Atrial fibrillation (chronic)

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Christopher J Boos, Deirdre A Lane, and Gregory YH Lip

ABSTRACT

INTRODUCTION: Atrial fibrillation is a supraventricular tachyarrhythmia, which is characterised by the presence of fast and uncoordinated atrial activation leading to reduced atrial mechanical function. Risk factors for atrial fibrillation include increasing age, coexisting cardiac and thyroid disease, pyrexial illness, electrolyte imbalance, cancer, and coexisting infection. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of oral medical treatments to control heart rate in people with chronic (defined as longer than 1 week for this review) non-valvular atrial fibrillation? What is the effect of different treatment strategies (rate vs. rhythm) for people with persistent non-valvular atrial fibrillation? We searched: Medline, Embase, The Cochrane Library and other important databases up to August 2007 (BMJ Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 18 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: beta-blockers (with or without digoxin), calcium channel blockers (with or without digoxin), calcium channel blockers (rate limiting), digoxin, and rate versus rhythm control strategies.

QUESTIONS

INTERVENTIONS

ORAL TREATMENTS

Likely to be beneficial

Trade off between benefits and harms

RHYTHM-CONTROL VERSUS RATE-CONTROL TREATMENT STRATEGIES

Trade off between benefits and harms

Covered elsewhere in Clinical Evidence

Atrial fibrillation (acute onset)

Stroke prevention

To be covered in future updates

Percutaneous catheter ablation for persistent or paroxysmal atrial fibrillation

Surgical treatments for chronic atrial fibrillation

Footnote

*Categorisation based on consensus.

Key points

- Atrial fibrillation is a supraventricular tachyarrhythmia, which is characterised by the presence of uncoordinated atrial activation and deteriorating atrial mechanical function of over 7 days' duration.

  Risk factors for chronic atrial fibrillation are increasing age, male sex, co-existing cardiac disease, thyroid disease, pyrexial illness, electrolyte imbalance, cancer, and acute infections.
- Consensus is that beta-blockers are more effective than digoxin for controlling symptoms of chronic atrial fibrillation, but very few studies have been found. When a beta-blocker alone is ineffective, the addition of digoxin is likely to be beneficial.
- Current consensus is that calcium channel blockers are more effective than digoxin for controlling heart rate, but very few studies have been found. When a calcium channel blocker alone is ineffective, the addition of digoxin is likely to be beneficial.
- The choice between using a beta-blocker or a calcium channel blocker is dependent on individual risk factors and co-existing morbidities.

- We found inconclusive evidence comparing rhythm versus rate control strategies. Current consensus supports the use of either strategy, depending on individual risk factors and co-existing morbidities.

  Adverse effects are likely to be more common with rhythm control strategies.

DEFINITION

Atrial fibrillation is the most frequently encountered and sustained cardiac arrhythmia in clinical practice. [1] It is a supraventricular tachyarrhythmia, which is characterised by the presence of uncoordinated atrial activation and deteriorating atrial mechanical function. [1] [2] On the surface ECG P waves are absent and are replaced by rapid fibrillatory waves that vary in size, shape, and timing, leading to an irregular ventricular response when atrioventricular conduction is intact. **Classification:** Chronic atrial fibrillation is most commonly classified according to its temporal pattern. [3] Faced with a first detected episode of atrial fibrillation, three recognised patterns of chronic disease may develop: (1) "persistent atrial fibrillation" describes an episode of sustained atrial fibrillation (usually longer than 7 days) that does not convert to sinus rhythm without medical intervention, with the achievement of sinus rhythm either by pharmacological or electrical cardioversion; (2) "paroxysmal atrial fibrillation" refers to self-terminating episodes of atrial fibrillation, usually lasting less than 48 hours (both paroxysmal and persistent atrial fibrillation may be recurrent); (3) "permanent atrial fibrillation" where episodes of persistent (usually longer than 1 year) atrial fibrillation, in which cardioversion is not attempted or is unsuccessful, with atrial fibrillation accepted as the long-term rhythm for that person. "Lone atrial fibrillation" is largely a diagnosis of exclusion and refers to atrial fibrillation occurring in the absence of concomitant CVD (e.g. hypertension), structural heart disease (normal echocardiogram), with a normal ECG and chest x ray. [2] This review covers only chronic atrial fibrillation (persistent and permanent). Acute atrial fibrillation is covered in a separate review (see atrial fibrillation (acute onset). **Diagnosis:** In most cases of suspected atrial fibrillation, a 12-lead ECG is sufficient for diagnosis confirmation. [2] However, where diagnostic uncertainty remains, such as in chronic permanent atrial fibrillation, the use of 24-hour (or even 7-day) Holter monitoring or event recorder (e.g. Cardiomemo®) may also be required. [2] The most common presenting symptoms of chronic atrial fibrillation are palpitations, shortness of breath, fatigue, chest pain, dizziness, and stroke. [1] [2]

INCIDENCE/ PREVALENCE

Atrial fibrillation carries an overall population prevalence of 0.5–1.0%, and an incidence of 0.54 cases per 1000 person-years. [4] [5] The prevalence of atrial fibrillation is highly age dependent, and increases markedly with each advancing decade of age, from 0.5% at age 50–59 years to almost 9% at age 80–90 years. [6] Data from the Framingham Heart Study [7] suggests that the lifetime risk for development of atrial fibrillation for men and women aged 40 years and older is approximately 1 in 4. This risk is similar to that reported by the Rotterdam Study investigators [8] , which found that the lifetime risk associated with developing atrial fibrillation in men and women aged 55 years and above was 24% and 22%, respectively. The Screening for Atrial Fibrillation in the Elderly (SAFE) project reported that the baseline prevalence of atrial fibrillation in people aged over 65 years was 7.2%, with a higher prevalence in men (7.8%) and in people aged 75 years or more, with an incidence of 0.69–1.64% a year, depending on screening method. [9] The US Census Bureau reports that the number of people with atrial fibrillation is projected to be 12.1 million by 2050, assuming that there are no further increases in age-adjusted incidence of atrial fibrillation. [10] These incidence data refer to cross-sectional study data, whereby most people would have atrial fibrillation of over 7 days' duration (persistent, paroxysmal, or permanent atrial fibrillation), and not to acute atrial fibrillation.

