REVIEW

Rate versus rhythm control in atrial fibrillation and clinical outcomes: Updated systematic review and meta-analysis of randomized controlled trials

Contrôle de la fréquence ou du rythme cardiaque dans la fibrillation atriale : méta-analyse des études randomisées contrôlées

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Summary   Atrial fibrillation is the most frequently occurring sustained cardiac arrhythmia and is associated with a significantly increased risk of thromboembolic events and death. We sought to compare the clinical efficacy of rate and rhythm control strategies in patients with non-postoperative atrial fibrillation. We searched the PubMed database and the Cochrane Central Register of Controlled Trials for randomized controlled trials comparing rate versus rhythm control in patients with atrial fibrillation. Studies were retrieved and we analysed major clinical outcomes. Risk ratios (RRs) and 95% confidence intervals were calculated assuming random effects due to the clinical heterogeneity of the study populations. Eight randomized controlled trials were identified, with a total of 7499 patients with atrial fibrillation. There were no significant differences in the effects of rate and rhythm control on any outcome:

all-cause mortality (RR: 0.95; CI: 0.86−1.05), cardiovascular mortality (RR: 0.99; CI: 0.87−1.13), arrhythmic/sudden death (RR: 1.12; CI: 0.91−1.38), ischaemic stroke (RR: 0.89; CI: 0.52−1.53), systemic embolism (RR: 0.89; CI: 0.69−1.14) and major bleeding (RR: 1.10; CI: 0.89−1.36). Updated data pooled from a large population of patients with atrial fibrillation suggests that rate and rhythm control strategies have similar effects on major clinical outcomes. Other factors, including individual preferences, comorbidities, drug tolerance and cost issues, should be considered when choosing the approach for these patients.

MOTS CLÉS
Bêtabloquants ;
Antagonistes
calciques ;
Digitaliques ;
Agents
antiarythmiques ;
Fibrillation atriale

Résumé   La fibrillation atriale est l'arythmie cardiaque soutenue la plus fréquente et est associée avec une augmentation du risque de complication thromboembolique et de décès. Notre objectif a été de comparer l'efficacité clinique des stratégies contrôles du rythme versus contrôle de la fréquence cardiaque chez des patients en fibrillation atriale en excluant la phase postopératoire. Notre recherche a été centrée sur les bases de données PubMed et CENTRAL, avec les mots clés « essais randomisés contrôlés » comparant les stratégies de contrôle de la fréquence du rythme cardiaque chez les patients en fibrillation atriale. Les études ont été analysées pour ce qui concerne les évènements cliniques majeurs. Le risque relatif et les intervalles de confiance à 95 % ont été calculés, en retenant l'hypothèse d'effets au hasard dus à l'hétérogénéité clinique des populations incluses dans les différentes études. Huit essais randomisés contrôlés ont été identifiés, incluant un total de 7499 patients en fibrillation atriale. Il n'y avait pas de différence significative entre les deux stratégies pour ce qui concerne le taux de mortalité globale (RR : 0,95 ; IC 95 % : 0,86−1,05), la mortalité cardiovasculaire (RR : 0,99 ; IC 95 % : 0,87−1,13), la mort subite ou arythmique (RR : 1,12 ; IC 95 % : 0,91−1,38), le taux d'accident ischémique cérébral (RR : 0,89 ; IC 95 % : 0,52−1,53), d'embolie systémique (RR : 0,89 ; IC 95 % : 0,69−1,14) et le taux de saignement majeur (RR : 1,10 ; IC 95 % : 0,89−1,36). Cette méta-analyse, mise à jour des précédentes, basée sur une population importante de patients en fibrillation atriale suggère que les deux stratégies: contrôle du rythme ou de la fréquence cardiaque dans la fibrillation atriale, ont des effets similaires sur les évènements cardiovasculaires majeurs. D'autres facteurs prenant en considération les préférences individuelles, les comorbidités, la tolérance des médicaments ou encore les coûts devraient être pris en considération lorsqu'une des deux stratégies est retenue dans la prise de ces patients.

