for decision-making. No additional important outcomes were specified in the protocol.

In this review, no clinical evidence was identified for the hospitalisation outcome for any of the comparisons specified in the protocol.

1.7.1.2 The quality of the evidence

The quality of the evidence for all outcomes included in this review was of very low quality according to GRADE analysis. The primary reasons for this were a very high risk of bias due to issues with selection and blinding of participants and attrition, as well as imprecision detected for all included outcomes.

Inconsistency, which refers to the presence of heterogeneity between effects across different studies in a meta-analysis, was also an issue for one of the outcomes in the amiodarone vs. digoxin comparison.

Limited evidence was identified for this review, and the available evidence only covered two comparisons: amiodarone vs. digoxin and beta blockers vs. digoxin. In terms of interpreting the evidence, imprecision made it difficult for the committee to determine the true effect of the interventions relative to one another, as there was too much uncertainty. This uncertainty was exacerbated by the fact that for most of the reported outcomes, pooling of multiple studies was not possible and effect sizes were based on only one study with small numbers of participants. These limitations in the amount and quality of the evidence meant that the committee did not feel able to change existing recommendations based on the evidence, and instead changes were made based on consensus and current practice.

1.7.1.3 Benefits and harms

The evidence included in this review was obtained from five RCTs, with evidence available for the comparisons between beta-blockers and digoxin, and amiodarone and digoxin.

For the amiodarone vs. digoxin comparison, there was some evidence to suggest a benefit of amiodarone over digoxin in terms of failure of non-ablative rate control, with a meta-analysis consisting of three studies indicating fewer failures in the amiodarone group compared with the digoxin group. However, concerns were raised by the committee about whether the time-point at which failure of rate control was measured was suitable to be able to detect effects of digoxin; one study measured rate control failure at 30 min post-initial dose, which was considered to be too short to measure an effect of digoxin and therefore the time-point at which this outcome was measured may have been biased towards amiodarone for this study.

There was no clear evidence for any of the other outcomes reported for this comparison. One study provided data on the quality of life of those receiving oral doses of amiodarone or digoxin; however, this was based on a very small number of participants and there was too much variability in effect sizes for most of the quality of life domains to determine whether a difference existed between the two groups. Additionally, the committee noted that the composite mental and physical scores that are usually reported for the SF-36 quality of life scoring system had not been reported in this study, suggesting that there was likely to be no

important difference between the two groups overall and this may be why these composite scores were not reported in the study. Similarly, no strong evidence favouring either amiodarone or digoxin in studies with intravenous dosing in the emergency department was available for in-hospital mortality or heart failure onset outcomes, with either no clinical difference being reported or substantial variation in the effect estimate making it difficult to determine the true effect.

For the beta-blockers vs. digoxin comparison, only one study was available, which compared oral dosing with carvedilol or digoxin. Although point estimates appeared to favour digoxin in terms of mortality and worsening of heart failure symptoms during the second phase of this trial, the wide confidence intervals meant that there was substantial uncertainty in the true effect.

As the committee considered the evidence to be insufficient to support significant changes to the current recommendations in this area, the committee instead amended the existing recommendations based on consensus and current practice. The committee noted that recommendations for chronic heart failure were published in 2018 (NICE guideline NG106) and when considering drug therapy in those with atrial fibrillation and chronic heart failure, clinicians should refer to the chronic heart failure guideline for the use of calcium channel blockers, as it advises that calcium channel blockers such as diltiazem and verapamil be avoided in those with heart failure and reduced left ventricular ejection fraction. Additionally, the chronic heart failure guideline (NICE guideline NG106) had already reviewed the evidence for beta-blockers vs. placebo in those with atrial fibrillation and heart failure by including an individual patient data meta-analysis of atrial fibrillation subsets of heart failure trials; no recommendations were made regarding the use of beta-blockers in those with atrial fibrillation and heart failure. There was some evidence of a small increase in all-cause mortality and stroke but the chronic heart failure committee were not confidence in the effect estimate due to the presence of very serious imprecision. The evidence did not show a clinical important reduction in the number of heart failure hospitalisations. Due to the uncertainty in the evidence the committee made a research recommendation. Therefore, to avoid contradicting decisions made in NG106 based on the same set of evidence, the individual patient data meta-analysis mentioned above was not included in the review, and it was agreed that referring to NG106 for beta-blocker use in those with atrial fibrillation and chronic heart failure was preferable.

The existing recommendation of beta-blockers or rate-limiting calcium channel blockers as the choice for initial rate control treatment in those requiring a rate control strategy was retained by the committee as they agreed that this recommendation was still current practice and there was insufficient evidence to suggest an alternative recommendation, with potential adverse events of other alternative options being highlighted. The committee agreed that the choice should still be made based on the symptoms, heart rate, comorbidities and preferences of those being treated. The committee also agreed with the existing recommendations for this area concerning combination therapy options if initial monotherapy fails and the decision not to use amiodarone long-term, as the evidence included in the review was insufficient to suggest otherwise and there were significant concerns about the serious side effects associated with long-term use of amiodarone. However, the committee highlighted that digoxin monotherapy in those with non-paroxysmal atrial fibrillation was not always limited to people that are sedentary and may also be considered in those with comorbidities or because of patient preferences that prevent the use of other rate control drugs. The reasoning given by the previous guideline committee to limit digoxin use in non-paroxysmal atrial fibrillation to those that are sedentary was due to concerns about reduced effectiveness during exercise. However, the current guideline committee agreed that there was not considered to be any evidence against considering digoxin in these additional groups and a number of committee members confirmed that from their experience digoxin was sometimes considered in those that were not sedentary if other options for monotherapy were not suitable.

1.7.2 Cost effectiveness and resource use

No relevant health economic analyses were identified for this review. The unit costs of rate control drugs were presented. The unit costs are low and although there was limited clinical evidence, the committee felt that these costs were likely to be offset by the gains in quality of life. In discussion, the committee noted that the drugs considered are already in widespread use in current practice, and as such the cost impact of the recommendation is likely to be low. The committee considered other factors which may influence the resource use associated with any of the drugs. In particular, they discussed the serious adverse effects associated with the long-term use of amiodarone (including thyroid, lung and nerve damage), many of which are irreversible. The committee noted amiodarone requires intensive monitoring which has an associated cost. Furthermore, if a patient experiences these serious adverse events then there would be a significant cost to both the patient in terms of prognosis and NHS in terms of treatment and long-term management.

Due to the limited evidence available in the clinical review and lack of health economic evidence the committee decided to keep the existing recommendations, making only small amendments and additions. The consensus-based edits included cross referring to the chronic heart failure guideline, where the use of calcium channel blockers and beta blockers is not recommended in people with AF and concomitant heart failure. This is further supported by the acute heart failure guideline which advises caution when using beta blockers and that calcium channel blockers should not be used. This addition is not expected to have any resource impact on the NHS as this should already be current practice. The second amendment is expanding the population for whom digoxin monotherapy is considered to include those with comorbidities and/or patient preferences that rule out other rate-limiting drug options. The committee noted that this sometimes occurs in current practice and they do not anticipate this change in recommendation to have a significant resource impact to NHS resources.

1.7.2.1 Other factors the committee took into account

The committee was aware of a recently published study in recent-onset (acute) AF, which indicated that rate control with delayed cardioversion if AF did not resolve within 48 h was non-inferior to early cardioversion. This supports the use of rate control, with delayed cardioversion if required, as an appropriate treatment strategy in acute AF, meaning its inclusion as an option in the recommendations for acute AF rate control was considered to be appropriate.

References

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Appendices

Appendix A: Review protocols

Table 6: Review protocol: Non-ablative rate control in AF

ID	Field	Content
0.	PROSPERO registration number	[Complete this section with the PROSPERO registration number once allocated]
1.	Review title	Clinical and cost effectiveness of different non-ablative rate control therapies in people with atrial fibrillation
2.	Review question	What is the clinical and cost effectiveness of different non-ablative rate control therapies in people with atrial fibrillation?
3.	Objective	To identify the clinical effects of the different rate therapies in this population
4.	Searches	The following databases will be searched: Cochrane Central Register of Controlled Trials (CENTRAL) Cochrane Database of Systematic Reviews (CDSR) Embase MEDLINE Epistemonikos Searches will be restricted by: English language Human studies Letters and comments are excluded. Other searches: Inclusion lists of relevant systematic reviews will be checked by the reviewer. The searches may be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion if relevant. The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Atrial Fibrillation
6.	Population	Inclusion: People aged over 18 with a diagnosis of AF Exclusion: Severe valve disease
7.	Intervention/Exposure/Test	Rate limiting Beta-blockers (e.g*. acebutolol, metoprolol, nadolol, pindolol, propranolol, esmalol) Rate limiting Ca2+ channel blockers (i.e.* diltiazem hydrochloride, verapamil) Digoxin

ID	Field	Content
		Amiodarone Combinations of the above (i.e. Digoxin and Beta-blockers) drugs (licensed individually) are also included. UK licensed doses only Only UK licenced drugs (for any indication)
8.	Comparator/Reference standard/Confounding factors	• To each other (BETWEEN the above 4 main CLASSES OF INTERVENTION ONLY - i.e. no comparisons between different types of beta-blockers or between different types of Ca2+ channel blockers will be undertaken) • Placebo • Usual Care / no treatment
9.	Types of study to be included	Systematic reviews RCTs (including those with a cross-over design). Non-randomised studies will be excluded.
10.	Other exclusion criteria	Non-English language studies. AF secondary to Cardiothoracic surgery is excluded from this question - it will be dealt with separately in Q9 because it is a different population that may respond differently. 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 hospitalisation HF/exacerbation of heart failure. Failure of non-ablative rate control Longest follow up point always used
13.	Secondary outcomes (important outcomes)	None
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