AETIOLOGY/ RISK FACTORS

Atrial fibrillation is linked to all types of cardiac disease, including cardiothoracic surgery, as well as to a large number of non-cardiac conditions, such as thyroid disease, any pyrexial illness, electrolyte imbalance, cancer, and acute infections. [1] [2]

PROGNOSIS

Chronic atrial fibrillation confers an enormous and significant clinical burden. It is an independent predictor of mortality, and is associated with an odds ratio for death of 1.5 for men and 1.9 in women, independent of other risk factors. [11] It increases the risk of ischaemic stroke and thromboembolism an average of fivefold. [12] Furthermore, the presence of chronic atrial fibrillation is linked to far more severe strokes, with greater disability and lower discharge rate to home. [12] [13] Chronic atrial fibrillation is frequent (3–6% of all medical admissions) [2] and results in longer hospital stay. In addition, chronic atrial fibrillation increases the risk of developing heart failure and adversely affects quality of life, including cognitive function. [14]

AIMS OF INTERVENTION

To prevent stroke and achieve ventricular rate control and rhythm control (conversion to and maintenance of sinus rhythm), with minimal adverse effects of treatments.

OUTCOMES Mortality, recurrent strokes or transient ischaemic attacks, thromboembolism, major bleeding, heart rhythm, ventricular rate, length of time to restoration of sinus rhythm, symptoms (palpitations, dyspnoea, dizziness), quality of life, adverse effects of treatment.

METHODS *BMJ Clinical Evidence* search and appraisal August 2007. For this review the following were used for the identification of studies: Medline 1986 to August 2007, Embase 1986 to August 2007, and The Cochrane Library Issue 1, 2007. Additional searches were carried out on the NHS Centre for Reviews and Dissemination (CRD), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA), Turning Research into Practice (TRIP), and the NICE websites. Abstracts of studies retrieved in the search were assessed independently by two information specialists. Predetermined criteria were used to identify relevant studies. Study design criteria included: systematic reviews, RCTs including at least 20 people, 80% of whom were followed up. We included studies described as "open", "open label", or non-blinded, single blinded, or double blinded. There was no minimum length of follow-up. We only included RCTs of adults aged above 18 years, and excluded atrial fibrillation arising during or soon after cardiac surgery, "new onset"/acute atrial fibrillation (covered by *BMJ Clinical Evidence* in atrial fibrillation [acute]) and people with valvular atrial fibrillation. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 13).

QUESTION What are the effects of oral medical treatments to control heart rate in people with chronic (longer than 1 week) non-valvular atrial fibrillation?

OPTION BETA-BLOCKERS VERSUS DIGOXIN

Control of heart rate

Carvedilol compared with digoxin Carvedilol is no more effective at 6 months at improving 24-hour ventricular heart rate or daytime and exercise heart rate in people with chronic non-valvular atrial fibrillation (moderate-quality evidence). Carvedilol may be less effective at reducing noctural heart rate at 6 months in people with chronic non-valvular atrial fibrillation (low-quality evidence).

Symptom severity

Carvedilol compared with digoxin Carvedilol is as effective at 6 months as digoxin at improving exercise tolerance in people with chronic non-valvular atrial fibrillation (moderate-quality evidence).

Note

Current consensus is that beta-blockers should be used in preference to digoxin in non-sedentary people.

For GRADE evaluation of interventions for atrial fibrillation (chronic), see table, p 13 .

Benefits: We found one systematic review (search date 2005), which did not perform a meta-analysis. [2] It identified four RCTs, one of which met *BMJ Clinical Evidence* inclusion criteria. The RCT (47 people with persistent atrial fibrillation for longer than 1 month and heart failure; mean age 68 years; crossover design) compared the beta-blocker carvedilol versus digoxin. [15] At 6 months' follow-up there was no significant difference between carvedilol and digoxin in controlling the average 24-hour ventricular rate, the 6-minute walk distance, and the symptom scores (average 24-hour ventricular rate a minute: 88.8 with carvedilol *v* 75.7 with digoxin; P = 0.13; 6-minute walk distance: 374 m with carvedilol *v* 414 m with digoxin; P = 0.49; symptom scores: 6 with carvedilol *v* 8 with digoxin; P = 0.08). Carvedilol and digoxin were similar in controlling the daytime and exercise-related ventricular rate. However, digoxin lowered the nocturnal heart rate to a greater extent (absolute numbers and significance assessment not reported).

Harms: The RCT reported two deaths in people taking carvedilol (1 due to MI and 1 due to stroke) compared with none in people taking digoxin (significance not assessed). Other adverse effects were not reported.

Comment: **Clinical guide:**
Based on comparative data from small (fewer than 20 people), older RCTs that did not meet *BMJ Clinical Evidence* inclusion criteria, an RCT on xamoterol (which has been withdrawn owing to safety concerns), and expert opinion, the systematic review concluded that beta-blockers lower exercise-related (but not resting) heart rate to a greater extent than digoxin. [2] It also concluded that beta-blockers should be used in preference to digoxin as a first-choice rate-controlling agent for most people with chronic atrial fibrillation, with the exception of sedentary people, where the requirement for exercise-related rate control is limited. [2]

OPTION BETA-BLOCKERS PLUS DIGOXIN VERSUS BETA-BLOCKERS ALONE

We found no clinically important results about beta-blockers plus dixogin in people with chronic non-valvular atrial fibrillation. Current consensus supports the addition of digoxin when a beta-blocker alone is ineffective.