Introduction

AF is the most common sustained cardiac arrhythmia. Risk factors for this condition include male sex, smoking, heart failure, diabetes, arterial hypertension, left ventricular hypertrophy, valvular heart disease, myocardial infarction and advanced age. The lifetime risk of developing AF in subjects aged greater than 40 years is around 25% [1,2].

AF is associated with increased cardiovascular morbidity and mortality. In addition to the deleterious haemodynamic effects that can trigger or worsen heart failure, AF also predisposes to thromboembolic events; stroke incidence increases with age, with the 5-year risk rising from 1.5% in the 6th decade of life to 23.5% in those aged more than 80 years [3]. AF is an independent risk factor for death [4].

The pharmacological treatment of AF follows one of two strategies: rate control (controlling the ventricular rate with beta-blockers, non-dihydropyridine calcium-channel blockers and/or digitalis); or rhythm control (restoring and maintaining sinus rhythm with electrical cardioversion and/or antiarrhythmic agents) [5]. Rhythm control maintenance with antiarrhythmic drugs can improve symptoms and reduce the incidence of stroke but may lead to an increased risk of adverse events due to negative inotropic and proarrhythmic effects [6]. The rate control strategy may have

fewer adverse events [7]. Antithrombotic agents are usually used to prevent thromboembolic events in association with rate control drugs, whereas their use after sinus rhythm is restored in rhythm control depends on the patient's risk factors.

Our aim was to systematically review RCTs and compare the relative effects of rate and rhythm control in AF. We proposed to analyse clinically relevant outcomes: all-cause mortality, cardiovascular mortality, arrhythmic/sudden death, ischaemic stroke, systemic embolism and major bleeding.

Methods

Searching

A search strategy was developed in September 2011 using the PubMed and Cochrane Central Register of Controlled Trials (CENTRAL) databases for study identification. There were no language limitations. References of obtained studies were also comprehensively searched.

The electronic search for RCT publication type was undertaken using the following keywords: rate, beta-blocker, acebutolol, atenolol, bisoprolol, carvedilol,

esmolol, metoprolol, nadolol, pindolol, propranolol, timolol, calcium-channel blocker, verapamil, diltiazem, digitalis, digoxin, rhythm, amiodarone, sotalol, propafenone, disopyramide, dofetilide, flecainide, ibutilide, dronedarone and azimilide, mortality, death, stroke, embolism, thromboembolic, thromboembolism, bleeding and atrial fibrillation. Boolean operators AND and OR were used to combine terms. Postoperative and postpercutaneous intervention studies were excluded from the search using the Boolean operator NOT.

Selection

We included RCTs comparing pharmacological approaches to maintaining rate or rhythm control in patients with AF. Quasi-randomized studies and prospective cohorts were not included. The patients' mean age had to be greater than 55 years due to the low risk of death or stroke in patients with AF under this age [4,8]. To determine the efficacy of the interventions as primary strategies, the trials had to have intention-to-treat analysis or provide data that allowed this type of calculation. The analysed outcomes were all-cause mortality, cardiovascular mortality, arrhythmic/sudden death, ischaemic stroke, systemic embolism (combining ischaemic stroke and other systemic embolic events) and major bleeding.

Validity assessment

The PEDro score was used to assess the methodological quality of data reporting in the studies [9]. This score is based on the presence/absence of 11 items: eligibility criteria, random allocation, allocation concealment, similar baseline characteristics, blinding of all subjects, blinding of therapists, blinding of outcome assessors, crossover rate less than 15%, intention-to treat analysis, statistical comparisons between groups and measures of variability.

Data abstraction

Studies that met the criteria outlined above were assessed by one review author and checked by another. AF population, study size, follow-up, primary outcome, demographic characteristics and comorbidities were retrieved. Anticoagulation therapy, and rate and rhythm interventions were also sought. Data entry into software was also double checked. All disagreements were solved by consensus.