ID	Field	Content
		(see Developing NICE guidelines: the manual section 6.4) and for undertaking assessment of study quality. Summary evidence tables will be produced including information on: study setting; study population and participant demographics and baseline characteristics; details of the intervention and control interventions; study methodology' recruitment and missing data rates; outcomes and times of measurement; critical appraisal ratings. A second reviewer will quality assure the extracted data. Discrepancies will be identified and resolved through discussion (with a third reviewer where necessary).
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. For Intervention reviews the following checklist will be used according to study design being assessed: Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) Randomised Controlled Trial: Cochrane RoB (2.0) Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
16.	Strategy for data synthesis	Where possible, data will be meta-analysed. Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5) to combine the data given in all studies for each of the outcomes stated above. A fixed effect meta-analysis, with weighted mean differences for continuous outcomes and risk ratios for binary outcomes will be used, and 95% confidence intervals will be calculated for each outcome. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. We will consider an I^2 value greater than 50% indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented using random-effects. GRADE pro will be used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. Other bias will only be taken into consideration in the quality assessment if it is apparent. Where meta-analysis is not possible, data will be presented, and quality assessed individually per outcome. If sufficient data is available to make a network of treatments, WinBUGS will be used for network meta-analysis.
17.	Analysis of sub-groups	Stratification • None, though of course there will be separate analyses for each separate permutation of intervention and comparator Sub-grouping

ID	Field	Content		
		If serious or very serious heterogeneity (I2>50%) is present within any stratum, sub-grouping will occur according to the following strategies: Existence of HF (yes vs No) Renal failure (eGFR<30 vs >30)		
18.	Type and method of review	☒	Intervention	
		☐	Diagnostic	
		☐	Prognostic	
		☐	Qualitative	
		☐	Epidemiologic	
		☐	Service Delivery	
		☐	Other (please specify)	
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date			
22.	Anticipated completion date			
23.	Stage of review at time of this submission	Review stage	Started	Completed
		Preliminary searches	☐	☑
		Piloting of the study selection process	☐	☑
		Formal screening of search results against eligibility criteria	☐	☑
		Data extraction	☐	☑
		Risk of bias (quality) assessment	☐	☑
		Data analysis	☐	☑
24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre		

ID	Field	Content	
25.	Review team members	From the National Guideline Centre: Sharon Swain Mark Perry Nicole Downes Sophia Kemmis Betty Elizabeth Pearton	
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.	
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: [NICE guideline webpage].	
29.	Other registration details		
30.	Reference/URL for published protocol		
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: notifying registered stakeholders of publication publicising the guideline through NICE's newsletter and alerts issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Atrial Fibrillation, 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	

ID	Field	Content
36.	Details of final publication	www.nice.org.uk

1

2 **Table 7: Health economic review protocol**

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below. For questions being updated from NICE guideline CG180, the search will be run from October 2013, which was the cut-off date for the searches. For questions being updated from the NICE guideline CG36 and for new questions, the search will be run from 2003.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2003, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Studies published after 2003 that were included in the previous guideline(s) will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual.[101] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed, and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded, then a health economic evidence table will not be completed, and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in

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

1
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Appendix B: Literature search strategies

This literature search strategy was used for the following reviews;

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

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[101]

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 8: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 31 December 2019	Exclusions Randomised controlled trials Systematic review studies
Embase (OVID)	1974 – 31 December 2019	Exclusions Randomised controlled trials Systematic review studies
The Cochrane Library (Wiley)	Cochrane Reviews to 2019 Issue 12 of 12 CENTRAL to 2019 Issue 12 of 12	None
Epistemonikos (Epistemonikos Foundation)	Inception – 31 December 2019	Systematic review studies

Medline (Ovid) search terms

1.	exp atrial fibrillation/
2.	((atrial or atria or atrium or auricular) adj3 fibrillat*).ti,ab.
3.	AF.ti,ab.
4.	1 or 2 or 3
5.	letter/
6.	editorial/
7.	news/
8.	exp historical article/
9.	Anecdotes as Topic/
10.	comment/
11.	case report/
12.	(letter or comment*).ti.
13.	or/5-12
14.	randomized controlled trial/ or random*.ti,ab.

15.	13 not 14
16.	animals/ not humans/
17.	exp Animals, Laboratory/
18.	exp Animal Experimentation/
19.	exp Models, Animal/
20.	exp Rodentia/
21.	(rat or rats or mouse or mice).ti.
22.	or/15-21
23.	4 not 22
24.	limit 23 to English language
25.	exp adrenergic beta-antagonists/
26.	(propranolol or acebutolol or atenolol or bisoprolol or celiprolol or co-tenidone or esmolol or metoprolol or nadolol or nebivolol or oxprenolol or pindolol or sotalol or timolol or carvedilol or labetalol).ti,ab.
27.	(beta adj3 block*).ti,ab.
28.	((beta-adrenoceptor or b-adrenoceptor or beta-adrenergic) adj (block* or antagonist*)).ti,ab.
29.	(b adj3 block*).ti,ab.
30.	(beta adj2 antagonist*).ti,ab.
31.	calcium channel blockers/
32.	((channel or calcium or ca) adj3 block*).ti,ab.
33.	(ca2* or CCB or CCBs).ti,ab.
34.	(diltiazem or verapamil).ti,ab.
35.	Digoxin/
36.	Digoxin.ti,ab.
37.	exp Amiodarone/
38.	Amiodarone.ti,ab.
39.	(ventricular adj3 (rate or control or limit*) adj3 (medicine* or medicat* or drug*)).ti,ab.
40.	(Rate adj2 (control or limit*) adj2 (medicine* or medicat* or drug*)).ti,ab.
41.	or/25-40
42.	24 and 41
43.	randomized controlled trial.pt.
44.	controlled clinical trial.pt.
45.	randomi#ed.ab.
46.	placebo.ab.
47.	randomly.ab.
48.	clinical trials as topic.sh.
49.	trial.ti.
50.	or/43-49
51.	Meta-Analysis/
52.	Meta-Analysis as Topic/
53.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
54.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
55.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.

56.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
57.	(search* adj4 literature).ab.
58.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
59.	cochrane.jw.
60.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
61.	or/51-60
62.	42 and (50 or 61)

1 **Embase (Ovid) search terms**

1.	exp atrial fibrillation/
2.	((atrial or atria or atrium or auricular) adj3 fibrillat*).ti,ab.
3.	AF.ti,ab.
4.	1 or 2 or 3
5.	letter.pt. or letter/
6.	note.pt.
7.	editorial.pt.
8.	case report/ or case study/
9.	(letter or comment*).ti.
10.	or/5-9
11.	randomized controlled trial/ or random*.ti,ab.
12.	10 not 11
13.	animal/ not human/
14.	nonhuman/
15.	exp Animal Experiment/
16.	exp Experimental Animal/
17.	animal model/
18.	exp Rodent/
19.	(rat or rats or mouse or mice).ti.
20.	or/12-19
21.	4 not 20
22.	limit 21 to English language
23.	exp *beta adrenergic receptor blocking agent/
24.	(propranolol or acebutolol or atenolol or bisoprolol or celiprolol or co-tenidone or esmolol or metoprolol or nadolol or nebivolol or oxprenolol or pindolol or sotalol or timolol or carvedilol or labetalol).ti,ab.
25.	(beta adj3 block*).ti,ab.
26.	((beta-adrenoceptor or b-adrenoceptor or beta-adrenergic) adj (block* or antagonist*)).ti,ab.
27.	(b adj3 block*).ti,ab.
28.	(beta adj2 antagonist*).ti,ab.
29.	*calcium channel blocking agent/
30.	((channel or calcium or ca) adj3 block*).ti,ab.
31.	(ca2* or CCB or CCBs).ti,ab.
32.	(diltiazem or verapamil).ti,ab.
33.	*digoxin/

34.	Digoxin.ti,ab.
35.	*amiodarone/
36.	(ventricular adj3 (rate or control or limit*) adj3 (medicine* or medicat* or drug*)).ti,ab.
37.	(Rate adj2 (control or limit*) adj2 (medicine* or medicat* or drug*)).ti,ab.
38.	or/23-37
39.	22 and 38
40.	random*.ti,ab.
41.	factorial*.ti,ab.
42.	(crossover* or cross over*).ti,ab.
43.	((doubl* or singl*) adj blind*).ti,ab.
44.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
45.	crossover procedure/
46.	single blind procedure/
47.	randomized controlled trial/
48.	double blind procedure/
49.	or/40-48
50.	systematic review/
51.	Meta-Analysis/
52.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
53.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
54.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
55.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
56.	(search* adj4 literature).ab.
57.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
58.	cochrane.jw.
59.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
60.	or/50-59
61.	39 and (49 or 60)

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Atrial Fibrillation] explode all trees
#2.	((atrial or atria or atrium or auricular) near/3 fibrillat*):ti,ab
#3.	AF:ti,ab
#4.	#1 or #2 or #3
#5.	MeSH descriptor: [Adrenergic beta-Antagonists] explode all trees
#6.	(propranolol or acebutolol or atenolol or bisoprolol or celiprolol or co-tenidone or esmolol or metoprolol or nadolol or nebivolol or oxprenolol or pindolol or sotalol or timolol or carvedilol or labetalol):ti,ab
#7.	(beta near/3 block*):ti,ab
#8.	((beta-adrenoceptor or b-adrenoceptor or beta-adrenergic) next (block* or antagonist*)):ti,ab
#9.	(b near/3 block*):ti,ab
#10.	(beta near/2 antagonist*):ti,ab
#11.	MeSH descriptor: [Calcium Channel Blockers] this term only

#12.	((channel or calcium or ca) near/3 block*):ti,ab
#13.	(ca2* or CCB or CCBs).ti,ab
#14.	(diltiazem or verapamil):ti,ab
#15.	MeSH descriptor: [Digoxin] this term only
#16.	Digoxin:ti,ab
#17.	MeSH descriptor: [Amiodarone] explode all trees
#18.	Amiodarone:ti,ab
#19.	(ventricular near/3 (rate or control or limit*) near/3 (medicine* or medicat* or drug*)):ti,ab
#20.	(Rate near/2 (control or limit*) near/2 (medicine* or medicat* or drug*)):ti,ab
#21.	(or #5-#20)
#22.	#4 and #21

Epistemonikos search terms

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

B.2 Health Economics literature search strategy

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

Table 9: Database date parameters and filters used

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

Medline (Ovid) search terms

1.	exp atrial fibrillation/
2.	((atrial or atria or atrium or auricular) adj3 fibrillat*).ti,ab.
3.	AF.ti,ab.
4.	1 or 2 or 3
5.	letter/
6.	editorial/
7.	news/
8.	exp historical article/
9.	Anecdotes as Topic/
10.	comment/
11.	case report/

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

1 **Embase (Ovid) search terms**

1.	exp atrial fibrillation/
2.	((atrial or atria or atrium or auricular) adj3 fibrillat*).ti,ab.
3.	AF.ti,ab.
4.	1 or 2 or 3
5.	letter.pt. or letter/
6.	note.pt.
7.	editorial.pt.
8.	case report/ or case study/
9.	(letter or comment*).ti.
10.	or/5-9
11.	randomized controlled trial/ or random*.ti,ab.