For GRADE evaluation of interventions for atrial fibrillation (chronic), see table, p 13 .

Benefits: We found no systematic review or RCT that met *BMJ Clinical Evidence* inclusion criteria in people with chronic non-valvular atrial fibrillation.

Harms: We found no RCTs.

Comment: **Clinical guide:**
We found one systematic review (search date 2005), which did not include a meta-analysis. [2] Based on data from small (fewer than 20 people), older RCTs that did not meet *BMJ Clinical Evidence* inclusion criteria, an RCT on xamoterol (which has been withdrawn owing to safety concerns), and expert opinion, the systematic review supported the use of combination treatment with either rate-limiting calcium channel blockers or beta-blockers plus digoxin when rate control with either a beta-blocker or rate-limiting calcium channel blocker alone is found to be inadequate. [2]

OPTION CALCIUM CHANNEL BLOCKERS (RATE-LIMITING) VERSUS DIGOXIN

Control of heart rate
Verapamil compared with digoxin Verapamil may be more effective at 2 weeks than digoxin at lowering rest and exercise heart rates in people with chronic non-valvular atrial fibrillation (low-quality evidence).

Note
Current consensus supports the use of rate-limiting calcium channel blockers over digoxin as initial monotherapy in most people, with the exception of sedentary people.

For GRADE evaluation of interventions for atrial fibrillation (chronic), see table, p 13 .

Benefits: We found one systematic review (search date 2005), which did not perform a meta-analysis. [2] It identified seven RCTs in people with chronic non-valvular atrial fibrillation, one of which met *BMJ Clinical Evidence* inclusion criteria. [16] The RCT (complex multiphase) compared the rate-limiting calcium channel blocker verapamil versus digoxin 0.25 mg daily alone, digoxin 0.5 mg daily alone, and verapamil plus digoxin 0.25 mg daily (see calcium channel blocker plus digoxin versus calcium channel blocker alone, p 4) in 24 people with chronic atrial fibrillation (longer than 1 year; aged 30–82 years, mean age 61 years). [16] At at least 2 weeks' follow-up, verapamil alone reduced both resting and exercise heart rate compared with digoxin; however, significance was not assessed (resting heart rate: 86 beats a minute with verapamil *v* 95 beats a minute with digoxin 0.25 mg daily *v* 88 beats a minute with digoxin 0.5 mg daily; exercise-induced heart rate 122 beats a minute with verapamil *v* 155 beats a minute with digoxin 0.25 mg daily *v* 147 beats a minute with digoxin 0.5 mg daily).

Harms: The RCT did not comment on adverse events. [16]

Comment: **Clinical guide:**
Based on data from predominantly small (fewer than 20 people), older RCTs that did not meet *BMJ Clinical Evidence* inclusion criteria, and on expert opinion, the systematic review concluded that rate-limiting calcium channel blockers lower exercise-related heart rate (but not resting heart rate) more effectively than digoxin in most people, with the exception of sedentary people, where the requirement for exercise-related rate control is limited. [2]

OPTION CALCIUM CHANNEL BLOCKERS (RATE-LIMITING) PLUS DIGOXIN VERSUS CALCIUM CHANNEL BLOCKERS (RATE-LIMITING) ALONE

Control of heart rate
Verapamil plus digoxin compared with verapamil alone Verapamil plus digoxin is more effective at 2 weeks at reducing resting and exercise heart rate (moderate-quality evidence).

Symptom severity
Verapamil plus digoxin compared with verapamil alone Verapamil plus digoxin may be more effective at 2 weeks at improving maximal effort capacity (low-quality evidence).

Note
Current consensus supports the addition of digoxin when a calcium channel blocker alone is ineffective.

For GRADE evaluation of interventions for atrial fibrillation (chronic), see table, p 13 .

Benefits: We found one systematic review (search date 2005), [2] which did not perform a meta-analysis, and which identified four RCTs, one of which met *BMJ Clinical Evidence* inclusion criteria. [16] The RCT (see rate-limiting calcium channel blockers versus digoxin, p 4) found that, at follow-up of at least 2 weeks, combination treatment with digoxin plus verapamil significantly decreased resting and exercise heart rate compared with verapamil alone (resting heart rate: 75 beats a minute with verapamil plus digoxin *v* 86 beats a minute with verapamil alone; P less than 0.01; exercise heart rate: 114 beats a minute with verapamil plus digoxin *v* 122 beats a minute with verapamil alone; P less than 0.05). [16] In addition, maximal effort capacity (time to fatigue on bicycle ergometry) was improved during combination treatment (data presented graphically, significance not assessed).

Harms: The RCT gave no information on adverse effects. [16]

Comment: Based on data from small (fewer than 20 people), older RCTs that did not meet *BMJ Clinical Evidence* inclusion criteria, and on expert opinion, the systematic review supported the use of combination treatment with rate-limiting calcium channel blockers plus digoxin when rate control with a rate-limiting calcium channel blocker alone is inadequate. [2]

OPTION BETA-BLOCKERS VERSUS RATE-LIMITING CALCIUM CHANNEL BLOCKERS

Control of heart rate
Betaxolol compared with diltiazem Betaxolol is more effective at 7 months at decreasing ventricular rates during rest and exercise, and at lowering average and maximal heart rates, in people with chronic atrial fibrillation who are also taking digoxin (moderate-quality evidence). Betaxolol may be as effective at controlling minimal heart rates in people with chronic atrial fibrillation who are also taking digoxin (low-quality evidence).

Adverse effects
Beta-blockers have been associated with more adverse effects compared with the calcium channel blockers. Consensus supports the use of either beta-blockers or calcium channel blockers.

For GRADE evaluation of interventions for atrial fibrillation (chronic), see table, p 13 .

Benefits: We found one systematic review (search date 2005), [2] which did not perform a meta-analysis, and which identified four RCTs, one of which met *BMJ Clinical Evidence* inclusion criteria. [17] The RCT (a prospective crossover study, 35 people, mean age 52 years with chronic atrial fibrillation of longer than 1 month) compared digoxin plus the beta-blocker betaxolol versus digoxin plus the rate-limiting calcium channel blocker diltiazem. [17] As this was strictly a comparative combination treatment RCT, the doses of digoxin were made similar in both groups by adjusting them until the serum digoxin concentration was within 0.8–2.0 nmol/L. At 7 months' follow-up, people taking betaxolol had significantly lower ventricular rates both during rest and exercise compared with people taking diltiazem (ventricular rate during rest: 67 beats a minute with betaxolol *v* 80 beats a minute with diltiazem; P less than 0.005; during exercise: 135 beats a minute with betaxolol *v* 154 beats a minute with diltiazem; P less than 0.05). On 24-hour ambulatory recording, people taking betaxolol had significantly lower average and maximal heart rates compared with diltiazem, but minimal heart rate was similar in both groups (average heart rate: 64 beats a minute with betaxolol *v* 73 beats a minute with diltiazem; P less than 0.05; maximal heart rate: 105 beats a minute with betaxolol *v* 131 beats a minute with diltiazem; P less than 0.05; minimal heart rate: 46 beats a minute with betaxolol *v* 48 beats a minute with diltiazem; significance not assessed).

Harms: There were no withdrawals caused by treatment adverse effects in either group. [17] Assessment after crossover suggested that there were more adverse effects with betaxolol than with diltiazem; however, no washout period was reported (dizziness: 2/35 [6%] with betaxolol *v* 2/35 [6%] with diltiazem; dyspnoea: 3/35 [9%] with betaxolol *v* 0/35 [0%] with diltiazem; gastric pain: 2/35 [6%] with betaxolol *v* 1/35 [3%] with diltiazem; headache: 1/35 [3%] with betaxolol *v* 2/35 [6%] with diltiazem; fatigue: 3/35 [9%] with betaxolol *v* 1/35 [3%] with diltiazem; nausea: 2/35 [6%] with betaxolol *v* 2/35 [6%] with diltiazem; constipation: 1/35 [3%] with betaxolol *v* 0/35 [0%] with diltiazem; oedema: 1/35 [3%] with betaxolol *v* 0/35 [0%] with diltiazem; significance not assessed).

Comment: **Clinical guide:**
Based on data from small (fewer than 20 people), older RCTs which did not meet the *BMJ Clinical Evidence* inclusion criteria, the systematic review supported the use of either beta-blockers or rate-limiting calcium channel blockers as initial monotherapy. [2] The decision to use a beta-blocker or a rate-limiting calcium channel blocker is dependent on individual risk factors and co-existing

morbidities. Beta-blockers are contraindicated in people also suffering from asthma, and a rate-limiting calcium channel blocker is inappropriate in people with co-existent heart failure. Betaxolol is an outdated beta-blocker no longer used in the UK.

QUESTION **What is the effect of different treatment strategies for people with persistent non-valvular atrial fibrillation?**

OPTION **RHYTHM CONTROL VERSUS RATE CONTROL**

Mortality
Rhythm control compared with rate control We don't know whether rhythm control reduces mortality (low-quality evidence).

Thromboembolic events
Rhythm control compared with rate control We don't know whether rhythm control reduces thromboembolism (very low-quality evidence).

Bleeds
Rhythm control compared with rate control Rhythm control and rate control are equally effective at reducing the incidence of major bleeding, intracranial bleeds, and extracranial bleeds (moderate-quality evidence).

Control of heart rate
Rhythm control compared with rate control Rhythm control is more effective at achieving sinus rhythm (high-quality evidence). We don't know how rhythm control compares with rate control at controlling ventricular heart rate (very low-quality evidence).

Symptom severity
Rhythm control compared with rate control Rhythm control is less effective at improving quality of life and atrial fibrillation-related symptoms (such as palpitations, dyspnoea, and dizziness) (moderate-quality evidence). Rhythm control may increase exercise tolerance (very low-quality evidence).

Adverse effects
Rhythm-control strategies have been associated with more adverse effects compared with rate-control strategies.

Note
Current consensus supports the use of either rhythm or rate control depending on individual risk factors and co-existing morbidities.

For GRADE evaluation of interventions for atrial fibrillation (chronic), see table, p 13 .

Benefits:

Mortality, thromboembolism, strokes, and major bleeding:
We found two systematic reviews [18] [19] and one subsequent RCT. [20] The first review (5 RCTs, 5239 people, overall mean age 65.1 years, 65.3% men, 29.9% people with history of coronary artery disease, and 52.7% with arterial hypertension, with first or recurrent atrial fibrillation, followed up for 1.0–3.5 years, see table 1, p 11) examined the incidence of all-cause mortality, thromboembolic stroke, major bleeds (intracranial and extracranial), and systemic embolism, and the combined end point of all-cause mortality and thromboembolic stroke. At mean follow-up of 1.9 years there was a non-significant trend towards a reduction in the risk of death from any cause and thromboembolic stroke with rate control compared with rhythm control (death from any cause: 339/2609 [13%] with rate control *v* 383/2630 [15%] with rhythm control; OR 0.87, 95% CI 0.74 to 1.02; P = 0.09; death from thromboembolic stroke: OR 0.80, 95% CI 0.60 to 1.07; P = 0.14; absolute figures not reported separately for thromboembolic events). However, for the combined end point of death from any cause and thromboembolic stroke, the difference was significant (death from any cause and thromboembolic stroke: 424/2609 [16%] with rate control *v* 489/2630 [19%] with rhythm control; OR 0.84, 95% CI 0.73 to 0.98; P = 0.02; NNT 50). [18] This review also found no significant difference between rate control and rhythm control in all major bleeds, intracranial bleeds, extracranial bleeds, or systemic embolism (all major bleeds: 151/2609 [6%] with rate control *v* 134/2630 [5%] with rhythm control; OR 1.14, 95% CI 0.90 to 1.45; P = 0.28; intracranial bleeds: absolute figures not reported; OR 1.16, 95% CI 0.64 to 2.10; P = 0.60; extracranial bleeds: absolute figures not reported; OR 1.09, 95% CI 0.94 to 1.41; P = 0.50; systemic embolism: absolute figures not reported; OR 0.93, 95% CI, 0.43 to 2.02; P = 0.90). The review compared rhythm control and rate control in older people (mean age at least 65 years) and in older people with longer follow-up (at least 20 months). Rate control significantly reduced both the combined end point of all-cause mortality and thromboembolic events for older people compared with rhythm control (mean follow-up 1.9 years: 3 RCTs, [21] [22] [23] death from any cause and thromboembolic stroke: 421/2383 [18%] with rate control *v* 479/2399 [20%] with rhythm control; OR 0.86, 95% CI 0.74 to 0.99, P = 0.04; and in older