12.	10 not 11
13.	animal/ not human/
14.	nonhuman/
15.	exp Animal Experiment/
16.	exp Experimental Animal/
17.	animal model/
18.	exp Rodent/
19.	(rat or rats or mouse or mice).ti.
20.	or/12-19
21.	4 not 20
22.	limit 21 to English language
23.	health economics/
24.	exp economic evaluation/
25.	exp health care cost/
26.	exp fee/
27.	budget/
28.	funding/
29.	budget*.ti,ab.
30.	cost*.ti.
31.	(economic* or pharmaco?economic*).ti.
32.	(price* or pricing*).ti,ab.
33.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
34.	(financ* or fee or fees).ti,ab.
35.	(value adj2 (money or monetary)).ti,ab.
36.	or/23-35
37.	22 and 36

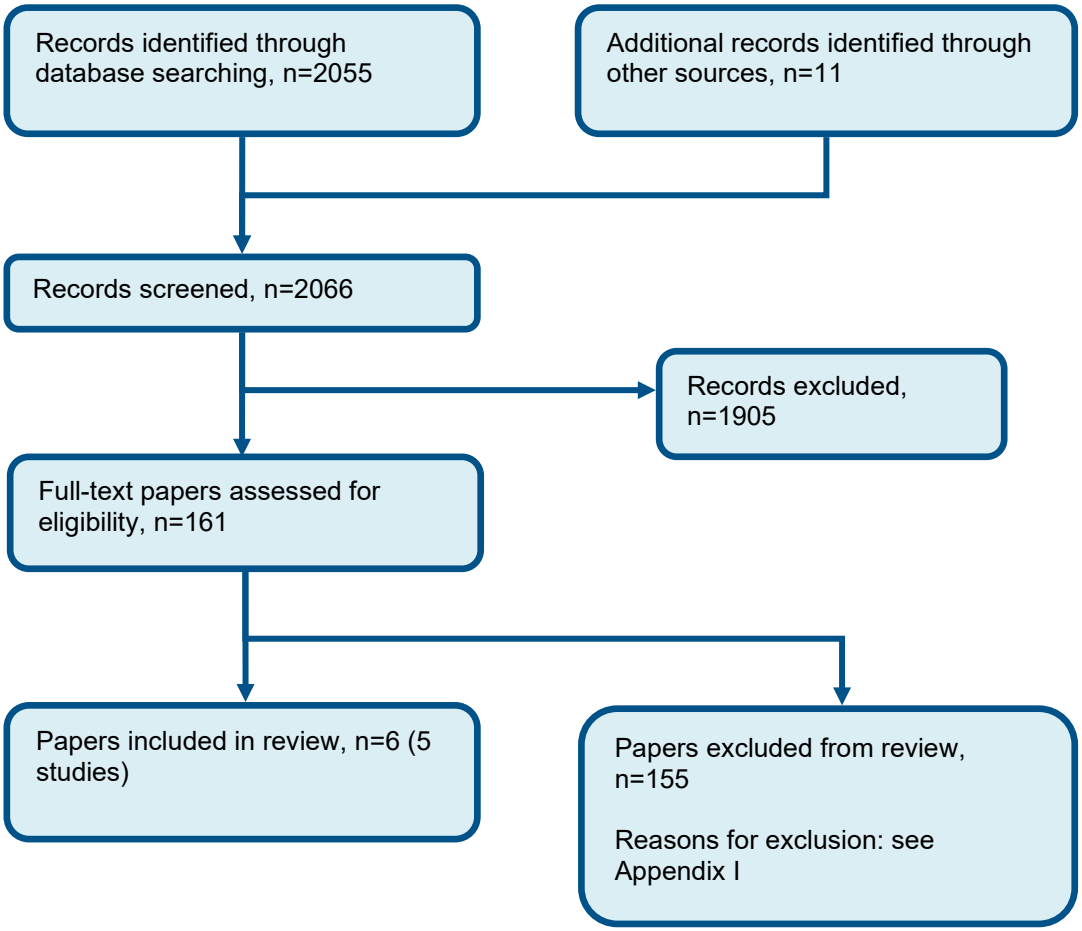
1 **NHS EED and HTA (CRD) search terms**

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

2

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of non-ablative rate control in AF



Appendix D: Clinical evidence tables

Study	Hofmann 2006[57]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=100)
Countries and setting	Conducted in Austria; Setting: Coronary care unit of hospital - secondary care.
Line of therapy	Unclear
Duration of study	Intervention + follow up: Followed up during intervention until discharge from hospital
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: 12-lead ECG
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Atrial fibrillation and a mean ventricular rate >135 bpm measured during a period of 5 min of monitoring in coronary care unit. Atrial fibrillation primary diagnosis and main reason for hospital admission.
Exclusion criteria	Age <18 years; baseline systolic blood pressure <100 mmHg; known thyroid function disorder; serum potassium <3.5 mmol/l; pretreatment with any antiarrhythmic drug with class I or class III properties; history of torsade de pointes arrhythmia; documented permanent atrial fibrillation; QTc interval of above 440 ms measured in the qualifying ECG.
Recruitment/selection of patients	Consecutive patients presenting during daytime working hours in coronary care unit
Age, gender and ethnicity	Age - Mean (SD): Amiodarone, 68.3 (13); digoxin, 69.3 (13). Gender (M:F): Amiodarone, 28/22; digoxin, 28/22. Ethnicity: Not reported
Further population details	1. heart failure: Not stated / Unclear (Proportion with HF unclear - mean LVEF of 54/55% in each group.). 2. Renal failure: Not stated / Unclear (No details given).
Extra comments	Mean (SD) ejection fraction (%): amiodarone, 55.2 (19); digoxin, 54.3 (14) History of myocardial infarction, coronary bypass surgery, valve replacement, percutaneous coronary intervention, hypertension, diabetes, chronic obstructive lung disease, stroke, congestive heart failure, persistent atrial fibrillation, paroxysmal atrial fibrillation, or no specific cardiovascular history, similar between both groups.

	Mean (SD) potassium (mmol/l): amiodarone, 4.2 (0.5); digoxin, 4.3 (0.5) Mean (SD) creatine kinase (mg/dl): amiodarone, 1.2 (0.3); digoxin, 1.1 (0.2) Mean (SD) duration of AF (days): amiodarone, 1.93 (2.6); digoxin, 2.08 (3.0)
Indirectness of population	Serious indirectness: Some with history of coronary bypass surgery (but less than 10%). Also some with valve replacement suggesting valve disease but less than 10%.
Interventions	(n=50) Intervention 1: Amiodarone. Patients received 450 mg amiodarone through peripheral vein access within 1 min, followed by flush of 10 ml saline solution. If ventricular rate was above 100 bpm after 30 min, patients received another 300 mg intravenously. Duration 1 min initial dose. Concurrent medication/care: 28 and 12% of patients in this group were already taking beta blockers and calcium channel blockers, respectively. Further treatment after intervention was performed on an individual basis and depended on various clinical factors such as clinical history of previous episodes of AF, concomitant cardiac diseases and symptom severity. Indirectness: No indirectness (n=50) Intervention 2: digoxin. Patients received 0.6 mg digoxin through peripheral vein access within 1 min. If ventricular rate was above 100 bpm after 30 min then second bolus of 0.4 mg digoxin was given. Duration 1 min initial dose. Concurrent medication/care: 30 and 8% of patients in this group were already taking beta blockers and calcium channel blockers, respectively. Further treatment after intervention was performed on an individual basis and depended on various clinical factors such as clinical history of previous episodes of AF, concomitant cardiac diseases and symptom severity. Indirectness: No indirectness
Funding	Funding not stated

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

Protocol outcome 1: mortality at Define
- Actual outcome: In-hospital mortality at In-hospital; Group 1: 1/50, Group 2: 2/50; Comments: Note causes of death: amiodarone - 8 days after administration during bypass surgery, digoxin - recurrent pulmonary embolism and coronary ischaemia.
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 outcome measured not prespecified and unclear if similar between groups.; Indirectness of outcome: No indirectness ; Baseline details: All reported baseline characteristics similar between groups.; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Failure of non-ablative rate control at Define
- Actual outcome: Failure to reduce ventricular rate below 100 bpm at 30 min post-initial dose; Group 1: 28/50, Group 2: 40/50; Comments: Second doses of relevant drug were then given for these individuals.
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: All reported baseline characteristics similar

between groups.; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at Define; Hospitalisation at Define; heart failure onset or exacerbation at Define