people with longer follow-ups: 2 RCTs, [21] [23] death from any cause and thromboembolic stroke: 421/2283 [18%] with rate control *v* 470/2299 [20%] with rhythm control; OR 0.85, 95% CI 0.74 to 0.99; P = 0.04). [18] The same RCTs were analysed in an earlier systematic review (search date 2003, 5239 people, overall mean age 69 years, 62% male, 28% people with history of heart failure, and 67% with arterial hypertension, with first or recurrent atrial fibrillation, followed up for 1.0–3.5 year, see comment below). [19] It found no significant difference between rhythm control and rate control in reducing the risk of ischaemic stroke (78/2228 [3.5%] with rate control *v* 88/2237 [4.0%] with rhythm control; OR 0.50, 95% CI 0.14 to 1.83, P = 0.30). We found one subsequent RCT (see table 1, p 11), [20] which found that significantly fewer people receiving rhythm control died compared with people receiving rate control (6/39 [15%] with rhythm control *v* 36/84 [43%] with rate control; P less than 0.0001). It found no significant differences in embolic events between rhythm control and rate control (6/39 [15%] with rhythm control *v* 9/84 [11%] with rate control; P value reported as not significant). [20]

Exercise tolerance:
We found no systematic review that examined the effects on exercise tolerance of rate-control strategies versus rhythm-control strategies. We found three RCTs. [24] [25] [20] The first RCT (see table 1, p 11) found that, at 6 months' follow-up, people receiving rhythm control significantly increased their walking distance compared with people receiving rate control. However, the difference did not reach significance at 3 and 12 months' follow-up (walking distance assessed by the 6-minute walk test at 3 weeks' follow-up: absolute distances not reported; P = 0.201; at 3 months' follow-up: P = 0.012, at 6 months' follow-up: P = 0.059; at 1-year follow-up: P = 0.008). [24] In the second RCT (a sub-study of a larger RCT, [21] 245 people with atrial fibrillation, aged over 65 years with another risk factor for stroke or death, see table 1, p 11), people assigned to rhythm control walked on average 100 feet farther (about 30.5 m) during a 6-minute walk test at all follow-up visits compared with those in the rate-control group, although the difference between groups was not significant (P = 0.06; absolute numbers not reported; follow-up visits were at 2 months and yearly thereafter for 5 years). [25] The third RCT (see table 1, p 11) found that, in people with atrial fibrillation and non-ischaemic heart failure, rhythm control significantly increased exercise capacity compared with rate control (exercise duration: 9.1 minutes with rhythm control *v* 7.3 minutes with rate control; P less than 0.0001; metabolic equivalent task value: 6.3 with rhythm control *v* 5.4 with rate control; P = 0.0001). [20]

Ventricular heart rate:
We found no systematic review that investigated the impact of rate control or rhythm control on ventricular heart rate. We found four RCTs (see table 1, p 11). [25] [26] [20] [23] In the first RCT (see table 1, p 11), rhythm control significantly lowered mean heart rate compared with rate control (79.1 beats a minute with rhythm control *v* 85.8 beats a minute with rate control; P less than 0.003). [26] In the second RCT (see table 1, p 11), the mean heart rate was lower with rhythm control compared with rate control (73 beats a minute with rhythm control *v* 82 beats a minute with rate control; P value not reported but difference reported as significant). However, the difference was attributed to the presence of sinus rhythm or atrial fibrillation rather than treatment assignment. [23] In the third RCT (see table 1, p 11 , a sub-study of a larger RCT; [21] 245 people had 6-minute walk tests at baseline, 2 months, and 1, 2, 3, and 4 years, intention to treat-adjusted analyses), heart rates before walking were significantly higher in the rate-control group compared with the rhythm-control group (mean difference: 3.6 beats a minute; P = 0.004), but there were no significant differences between treatment groups in heart rates after walking (absolute values not reported). [25] In the fourth RCT (see table 1, p 11), there were no significant differences between rhythm control and rate control for resting and peak heart rate (resting heart rate: 82 beats a minute with rhythm control *v* 81 beats a minute with rate control; P value reported as not significant; peak heart rate: 154 beats a minute with rhythm control *v* 153 beats a minute with rate control; P value reported as not significant). [20]

Restoration of sinus rhythm:
We found no systematic review comparing rhythm control and rate control for restoration of sinus rhythm. We found three RCTs (see table 1, p 11). [24] [22] [23] In the first RCT, more people receiving rhythm control achieved sinus rhythm compared with people assigned to rate control (38/100 [38%] with rhythm control *v* 9/100 [9%] with rate control; P less than 0.001). [22] In the second RCT, more people in the rhythm-control group achieved sinus rhythm compared with those in the rate-control group (number of people in sinus rhythm: 103/266 [39%] with rhythm control *v* 26/256 [10%] with rate control; significance not reported). [23] In the third RCT, significantly more people in the rhythm-control group achieved sinus rhythm compared with people in the rate-control group (56% with rhythm control *v* 10% with rate control; P less than 0.001). [24]

Improvement in atrial fibrillation-related symptoms:
We found no systematic review examining the impact of rate control and rhythm control on atrial fibrillation-related symptoms. We found one RCT (see table 1, p 11), which found no difference

in atrial fibrillation-related symptoms between rhythm control and rate control (palpitations: 87/127 [69%] with rhythm control *v* 88/125 [70%] with rate control; dyspnoea: 84/127 [66%] with rhythm control *v* 84/125 [67%] with rate control; dizziness: 37/127 [29%] with rhythm control *v* 38/125 [30%] with rate control; significance not assessed).