Study (subsidiary papers)	**Khand 2003[73] (Khand 2015[71])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=47)
Countries and setting	Conducted in United Kingdom; Setting: Unclear - outpatients?
Line of therapy	Unclear
Duration of study	Intervention time: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: 12-lead ECG
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with persistent AF (> 1 month) and heart failure (appropriate symptoms for >2 months and ECG evidence of cardiac dysfunction, for example LVEF <40%) who were receiving digoxin and diuretics
Exclusion criteria	Heart rate <60 bpm; systolic blood pressure <90 mmHg; sick sinus syndrome or complete heart block; current treatment with a beta blocker or heart rate-lowering calcium channel antagonist or >200 mg amiodarone; recent major cardiovascular event or procedure; asthma or reversible obstructive airways disease; serum creatinine >250 µmol/l or significant hepatic disease; uncorrected significant valvular heart disease; any life-threatening non-cardiac disease
Recruitment/selection of patients	Unclear.
Age, gender and ethnicity	Age - Mean (SD): Carvedilol, 68.6 (9.4) years; digoxin, 68.4 (9.8) years. Gender (M:F): Carvedilol, 14/10; digoxin, 15/8. Ethnicity: Not reported
Further population details	1. heart failure: >75% with HF in study (Concomitant heart failure was inclusion criterion). 2. Renal failure: Not stated / Unclear (No details given).
Extra comments	Further baseline characteristics: Ischaemic heart disease (33% vs. 47%). Duration of AF, mean (SD): carvedilol, 152.8 (204) weeks; digoxin, 109.2 (123.4) weeks. Resting heart rate on ECG (bpm), mean (SD): carvedilol, 88.5 (24.5); digoxin, 82.4 (19.7). LVEF (%), mean (SD): carvedilol, 23.7 (10.4); digoxin, 24.7 (9.5). LVEDD (mm), mean (SD): carvedilol, 53.3 (10.4); digoxin, 54.2 (9.7). LA size (mm), mean (SD): carvedilol, 48.9 (8.3); digoxin, 47.9 (8.0). NYHA

	class I (4.2% vs. 4.3%), class II (45.8% vs. 69.6%), class III (37.5% vs. 26%) and class IV (12.5% vs. 0%). Mean (SD) digoxin dose (mg) similar between groups: carvedilol, 0.25 (0.11); digoxin, 0.24 (0.1). Mean (SD) digoxin plasma concentration (nmol/l) similar between groups: carvedilol, 1.55 (0.8); digoxin, 1.52 (0.7). Proportion on ACE inhibitors (71% vs. 71%) and anticoagulation (79% vs. 83%) similar.
Indirectness of population	No indirectness
Interventions	(n=24) Intervention 1: rate limiting beta blockers - other rate limiting beta blockers. Carvedilol. Phase 1: Open-label digoxin use prior to study continued + double-blind carvedilol randomly assigned at starting dose of 3.125 mg b.i.d, which was increased at 2-week intervals to the target dose of 25 mg b.i.d (uptitration period of 2 months). Target dose was 50 mg b.i.d in those weighing >85 kg. Phase 1 lasted for duration of 4 months. Phase 2: Open-label digoxin in phase 1 replaced with double-blind placebo, and double-blind carvedilol use in phase 1 continued. Phase 2 lasted for duration of 2 months. . Duration 6 months. Concurrent medication/care: 71% and 79% using ACE inhibitors and anticoagulation at baseline. . Indirectness: No indirectness Comments: Complex study design consisting of two phases was performed as withdrawal of digoxin at the same time as initiating and uptitrating beta-blockers could increase the risk of worsening HF. This design allowed the double-blinded initiation of carvedilol first, followed by double-blinded withdrawal of digoxin once maintenance doses of carvedilol had been achieved. (n=23) Intervention 2: digoxin. Digoxin. Phase 1: Open-label digoxin use prior to study continued + double-blind placebo randomly assigned instead of carvedilol. Phase 1 lasted for duration of 4 months. Phase 2: Open-label digoxin in phase 1 replaced with double-blind digoxin, and double-blind placebo use in phase 1 continued. Phase 2 lasted for duration of 2 months. . Duration 6 months. Concurrent medication/care: 71% and 83% using ACE inhibitors and anticoagulation at baseline. . Indirectness: No indirectness Comments: Complex study design consisting of two phases was performed as withdrawal of digoxin at the same time as initiating and uptitrating beta-blockers could increase the risk of worsening HF. This design allowed the double-blinded initiation of carvedilol first, followed by double-blinded withdrawal of digoxin once maintenance doses of carvedilol had been achieved.
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OTHER RATE LIMITING BETA BLOCKERS (CARVEDILOL, ORAL) versus DIGOXIN (ORAL)

Protocol outcome 1: mortality at Define
- Actual outcome: Mortality during phase II (carvedilol + placebo vs. placebo + digoxin) at 6 months post-randomisation (2 months post-phase II); Group 1: 1/17, Group 2: 0/20; Comments: Phase II - patients receiving carvedilol + placebo or digoxin + placebo alone.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Differences for at least 1 factor, including

duration of AF between the two groups.; Group 1 Number missing: 7, Reason: 1 death in phase I, 3 withdrew during phase I due to adverse effects and 3 withdrawn due to worsening HF in phase II.; Group 2 Number missing: 3, Reason: 1 death in phase I, 1 self-withdrawal in phase I and 1 withdrawn due to worsening HF in phase II - Actual outcome: Mortality during phase I (carvedilol + digoxin vs. placebo + digoxin) at 4 months post-randomisation; Group 1: 1/21, Group 2: 1/22; Comments: Mortality during phase I when groups were receiving either carvedilol + digoxin or placebo + digoxin Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Differences for at least 1 factor, including duration of AF between the two groups.; Group 1 Number missing: 3, Reason: 3 withdrew during phase I due to adverse effects; Group 2 Number missing: 1, Reason: 1 self-withdrawal in phase I Protocol outcome 2: heart failure onset or exacerbation at Define - Actual outcome: Worsening of heart failure symptoms during phase II (carvedilol + placebo vs. placebo + digoxin) at 6 months post-randomisation (2 months post-phase II); Group 1: 3/19, Group 2: 1/21; Comments: Phase II - patients receiving carvedilol + placebo or digoxin + placebo Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Differences for at least 1 factor, including duration of AF between the two groups.; Group 1 Number missing: 5, Reason: 2 deaths (1 in phase I and 1 in phase II), 3 adverse events in phase I; Group 2 Number missing: 2, Reason: 1 death in phase 1, 1 self-withdrawal in phase I
Protocol outcomes not reported by the study	Quality of life at Define; Hospitalisation at Define; Failure of non-ablative rate control at Define

Study	**Shojaee 2017[132]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=84)
Countries and setting	Conducted in Iran; Setting: Emergency department of hospital - secondary care
Line of therapy	Unclear
Duration of study	Intervention + follow up: Followed up for at least 12 hours post-first dose
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: 12-lead ECG by emergency physician and confirmed by cardiologist
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients presenting to emergency department with atrial fibrillation and rapid ventricular rate and relative contraindication for first line drugs (calcium channel blockers and beta blockers); age between 18 and 80 years old; stable vital signs

Exclusion criteria	Unstable haemodynamics; chest pain or shortness of breath; heart failure; unconfirmed dysrhythmia; history of allergy to the drugs used in the trial; underlying kidney or liver diseases; use of anti-arrhythmic agents in the past 12 hours; patients not wishing to stay in hospital for at least 12 hours; patients not giving their consent for participation
Recruitment/selection of patients	Unclear
Age, gender and ethnicity	Age - Mean (SD): Amiodarone, 63.73 (11.06) years; digoxin, 59.88 (11.02) years. Gender (M:F): Amiodarone: 23/19; digoxin, 22/20. Ethnicity: Not reported
Further population details	1. heart failure: < 25% with HF in study (Heart failure was an exclusion criterion). 2. Renal failure: mean eGFR in study >=30 (Kidney disease was an exclusion criterion).
Extra comments	History of digoxin consumption: amiodarone, 71.4%; digoxin, 35.7%
Indirectness of population	No indirectness: Does not explicitly confirm non-valvular AF, but no mention of any concomitant valvular disease
Interventions	(n=42) Intervention 1: Amiodarone. Intravenous amiodarone. 150 mg amiodarone diluted in 5% dextrose intravenously infused over 10 min. If no improvement, another 150 mg dose was infused and all patients received a maintenance dose of 50 mg per hour during first 3 hours of treatment. Duration Unclear - 3 hours? Concurrent medication/care: Not reported. Indirectness: No indirectness Comments: Amiodarone used at half the dose needed for rhythm conversion as using in rate control context in this study (150 mg instead of 300 mg) (n=42) Intervention 2: digoxin. Intravenous digoxin. 1 mg digoxin infused with initial injection of 0.5 mg and then two 0.25 mg doses in second and fourth hour after intervention. Duration Unclear - 4 hours? Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AMIODARONE (INTRAVENOUS) versus DIGOXIN (INTRAVENOUS) Protocol outcome 1: Failure of non-ablative rate control at Define - Actual outcome: Treatment failure (rate control, heart rate below 80-100 bpm) at Unclear - 12 hours?; Group 1: 9/42, Group 2: 25/42 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 treatment failure reported not clear.; Indirectness of outcome: No indirectness ; Baseline details: Comparable for those factors reported, but only limited factors given at baseline. ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at Define; Hospitalisation at Define; mortality at Define; heart failure onset or exacerbation at Define

Study	**Siu 2009[137]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=150)
Countries and setting	Conducted in Hong Kong (China); Setting: Emergency department of hospital
Line of therapy	Unclear
Duration of study	Intervention time: Follow-up of 24 h after administration of first dose
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ECG
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Presenting to emergency department with symptomatic acute atrial fibrillation for <48 hours and a rapid ventricular rate (>120 bpm) requiring hospitalisation
Exclusion criteria	Ventricular rate >200 bpm; pre-excitation syndrome; hypotension (systolic blood pressure <90 mmHg); congestive heart failure; presence of implanted pacemaker and/or implantable cardioverter defibrillator; recent myocardial infarction; unstable angina; stroke or thromboembolism within the past 6 months; allergy to the study medications; use of antiarrhythmic and/or atrioventricular nodal blocking drug within last 7 days (in case of amiodarone, within past 3 months); other major medical conditions, including renal failure, respiratory failure and bleeding disorders
Recruitment/selection of patients	Unclear. Those presenting and matching inclusion criteria

Age, gender and ethnicity	Age - Mean (SD): Amiodarone, 73 (9.7); diltiazem, 70.6 (12.4); digoxin, 71 (13.1). Gender (M:F): Amiodarone, 30/20; diltiazem, 28/22; digoxin, 26/24. Ethnicity: Not reported
Further population details	1. heart failure: < 25% with HF in study (Congestive heart failure an exclusion criterion.). 2. Renal failure: mean eGFR in study >=30 (Renal failure an exclusion criterion.).
Extra comments	Hypertension (amiodarone, diltiazem and digoxin): 46%, 50% and 38% Proportion with diabetes (22-26%), COPD (8-10%) and thyroid dysfunction (2-10%) similar across groups. Left atrial dimension (cm) similar across groups (~4.2 cm) LVEF similar across groups (63-66%).
Indirectness of population	No indirectness
Interventions	(n=50) Intervention 1: Amiodarone. Intravenous amiodarone. Loading infusion of 300 mg over first hour followed by 10 mg/kg over 24 hours. . Duration 24 hours. Concurrent medication/care: Oral ventricular rate control agents, antiarrythmic and antithrombotic agents were started 24 hours after admission and choice of agents and consideration for cardioversion at discretion of attending physicians - after randomised treatments and outcomes measured? Indirectness: No indirectness Comments: Dose used lower than the maximal recommended dose (20 mg/kg over 24 hours) for pharmacological conversion as aim of study was to control rate not rhythm (n=50) Intervention 2: digoxin. Intravenous digoxin. Bolus of 0.5 mg followed by 0.25 mg every 8 hours (1.25 mg over 24 hours). Duration 24 hours. Concurrent medication/care: Oral ventricular rate control agents, antiarrythmic and antithrombotic agents were started 24 hours after admission and choice of agents and consideration for cardioversion at discretion of attending physicians - after randomised treatments and outcomes measured? Indirectness: No indirectness Comments: Dosage lower than maximal recommended dose to adjust for the lower body weight (range, 40-60 kg) in the Chinese cohort of patients.
Funding	Funding not stated

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

Protocol outcome 1: heart failure onset or exacerbation at Define
- Actual outcome: New-onset congestive heart failure at Follow-up unclear; Group 1: 0/50, Group 2: 0/50
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: time-point measured at not clear.; Indirectness of outcome: No indirectness ; Baseline details: Some differences for some reported parameters e.g. proportion with hypertension (46 vs. 50 vs. 38%) and left atrial dimension >4 cm (68 vs. 70 vs. 82%); Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Failure of ablation rate control at Define
- Actual outcome: Failure to achieve sustained VR control (HR <90 bpm for ≥ 4 hours) at 24 hours at 24 hours; Group 1: 13/50, Group 2: 13/50
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Some differences for some reported parameters e.g. proportion with hypertension (46 vs. 50 vs. 38%) and left atrial dimension >4 cm (68 vs. 70 vs. 82%); Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Quality of life at Define; Hospitalisation at Define; mortality at Define

Study	**Tse 2001[148]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=16)
Countries and setting	Conducted in Hong Kong (China); Setting: Unclear - outpatients?
Line of therapy	Unclear
Duration of study	Intervention time: 24 weeks of treatment
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: 12-lead ECG, 24 h Holter monitoring, transthoracic echocardiography

Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with chronic AF
Exclusion criteria	Intolerance of amiodarone or digoxin or contraindication to their therapy; amiodarone therapy in the past 6 months; clinically significant valvular heart disease; unstable angina or recent myocardial infarction in the past 6 months; class III or IV heart failure; sick sinus syndrome; implanted pacemaker
Recruitment/selection of patients	Consecutive patients matching inclusion criteria
Age, gender and ethnicity	Age - Mean (SD): Amiodarone, 61 (9); digoxin, 66 (10). Gender (M:F): Amiodarone, 7/2; digoxin, 6/7. Ethnicity: Not reported.
Further population details	1. heart failure: < 25% with HF in study (Unclear, but class III or IV heart failure an exclusion criterion. Unsure about other heart failure classes. Mean LVEF in both groups over 60). 2. Renal failure: Not stated / Unclear (No details given).
Extra comments	All had failed a previous attempt at restoring and maintaining sinus rhythm. Mean (SD) weight: Amiodarone, 62 (13) kg; digoxin, 60 (11). Mean (SD) height: Amiodarone, 162 (26) cm; digoxin, 164 (30) cm. Mean (SD) duration of AF: Amiodarone, 55 (20) months; digoxin, 57 (25) months. Mean (SD) LVEF: Amiodarone, 0.66 (0.11); digoxin, 0.63 (0.11). Underlying heart disease: Hypertension (amiodarone, 33%; digoxin, 29%), ischaemic heart disease (amiodarone, 22%; digoxin, 29%), dilated cardiomyopathy (amiodarone, 11%; digoxin, 14%)
Indirectness of population	No indirectness
Interventions	(n=9) Intervention 1: Amiodarone. 600 mg daily for 1 week as loading dose followed by 100 mg daily for remaining 23 weeks. Duration 24 weeks. Concurrent medication/care: All anti-arrhythmic drugs discontinued for at least 2 weeks prior to beginning of the study. All patients received anticoagulation therapy with warfarin for the prevention of thromboembolism. Indirectness: No indirectness (n=7) Intervention 2: digoxin. 0.25 mg daily, or 0.125 mg daily if body weight was <50 kg or serum creatinine >200 mmol/L. Duration 24 weeks. Concurrent medication/care: All anti-arrhythmic drugs discontinued for at least 2 weeks prior to beginning of the study. All patients received anticoagulation therapy with warfarin for the prevention of thromboembolism. Indirectness: No indirectness
Funding	Academic or government funding (Funding by Committee on Research and Conference Grant)

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

Protocol outcome 1: Quality of life at Define
- Actual outcome: SF-36 physical functioning domain at 24 weeks; Group 1: mean 92 (SD 10); n=8, Group 2: mean 78 (SD 16); n=7; SF-36 physical functioning domain 0-100 Top=High is good outcome; Comments: Baseline values: Amiodarone, 90 (8), n=9; digoxin, 77 (16), n=7
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Comparable for all factors reported, including age, gender and duration of AF. Outcome at baseline quite different between the two groups - 77 vs. 90.; Blinding details: Patients were outcome assessors and therefore blinded.; Group 1 Number missing: 1, Reason: Withdrawn due to exertional dyspnoea during amiodarone loading.; Group 2 Number missing: 0
- Actual outcome: SF-36 physical role functioning domain at 24 weeks; Group 1: mean 83 (SD 35); n=8, Group 2: mean 92 (SD 12); n=7; SF-36 physical role functioning domain 0-100 Top=High is good outcome; Comments: Baseline values: Amiodarone, 97 (8); digoxin, 86 (28)
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Comparable for all factors reported, including age, gender and duration of AF. Outcome at baseline quite different between the two groups - 97 vs. 86.; Blinding details: Patients were outcome assessors and therefore blinded.; Group 1 Number missing: 1, Reason: Withdrawn due to exertional dyspnoea during amiodarone loading.; Group 2 Number missing: 0
- Actual outcome: SF-36 bodily pain domain at 24 weeks; Group 1: mean 71 (SD 25); n=8, Group 2: mean 77 (SD 30); n=7; SF-36 bodily pain domain 0-100 Top=High is good outcome; Comments: Baseline values: Amiodarone, 80 (23); digoxin, 84 (23)
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Comparable for all factors reported, including age, gender and duration of AF. Outcome at baseline similar between the two groups - 80 vs. 84.; Blinding details: Patients were outcome assessors and therefore blinded.; Group 1 Number missing: 1, Reason: Withdrawn due to exertional dyspnoea during amiodarone loading.; Group 2 Number missing: 0
- Actual outcome: SF-36 general health domain at 24 weeks; Group 1: mean 58 (SD 19); n=8, Group 2: mean 57 (SD 22); n=7; SF-36 general health domain 0-100 Top=High is good outcome; Comments: Baseline values: Amiodarone, 65 (18); digoxin, 63 (20)
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Comparable for all factors reported, including age, gender and duration of AF. Outcome at baseline similar between the two groups - 65 vs. 63.; Blinding details: Patients were outcome assessors and therefore blinded.; Group 1 Number missing: 1, Reason: Withdrawn due to exertional dyspnoea during amiodarone loading.; Group 2 Number missing: 0
- Actual outcome: SF-36 vitality domain at 24 weeks; Group 1: mean 67 (SD 23); n=8, Group 2: mean 58 (SD 20); n=7; Comments: Baseline values: Amiodarone, 77 (22); digoxin, 66 (18)
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Comparable for all factors reported, including age, gender and duration of AF. Outcome at baseline quite different between the two groups - 77 vs. 66.; Blinding details: Patients were outcome assessors and therefore blinded.; Group 1 Number missing: 1, Reason: Withdrawn due to exertional dyspnoea during amiodarone loading.;