Quality of life:
We found one systematic review (search date 2005) that did not perform a meta-analysis. [27] It examined the effect of a rate-control strategy versus a rhythm-control strategy on quality of life (assessed by Short-Form Health Survey-36 [SF-36]) in people with atrial fibrillation, and identified four RCTs, two of which compared rate and rhythm strategies directly and not against baseline only. [28] [29] The first RCT [29] (quality-of-life results from van Gelder et al, [23] see table 1, p 11) found no significant difference in any of the quality-of-life subscales between the rhythm-control and rate-control groups. [29] The second RCT (quality-of-life results from The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators [21] reported separately in Jenkins et al, [28] 716 people, quality of life assessed by SF-36 at baseline, 2 months, and then annually for 6 years' follow-up, see table 1, p 11), found no significant difference in quality of life between rate control and rhythm control (absolute values not reported). [28]

Harms:

We found one systematic review (search date not reported) examining the potential adverse effects of a rate- or rhythm-control strategy (5 RCTs; 5239 people with atrial fibrillation, followed up for 1.0–3.5 years). [30] It found that rhythm control was associated with significantly more hospital admissions caused by the adverse effects of treatment compared with rate control (1592/2364 [67%] with rhythm control *v* 1288/2353 [55%] with rate control; P less than 0.01). [30] Four RCTs reported on adverse drug effects. [24] [26] [23] [21] In the first RCT, significantly more people experienced an adverse effect with rhythm control compared with rate control (80/127 [64%] with rhythm control *v* 58/125 [47%] with rate control; P = 0.011). More people withdrew because of adverse effects in the rhythm-control group compared with the rate-control group (31/127 [25%] with rhythm control *v* 17/125 [14%] with rate control; P = 0.036). The most frequent adverse effects with rhythm control were corneal dispositions (10/127 [8%]), thyroid problems (7/127 [6%]), and photosensitivity (7/127 [6%]). The most frequent adverse effect with rate control was peripheral oedema (17/127 [13%]). [24] The second RCT reported adverse effects according to the drug used, and did not perform a between-group comparison. In those receiving sotalol, 2/25 (8%) people withdrew because of abdominal pain, diarrhoea, or eczema; 1/25 (4%) people had torsades des pointes; and 1/25 [4%] people had QT prolongation. In the rhythm-control group treated with propafenone, 2/38 (5%) people experienced drug intolerance, 1/38 (3%) people had complex ventricular arrhythmias, and 1/38 (3%) people had atrial flutter requiring cardioversion. In the rhythm-control group treated with disopyramide, 1/10 (10%) people had dyspepsia, and 1/10 (10%) people had dry mouth and urination difficulties. No adverse effects associated with rate-control strategies, such as cardioversion or AV node junction ablation with pacemaker insertion, were reported. [26] The third RCT found that severe adverse drug effects were more common in the rhythm-control group. [23] In those receiving antiarrhythmic drugs, 7/266 (3%) people had sick sinus syndrome or atrioventricular block; 3/266 (1%) people had torsades de pointes or ventricular fibrillation; 1/266 (0.4%) person had rapid, haemodynamically significant atrioventricular conduction during flutter; and 1/266 (0.4%) people had drug-induced heart failure. In the rate-control group, 2/256 (0.8%) people had non-lethal digitalis intoxication. [23] The fourth RCT found that more people in the rhythm-control group than in the rate-control group had adverse effects (bradycardia: 105/2033 [5%] with rhythm control *v* 64/2027 [3%] with rate control; P = 0.001; QT prolongation: 31/2033 [2%] with rhythm control *v* 4/2027 [0.2%] with rate control; P less than 0.001; torsades des pointes: 12/2033 [0.6%] with rhythm control *v* 2/2027 [0.1%] with rate control; P = 0.007; pulmonary events: 108/2033 [5%] with rhythm control *v* 24/2027 [1%] with rate control; P less than 0.001; gastrointestinal events: 127/2033 [6%] with rhythm control *v* 35/2027 [2%] with rate control; P less than 0.001; admission to hospital: 1374/2033 [68%] with rhythm control *v* 1220/2027 [60%] with rate control; P less than 0.0001). [21] The other two RCTs did not report on adverse drug reactions. [22] [20]

Comment:

Although both systematic reviews assessing thromboembolism, strokes, and major bleeding included the same RCTs, slightly different population characteristics were quoted in each review; the reason for the discrepancy is unclear. [18] [19] Crossover from one treatment strategy to the other was not reported by all five RCTs, which were analysed by intention to treat. Only two RCTs reported the number of people crossing over from one treatment strategy to the other. [21] [24] The first RCT reported that 248/2027 [12%] people initially assigned to the rate-control strategy crossed over to rhythm control; 86 crossed back to rate control by the end of the study. [21] Among those initially assigned to receive rhythm control, 594/2033 [29%] crossed over to rate control; 61 crossed back to rhythm control by the end of the study. In the second RCT, 4/125 (3%) people assigned to rate control crossed over to rhythm control compared with 6/127 [5%] people initially assigned to rhythm control who crossed over to rate control. [24] The Atrial Fibrillation and Congestive Heart Failure trial, [31] which began recruitment in May 2001, is examining whether restoring and maintaining sinus rhythm significantly reduces cardiovascular mortality in people with atrial fibrillation and

congestive heart failure compared with a rate-control strategy. In this RCT (1450 people with atrial fibrillation and congestive heart failure, left ventricular ejection fraction 35% or less, enrolled at 109 centres in the USA, Canada, South America, Europe, and Israel) people were randomised to either a rate-control (beta-blockers, digoxin, or pacemaker and AV node ablation) or rhythm-control (electrical cardioversion combined with antiarrhythmic drugs (amiodarone and class III antiarrhythmic agents) strategy. [31] The trial was due to complete follow-up in May 2005, but the results were not available for this review.