Group 2 Number missing: 0 - Actual outcome: SF-36 social functioning domain at 24 weeks; Group 1: mean 90 (SD 10); n=8, Group 2: mean 84 (SD 16); n=7; SF-36 social functioning domain 0-100 Top=High is good outcome; Comments: Baseline values: Amiodarone, 89 (15); digoxin, 88 (22) Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Comparable for all factors reported, including age, gender and duration of AF. Outcome at baseline similar between the two groups - 89 vs. 88.; Blinding details: Patients were outcome assessors and therefore blinded.; Group 1 Number missing: 1, Reason: Withdrawn due to exertional dyspnoea during amiodarone loading.; Group 2 Number missing: 0 - Actual outcome: SF-36 emotional role functioning domain at 24 weeks; Group 1: mean 81 (SD 34); n=8, Group 2: mean 86 (SD 26); n=7; SF-36 emotional role functioning domain 0-100 Top=High is good outcome; Comments: Baseline values: Amiodarone, 81 (34); digoxin, 90 (16) Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Comparable for all factors reported, including age, gender and duration of AF. Outcome at baseline similar between the two groups - 81 vs. 90.; Blinding details: Patients were outcome assessors and therefore blinded.; Group 1 Number missing: 1, Reason: Withdrawn due to exertional dyspnoea during amiodarone loading.; Group 2 Number missing: 0 - Actual outcome: SF-36 mental health domain at 24 weeks; Group 1: mean 68 (SD 27); n=8, Group 2: mean 58 (SD 23); n=7; SF-36 mental health domain 0-100 Top=High is good outcome; Comments: Baseline values: Amiodarone, 78 (20); digoxin, 71 (18) Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Comparable for all factors reported, including age, gender and duration of AF. Outcome at baseline similar between the two groups - 78 vs. 71.; Blinding details: Patients were outcome assessors and therefore blinded.; Group 1 Number missing: 1, Reason: Withdrawn due to exertional dyspnoea during amiodarone loading.; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Hospitalisation at Define; mortality at Define; heart failure onset or exacerbation at Define; Failure of non-ablative rate control at Define

Appendix E: Forest plots

E.1 Amiodarone vs. digoxin

Figure 2: Quality of life: SF-36 physical functioning domain

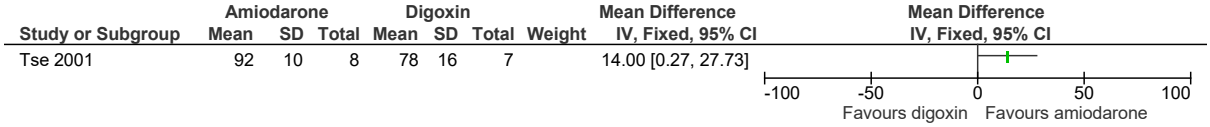


Figure 3: Quality of life: SF-36 physical role functioning domain

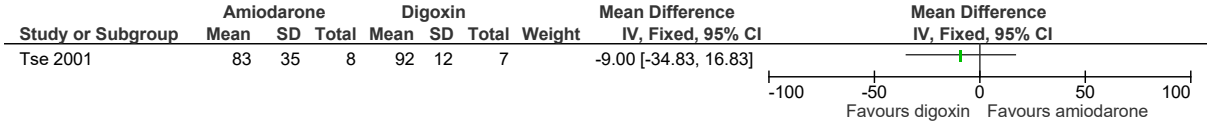


Figure 4: Quality of life: SF-36 bodily pain domain

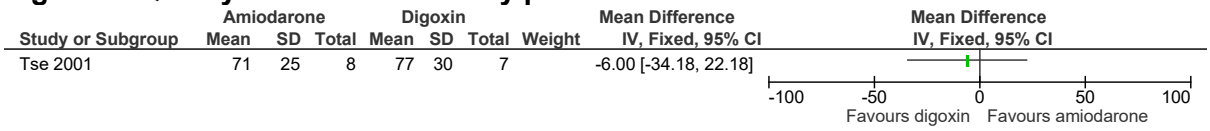


Figure 5: Quality of life: SF-36 general health domain

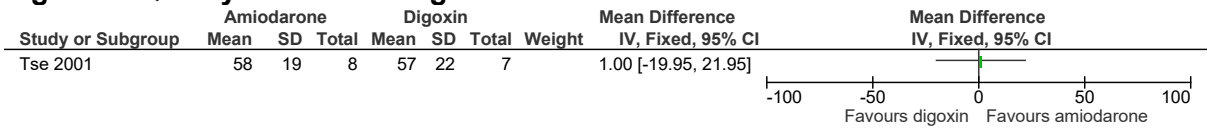


Figure 6: Quality of life: SF-36 vitality domain

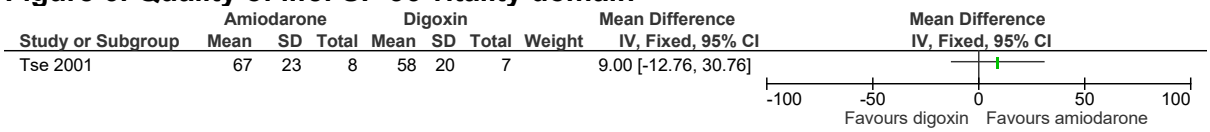
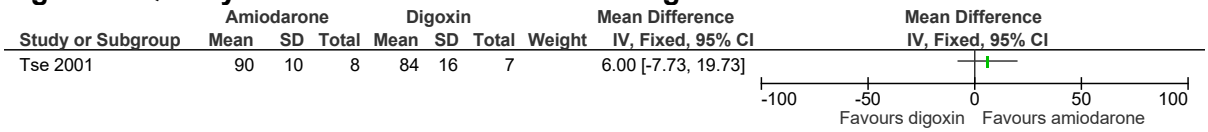
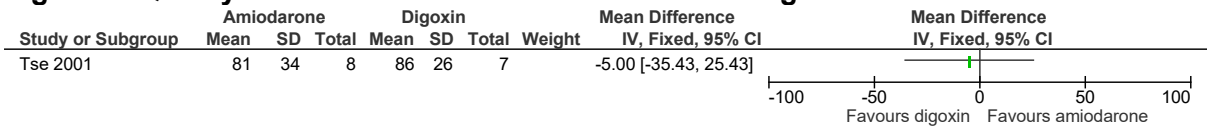


Figure 7: Quality of life: SF-36 social functioning domain



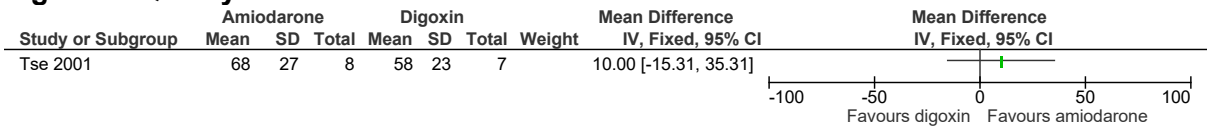
1

Figure 8: Quality of life: SF-36 emotional role functioning domain



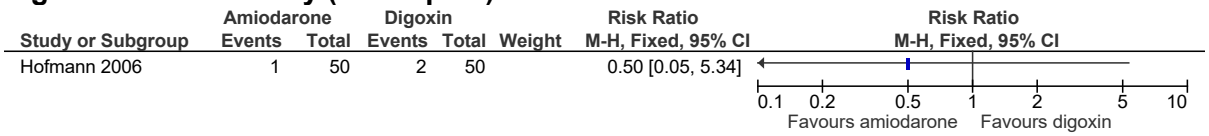
2

Figure 9: Quality of life: SF-36 mental health domain



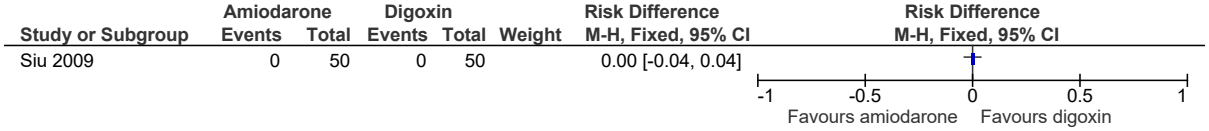
3

Figure 10: Mortality (in-hospital)



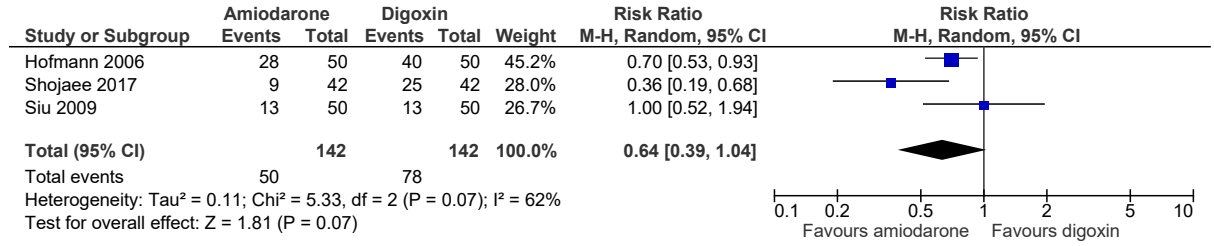
4

Figure 11: Heart failure onset or exacerbation: new-onset congestive heart failure



5

Figure 12: Failure of non-ablative rate control



E.2 Beta-blockers vs. digoxin

Figure 13: Mortality (phase I - carvedilol + digoxin vs. placebo + digoxin)

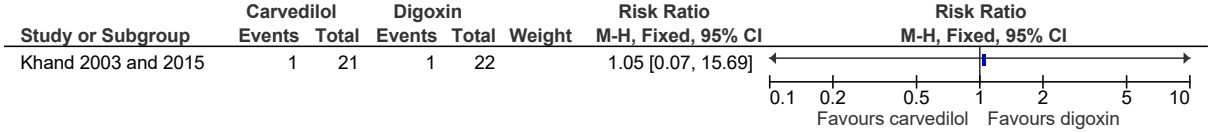


Figure 14: Mortality (phase II - carvedilol + placebo vs. placebo + digoxin)