Clinical guide:
A systematic review of all the available evidence, which also took into consideration expert opinion, showed that different situations may warrant adoption of either rate-control or rhythm-control strategy. [2] The systematic review recommended that a rate-control strategy should be the preferred initial treatment option in: people aged 65 years and older with persistent atrial fibrillation; people with coronary artery disease; people with contraindications to antiarrhythmic drugs; people unsuitable for cardioversion; and people without congestive heart failure. It recommended that a rhythm-control strategy should be the preferred initial option in: people with persistent atrial fibrillation who are symptomatic; younger people; people presenting for the first time with lone atrial fibrillation; people with atrial fibrillation secondary to a treated or corrected precipitant; and people with congestive heart failure. The potential advantages and disadvantages of each strategy should be explained to every person. The review also recommended that, regardless of which treatment strategy is used, appropriate antithrombotic treatment [1] [2] must be simultaneously initiated and maintained for the prevention of thromboembolism. A caveat to the findings reported here is that they may not be generalisable to younger people or to highly symptomatic people.

GLOSSARY

Metabolic equivalent task (MET) One MET is the energy expenditure and caloric requirement of the body at rest. Mild exercise such as walking at a leisurely pace increases energy expenditure to about 2.5 METs per hour of walking. Vigorous activity can result in 6 to more than 12 METs per hour of activity.
High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect
Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Rate-control treatment strategies employ beta-blockers, digoxin, and non-dihydropyridine calcium channel blockers (verapamil or diltiazem), either alone or in combination, to maintain a resting heart rate of 70–90 beats a minute. Highly symptomatic people may also be considered for cardioversion (electrical or pharmacological), atrioventricular node/junction ablation/modification or both, with or without pacemaker implantation.
Rhythm-control treatment strategies include cardioversion (either electrical or drug-induced) with or without the addition of antiarrhythmic drugs (amiodarone, sotalol, propafenone, disopyramide, flecainide, moracizine, procainamide, and quinidine).
Short-Form Health Survey-36 items (SF-36) A scale that assesses health-related quality of life across eight domains: limitations in physical activities (physical component); limitations in social activities; limitations in usual role activities due to physical problems; pain; psychological distress and wellbeing (mental health component); limitations in usual role activities because of emotional problems; energy and fatigue; and general health perceptions.
Very low-quality evidence Any estimate of effect is very uncertain.

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Christopher J Boos
Specialist Registrar in Cardiology
Dept of Cardiology
University Hospital
Birmingham
UK

Deirdre A Lane
Lecturer in Medicine
University Department of Medicine
City Hospital
Birmingham
UK

Gregory YH Lip
Consultant Cardiologist and Professor of Cardiovascular Medicine, Director of Haemostasis Thrombosis and Vascular Biology Unit
City Hospital
Birmingham
UK

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TABLE 1 **Study characteristics of six RCTs examining the effect of a rate-control strategy versus a rhythm-control strategy in people with recurrent or persistent atrial fibrillation.**

Trial, year, country	Number of people	Mean age (years)	Rate-control strategy	Rhythm-control strategy	Mean follow-up (years)	End points
PIAF (2000), Germany [24]	252 (73.0% male)	61.5	125 people Diltiazem first line, additional medication at physician discretion INR target: 2.0–3.0	127 people Drug-induced cardioversion, DC cardioversion if necessary followed by amiodarone. If AF recurred, DC cardioversion plus amiodarone INR target: 2.0–3.0	1	Primary: improvement in AF-related symptoms (palpitations, dyspnoea, dizziness) Secondary: change in mean heart rate (no between-group comparison reported), hospitalisations, QoL
AFFIRM (2002), US and Canada [21] [25] [28]	4060 (61.3% male)	69.7	2027 people Beta-blockers, non-dihydropyridine CCB, digitalis, or a combination ± radio-frequency ablation, maze procedure, or pacing, as appropriate INR target: 2.0–3.0	2033 people Amiodarone, disopyramide, flecainide, moracizine, procainamide, propafenone, quinidine, sotalol, or combination. DC cardioversion could be used to maintain sinus rhythm. Radio-frequency ablation, maze procedure, or pacing, as appropriate INR target: 2.0–3.0	3.5	Primary: ACM Secondary: composite of death, disabling stroke, disabling anoxic encephalopathy, major bleeding, cardiac arrest,admission to hospital, QoL, exercise tolerance
STAF (2003), Germany [22]	200 (63.5% male)	65.8	100 people	100 people	1.7	Primary: composite of ACM, stroke or TIA, systemic embolism, cardiopulmonary resuscitation
			Beta-blockers, digitalis, calcium channel blockers, or AV node ablation/modification ± pacemaker implantation	Internal or external DC cardioversion		
				Sotalol, amiodarone, class I antiarrhythmics		Secondary: syncope, bleeding (requiring hospitalisation, transfusion, or both), QoL, resting heart rate, and maintenance of sinus rhythm
			OAC as per ACCP guidelines [32]	INR target: 2.0–3.0 for 4 weeks before and 4 weeks after DC cardioversion		
HOT CAFÉ (2004), Poland [26]	205 (65.3% male)	60.8	101 people	104 people	1	Primary: composite of ACM, thromboembolic events, and major bleeding
			Beta-blockers, non-dihydropyridine CCB, digitalis, or a combination. DC cardioversion or AV node/junction ablation with pacemaker insertion	DC cardioversion without prior antiarrhythmic treatment. If sinus rhythm not maintained 2 hours after the procedure, antiarrhythmic drugs given (propafenone, disopyramide, or sotalol). DC cardioversion re-attempted if sinus rhythm not achieved		Secondary: rate control, maintenance of sinus rhythm, discontinuation of therapy, minor bleeding, hospitalisation, exercise tolerance (no direct group comparison)
			INR target: 2.5	INR target: 2.0–3.0 for 4 weeks before and 4 weeks after DC cardioversion		
Ökçün et al (2004), Turkey [20]	154 (66.0% male)	ND	84 people Digoxin and metoprolol, with metoprolol titrated to a maximum dose of 50 mg twice daily INR target: 2.0–3.0 for duration of trial	74 people Drug-induced cardioversion with iv amiodarone, followed by DC cardioversion if unsuccessful. Oral amiodarone given to all participants INR target: 2.0–3.0 for 4 weeks before and 4 weeks after cardioversion	3	Primary: composite of embolism, death, and exercise capacity