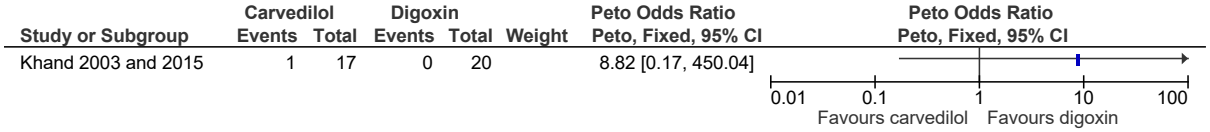
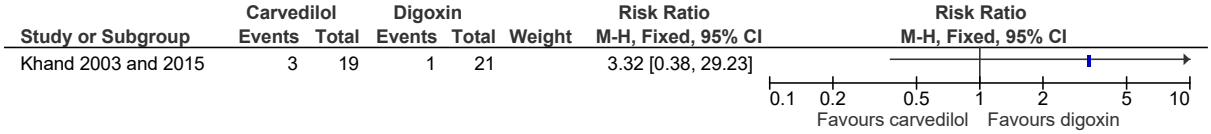


Figure 15: Heart failure onset or exacerbation: worsening heart failure symptoms (phase II - carvedilol + placebo vs. placebo + digoxin)



Appendix F: GRADE tables

Table 10: Clinical evidence profile: Amiodarone vs. digoxin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Amiodarone	digoxin	Relative (95% CI)	Absolute		
SF-36 physical functioning domain (24 weeks) (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	8	7	-	MD 14 higher (0.27 to 27.73 higher)	⊕OOO VERY LOW	CRITICAL
SF-36 physical role functioning domain (24 weeks) (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	8	7	-	MD 9 lower (34.83 lower to 16.83 higher)	⊕OOO VERY LOW	CRITICAL
SF-36 bodily pain domain (24 weeks) (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	8	7	-	MD 6 lower (34.18 lower to 22.18 higher)	⊕OOO VERY LOW	CRITICAL
SF-36 general health domain (24 weeks) (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[5]	none	8	7	-	MD 1 higher (19.95 lower to 21.95 higher)	⊕OOO VERY LOW	CRITICAL
SF-36 vitality domain (24 weeks) (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[6]	none	8	7	-	MD 9 higher (12.76 lower to 30.76 higher)	⊕OOO VERY LOW	CRITICAL

SF-36 social functioning domain (24 weeks) (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	8	7	-	MD 6 higher (7.73 lower to 19.73 higher)	⊕OOO VERY LOW	CRITICAL
SF-36 emotional role functioning domain (24 weeks) (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[7]	none	8	7	-	MD 5 lower (35.43 lower to 25.43 higher)	⊕OOO VERY LOW	CRITICAL
SF-36 mental health domain (24 weeks) (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[8]	none	8	7	-	MD 10 higher (15.31 lower to 35.31 higher)	⊕OOO VERY LOW	CRITICAL
Mortality (in-hospital)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[9]	none	1/50 (2%)	4%	RR 0.5 (0.05 to 5.34)	20 fewer per 1000 (from 38 fewer to 174 more)	⊕OOO VERY LOW	CRITICAL
Heart failure onset or exacerbation (new-onset congestive heart failure)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[10]	none	0/50 (0%)	0%	RD 0 (-0.04 to 0.04)	0 fewer per 1000 (from 40 fewer to 40 more)[11]	⊕OOO VERY LOW	CRITICAL
Failure of non-ablative rate control (follow-up 0.5-24 hours)												
3	randomised trials	very serious[1]	serious[12]	no serious indirectness	serious[9]	none	50/142 (35.2%)	59.5%	RR 0.64 (0.39 to 1.04)	214 fewer per 1000 (from 363 fewer to 24 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]Downgraded by 1 increment as the confidence intervals crossed the upper MID of 8
[3]Downgraded by 2 increments as the confidence intervals crossed the upper and lower MIDs of 6 and -6
[4]Downgraded by 2 increments as the confidence intervals crossed the upper and lower MIDs of 15 and -15
[5]Downgraded by 2 increments as the confidence intervals crossed the upper and lower MIDs of 11 and -11
[6]Downgraded by 2 increments as the confidence intervals crossed the upper and lower MIDs of 10 and -10
[7]Downgraded by 2 increments as the confidence intervals crossed the upper and lower MIDs of 13 and -13
[8]Downgraded by 2 increments as the confidence intervals crossed the upper and lower MIDs of 11.5 and -11.5

[9]Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[10]Absolute effect calculated manually using risk difference as zero events in both arms
[11]Serious imprecision as sample size >70 and <350
[12]Serious inconsistency as I2 >50% and some variation in point estimates on Forest plot. Switched to random effects and rated down for inconsistency.

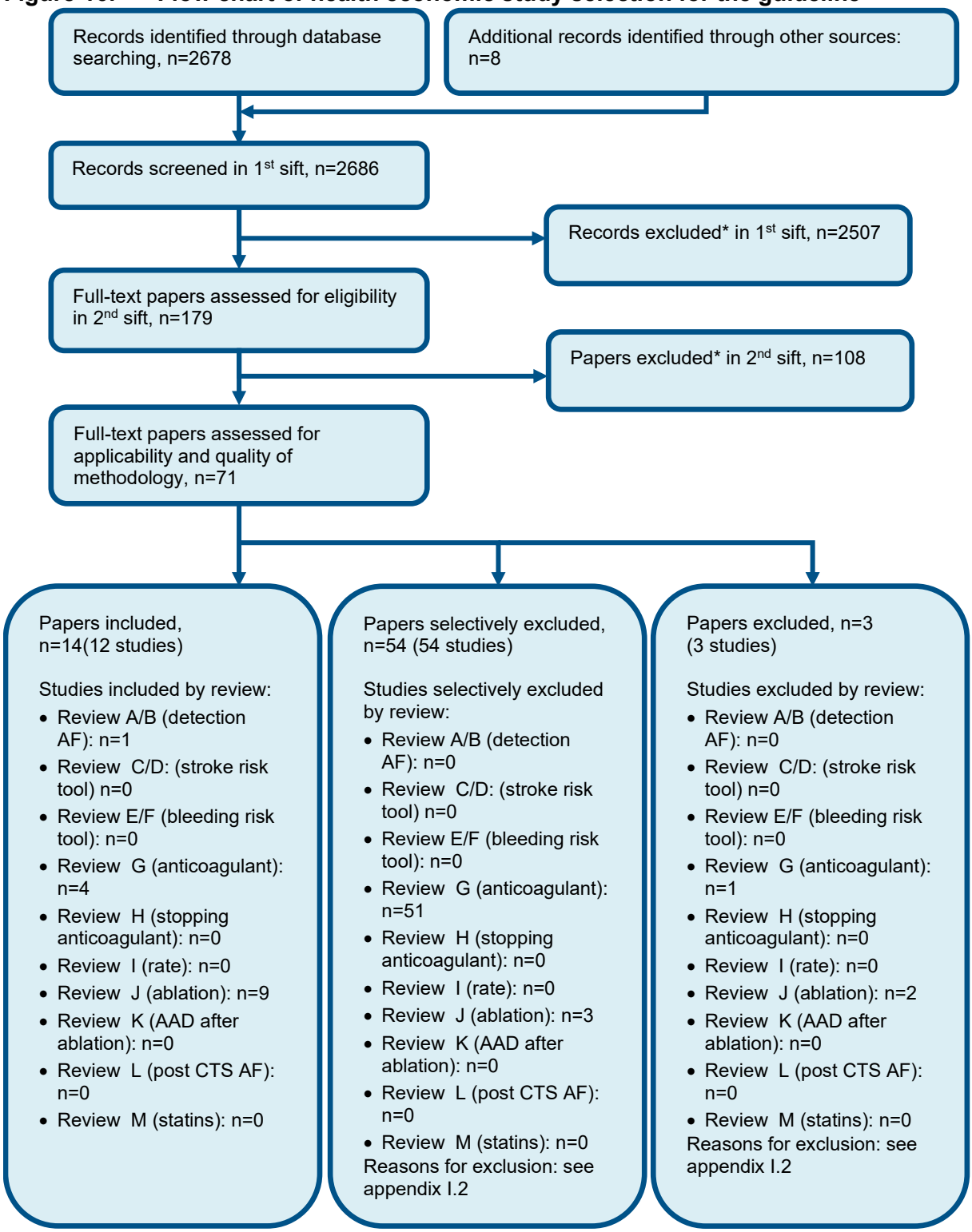
Table 11: Clinical evidence profile: Beta-blockers vs. digoxin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Beta-blockers	digoxin	Relative (95% CI)	Absolute		
Mortality (phase I - carvedilol + digoxin vs. placebo + digoxin)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	1/21 (4.8%)	4.6%	RR 1.05 (0.07 to 15.69)	2 more per 1000 (from 43 fewer to 676 more)	⊕OOO VERY LOW	CRITICAL
Mortality (phase II - carvedilol + placebo vs. placebo + digoxin)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/17 (5.9%)	0%	OR 8.82 (0.17 to 450.05)	60 more per 1000 (from 80 fewer to 200 more)[4]	⊕OOO VERY LOW	CRITICAL
Heart failure onset or exacerbation (worsening heart failure symptoms during phase II - carvedilol + placebo vs. placebo + digoxin)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	3/19 (15.8%)	4.8%	RR 3.32 (0.38 to 29.23)	111 more per 1000 (from 30 fewer to 1000 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] Indirectness for the intervention as during phase I of this study patients receiving carvedilol + digoxin or placebo + digoxin rather than carvedilol or digoxin only, which was initiated in phase II of the study.
[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 from risk difference as zero events in one arm of the only included study

Appendix G: Health economic evidence selection

Figure 16: 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 12: Studies excluded from the clinical review

Study	Exclusion reason
Al-Khatib 2013[1]	Systematic review: study designs inappropriate
Alcalde 2006[2]	Not guideline condition
Andrivet 1994[3]	Incorrect study design. Incorrect interventions
Anonymous 1997[4]	Interventions used in terms of rhythm control rather than rate control
Aronow 1979[7]	Incorrect study design
Aronow 1979[6]	Incorrect study design
Aronow 1980[5]	Incorrect study design
Atwood 1999[8]	Incorrect study design
Balser 1998[9]	Not guideline condition
Bavishi 2015[10]	Systematic review: study designs inappropriate
Bellandi 1995[11]	Not guideline condition. Interventions used in terms of rhythm control rather than rate control
Bianconi 1998[13]	Interventions used in terms of rhythm control rather than rate control
Bianconi 2000[12]	Not guideline condition. Interventions used in terms of rhythm control rather than rate control
Blevins 1987[14]	Incorrect study design
Bosi 1990[16]	Interventions used in terms of rhythm control rather than rate control
Brodsky 1994[17]	Not guideline condition
Capucci 1994[18]	Incorrect interventions
Chamaria 2015[19]	Systematic review: study designs inappropriate
Cheiman 1996[20]	Incorrect study design
Chen 2019[21]	AF starting after cardiothoracic surgery
Cheng 2010[22]	Incorrect study design
Cibis investigators and committees 1994[25]	Not guideline condition
Cleland 2003[23]	Not guideline condition
Cochrane 1994[24]	AF starting after cardiothoracic surgery
Cotter 1999[26]	Not guideline condition
Cowan 1986[27]	Interventions used in terms of rhythm control rather than rate control
Cowan 1986[28]	Interventions used in terms of rhythm control rather than rate control
Cybulski 1996[29]	Incorrect study design
Dargie 1999[31]	Not guideline condition
Dargie 2001[30]	Not guideline condition
Daubert 1993[32]	Incorrect study design
Deedwania 1998[33]	Interventions used in terms of rhythm control rather than rate control

Study	Exclusion reason
Delle karth 2001[34]	AF starting after cardiothoracic surgery
Demircan 2005[35]	Incorrect interventions - diltiazem not available in IV form in UK
Dias 1991[36]	Not guideline condition. AF starting after cardiothoracic surgery
Donovan 1995[37]	Interventions used in terms of rhythm control rather than rate control
Dorian 2002[38]	Interventions used in terms of rhythm control rather than rate control
Eichhorn 2001[39]	Not guideline condition
Ellenbogen 1991[41]	Not guideline condition
Ellenbogen 1995[40]	Incorrect study design
Falk 1987[43]	Interventions used in terms of rhythm control rather than rate control
Falk 1987[42]	Not guideline condition. Interventions used in terms of rhythm control rather than rate control
Fauchier 2009[44]	Incorrect study design
Flaker 2014[45]	Incorrect interventions
Flather 2005[46]	Not guideline condition
Freemantle 2011[47]	Not guideline condition
Fromm 2015[48]	Incorrect interventions - diltiazem not available in IV form in UK
Gallik 1997[49]	Inappropriate comparison
Galve 1996[50]	Not guideline condition. Interventions used in terms of rhythm control rather than rate control
Goldenberg 1994[51]	Not guideline condition
Gonzalez 1981[52]	Not guideline condition
Hassan 2007[53]	Not guideline condition
Hemels 2006[54]	Not guideline condition
Heywood 1995[55]	Incorrect study design
Hjalmarson 1985[56]	Not guideline condition
Hornestam 1999[58]	Interventions used in terms of rhythm control rather than rate control
Hou 1995[59]	Not guideline condition
Inoue 2017[60]	Inappropriate comparison
Joglar 2001[61]	Incorrect study design
Jordaens 1997[62]	Interventions used in terms of rhythm control rather than rate control
Joseph 2000[63]	Interventions used in terms of rhythm control rather than rate control
Kamali 2017[64]	AF starting after cardiothoracic surgery
Kanji 2008[65]	Systematic review is not relevant to review question or unclear PICO
Kao 2013[66]	Incorrect interventions
Karaca 2007[67]	No suitable outcomes
Kettering 2018[68]	Incorrect study design
Khairy 2014[69]	Incorrect study design
Khan 2015[70]	Incorrect study design
Khand 2000[72]	Systematic review: study designs inappropriate
Klein 1984[74]	Incorrect study design

Study	Exclusion reason
Kochiadakis 1998[76]	Not guideline condition. Interventions used in terms of rhythm control rather than rate control
Kochiadakis 2000[75]	Interventions used in terms of rhythm control rather than rate control
Kochiadakis 2005[77]	Incorrect study design
Koh 1995[78]	Not guideline condition
Kolokotroni 2017[79]	AF starting after cardiothoracic surgery. Systematic review: study designs inappropriate
Kotecha 2014[82]	Incorrect study design
Kotecha 2014[81]	Systematic review: study designs inappropriate
Kotecha 2017[80]	Protocol only for RATE-AF trial not yet published
Lane 2015[83]	Systematic review: study designs inappropriate
Lang 1983[84]	Incorrect study design
Lechat 2001[85]	Incorrect study design
Lip 2014[86]	Systematic review is not relevant to review question or unclear PICO
Lombardi 2006[87]	Interventions used in terms of rhythm control rather than rate control
Lumer 2002[88]	Not guideline condition. Interventions used in terms of rhythm control rather than rate control
Lundstrom 1990[89]	Incorrect study design
Macmahon 1997[90]	Not guideline condition
Maragno 1988[91]	Incorrect study design
Mareev 2015[92]	Incorrect study design
Martindale 2015[93]	Systematic review: methods are not adequate/unclear
McMurray 2005[94]	Not guideline condition
McNamara 2003[95]	Systematic review: study designs inappropriate
MERIT-HF study group 1999[96]	Not guideline condition
Afzali Moghadam 2012[97]	Incorrect study design
Mooss 2000[98]	AF starting after cardiothoracic surgery
Mount 2002[99]	Incorrect study design
Mulder 2012[100]	Incorrect study design
Nikolaidou 2009[102]	Systematic review: study designs inappropriate
Noble 1999[103]	Abstract only
Noc 1990[104]	Interventions used in terms of rhythm control rather than rate control
Ochs 1985[105]	Not guideline condition
Packer 1996[106]	Not guideline condition
Packer 2001[107]	Not guideline condition
Pan 2018[108]	Incorrect interventions
Patten 2006[109]	Interventions used in terms of rhythm control rather than rate control
Peuhkurinen 2000[110]	Interventions used in terms of rhythm control rather than rate control
Pinter 2003[111]	No suitable outcomes
Platia 1989[112]	Not guideline condition
Plumb 1982[113]	Incorrect study design

Study	Exclusion reason
Pluymaekers 2019[114]	Incorrect interventions
Qureshi 2016[115]	Systematic review: study designs inappropriate
Redfors 1971[116]	Incorrect study design
Redfors 1971[117]	Incorrect study design
Rehnqvist 1981[118]	Inappropriate comparison
Reynolds 2008[119]	Incorrect study design
Ribeiro 1986[120]	Incorrect study design
Rienstra 2013[121]	Systematic review is not relevant to review question or unclear PICO
Roth 1986[122]	Incorrect study design
Roy 1997[124]	Interventions used in terms of rhythm control rather than rate control
Roy 2000[123]	Not guideline condition. Interventions used in terms of rhythm control rather than rate control
Salerno 1989[125]	Not guideline condition
Sandberg 2015[126]	Incorrect study design
Santangeli 2012[127]	Systematic review is not relevant to review question or unclear PICO
Schreck 1997[128]	No suitable outcomes
Segal 2000[129]	Systematic review: study designs inappropriate
Sethi 2017[131]	Systematic review is not relevant to review question or unclear PICO
Sethi 2018[130]	Systematic review is not relevant to review question or unclear PICO
Shu 2005[133]	Not guideline condition
Simpson 2001[134]	No suitable outcomes
Singh 1991[135]	Interventions used in terms of rhythm control rather than rate control
Singh 2003[136]	Interventions used in terms of rhythm control rather than rate control
Stern 1982[138]	Incorrect study design
Sticherling 2002[140]	Interventions initiated following successful ablation
Sticherling 2002[139]	Interventions initiated following successful ablation
Sullivan 2013[141]	Systematic review: study designs inappropriate. Interventions used in terms of rhythm control rather than rate control
Sung 1980[143]	Incorrect study design
Sung 1995[142]	Not guideline condition
Sweany 1985[144]	Not guideline condition
Thomas 2004[145]	Interventions used in terms of rhythm control rather than rate control
Tisdale 1998[146]	AF starting after cardiothoracic surgery
Tommaso 1983[147]	Incorrect study design
Tse 2001[149]	Not review population
Tsuneda 2006[150]	Not guideline condition
Vamos 2015[152]	Systematic review: study designs inappropriate
Vamos 2019[151]	Systematic review: study designs inappropriate
Veloso 2001[154]	Letter only
Veloso 2005[153]	Letter

Study	Exclusion reason
Waagstein 1993[155]	Not guideline condition
Wang 2015[157]	Systematic review: study designs inappropriate
Wang 2019[156]	Not review population
Wanless 1997[158]	Not guideline condition
Wasir 1977[159]	Not guideline condition
Wattanasuwan 2001[160]	Incorrect interventions - diltiazem not available in IV form in UK
Williams 1979[161]	Incorrect study design
Xu 2019[162]	Incorrect study design
Zoble 1987[163]	No suitable outcomes

I.2 Excluded health economic studies

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

Table 13: Studies excluded from the health economic review

Reference	Reason for exclusion
None	