Trial, year, country	Number of people	Mean age (years)	Rate-control strategy	Rhythm-control strategy	Mean follow-up (years)	End points
RACE (2002), The Netherlands [23] [29]	522 (63.5% male)	68	256 people Beta-blockers, non-dihydropyridine CCB, digitalis, or a combination. DC cardioversion or AV node/junction ablation with pacemaker implantation INR target: 2.5	266 people DC cardioversion without prior antiarrhythmic treatment plus sotalol. If AF recurred within 6 months, repeat DC cardioversion plus flecainide or propafenone. Further recurrence of AF, loading dose of amiodarone and repeat DC cardioversion, followed by amiodarone INR target: 2.5–3.5 for 4 weeks before and 4 weeks after DC cardioversion	2.3	Primary: composite of cardiovascular death, thromboembolic events, major bleeding, and severe adverse drug reactions Secondary: QoL, heart rate, and maintenance of sinus rhythm

ACCP, American College of Chest Physicians; ACM, all-cause mortality; AF, atrial fibrillation; AFFIRM, Atrial Fibrillation Follow-up Investigation of Rhythm Management; AV, atrioventricular; CCB, calcium channel blocker; DC, direct current; HOT CAFEÉ, How to Treat Chronic Atrial Fibrillation; INR, international normalised ratio; iv, intravenous; ND, not reported; OAC, oral anticoagulation; PIAF, Pharmacological Intervention in Atrial Fibrillation; QoL, quality of life; RACE, Rate Control versus Electrical cardioversion for persistent atrial fibrillation; STAF, Strategies of Treatment of Atrial Fibrillation; TIA, transient ischaemic attack.

TABLE **GRADE evaluation of interventions for atrial fibrillation (chronic)**

Important outcomes	Heart rate control, restoration of sinus rhythm, symptom severity, quality of life, mortality, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of oral medical treatments to control heart rate in people with chronic (longer than 1 week) non-valvular atrial fibrillation?									
1 (47) [15]	Control of heart rate	Beta-blockers *v* digoxin	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (47) [15]	Control of heart rate (nocturnal)	Beta-blockers *v* digoxin	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (47) [15]	Symptom severity	Beta-blockers *v* digoxin	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (24) [16]	Control of heart rate	Calcium channel blockers *v* digoxin	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (24) [16]	Control of heart rate	Calcium channel blockers (verapamil) plus digoxin *v* calcium channel blockers alone	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (24) [16]	Symptom severity	Calcium channel blockers (verapamil) plus digoxin *v* calcium channel blockers alone	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (35) [17]	Control of heart rate	Beta-blockers *v* calcium channel blockers	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (35) [17]	Control of heart rate (minimal)	Beta-blockers *v* calcium channel blockers	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
What is the effect of different treatment strategies for people with persistent non-valvular atrial fibrillation?									
6 (5362) [18] [20]	Mortality	Rhythm control *v* rate control	4	0	–1	–1	0	Low	Consistency point deducted for conflicting results. Directness point deducted for population differences
9 (9827) [18] [19] [20]	Thromboembolic events	Rhythm control *v* rate control	4	–1	–1	–1	0	Very low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results. Directness point deducted for population differences
5 (5239) [18]	Bleeds	Rhythm control *v* rate control	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
3 (974) [22] [23] [20] [24]	Sinus rhythm	Rhythm control *v* rate control	4	0	0	0	0	High	
4 (4941) [20] [23] [25] [26]	Control of heart rate	Rhythm control *v* rate control	4	–1	–1	–1	0	Very low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results. Directness point deducted for uncertainty about treatment benefit
1 (252) [24]	Symptom severity (atrial fibrillation symptoms)	Rhythm control *v* rate control	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
2 (1238) [28] [29]	Symptom severity (quality of life)	Rhythm control *v* rate control	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results

Important outcomes	**Heart rate control, restoration of sinus rhythm, symptom severity, quality of life, mortality, adverse effects**								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consis-tency**	**Direct-ness**	**Effect size**	**GRADE**	**Comment**
3 (4466) [20] [24] [25]	Symptom severity (exercise tolerance)	Rhythm control *v* rate control	4	–1	–1	0	0	Low	Quality points deducted for incomplete reporting ofresults. Consistency point deducted for different results at different endpoints

Type of evidence: 4 = RCT; 2 = Observational; 1 = Non-analytical/expert opinion. Consistency: similarity of results across studies
Directness: generalisability of population or outcomes
Effect size: based on relative risk or odds ratio