Quantitative data synthesis

The statistical analyses were performed using the RevMan software (version 5.1.4) provided by the Cochrane Collaboration when more than one trial had data for pooled analysis. Dichotomous outcomes were analysed by the Mantel-Haenszel method. RR and 95% CI were calculated. When zero cells were present in one arm, RevMan automatically added 0.5 to them to perform the calculations. The results estimates were based on a fixed-effects model or a random effects model, depending on heterogeneity. Statistical heterogeneity was assumed if I^2 was greater than 50%. Clinical heterogeneity was analysed by authors according to

clinical differences between study patients. Publication bias assessment with a funnel plot was planned if more than 10 studies were retrieved.

Sensitivity analysis was planned according to baseline heart failure, age, anticoagulation treatment, mean follow-up and study size.

Results

One hundred and fifty-seven studies were found in the database search and 146 studies were excluded: 11 were not RCTs; 36 were not AF studies; 73 citations reported trials that did not compare pharmacological rate versus rhythm control in AF; and 26 records were substudies of eligible trials. Eleven RCTs remained and three were excluded due to lack of data necessary for analysis based on intention-to-treat.

Eight RCTs were included for meta-analysis [10—17]. Data not provided in the main papers were sought from the RACE and AFFIRM post-hoc studies (Fig. 1) [18,19].

Included studies enrolled a total of 7499 AF patients with a mean age of 68 years. In all these trials the majority of patients were men (63.4—82.0%). Prevalence of hypertension ranged from 42.8 to 64.3%, valvular disease from 4.9 to 17% and coronary disease from 7.4% to 43.5%. The AF-CHF study and the CAFÉ-II study included only heart failure patients. The PIAF study provided no heart failure data. In the other trials, the prevalence of heart failure ranged from 3.6 to 70%. Weighted mean follow-up was 2.9 years, ranging from 1 year (PIAF) to 3.5 years (AFFIRM).

The PEDro quality score (scale range 1—11) for the obtained trials varied between 6 and 7. None of the trials described allocation concealment methods and interventions were unblinded for patients and physicians. The RACE study was the only one that reported blinding of the researchers who recorded the outcomes. The PIAF and RACE studies had differences in relevant baseline characteristics. The AFFIRM and AF-CHF studies and the J-RHYTHM had crossover rates greater than 15%. Table 1 details the main characteristics of each study and Table 2 contains their conclusions.

Rate and rhythm control showed no statistical heterogeneity in any outcome. The I^2 test was 0% for all outcomes, with the exception of ischaemic stroke, which reported an I^2 of 26%. However, the authors stated that the existence of clinical heterogeneity was due to differences in the patients included in the studies. The different types of AF (paroxysmal and persistent), the existence of studies that included heart failure patients exclusively and the different therapeutic combinations/sequences used in the rate and rhythm control strategies led us to choose the random effects model for pooled analysis. A funnel plot for publication bias analysis was not done because it is not recommended when fewer than 10 studies are analysed [20].

All-cause mortality was assessed in all trials and no intervention showed significant superiority in any individual study. To determine the overall effect, a meta-analysis was done and the calculated death RR was 0.95 (95% CI: 0.86—1.05) (Fig. 2). In six trials with a total of 6615 patients, the cardiovascular mortality RR was 0.99 (95% CI: 0.87—1.13) (Fig. 3).

Table 1 Main study characteristics.

	PIAF [11]	RACE [16,18]	AFFIRM [17,19]	STAF [10]	HOT CAFÉ [13]	AF-CHF [14]	J-RHYTHM [12]	CAFÉ-II [15]
AF population	New-onset AF present for ≥ 7 days and < 1 year	Recurrent and persistent AF or flutter for < 1 year	Likely to be recurrent AF in pts aged > 65 years with risk factors for stroke or death	Recurrent and persistent AF present for ≥ 4 weeks and < 2 years with ≥ 1 previous cardioversion	AF present for ≥ 7 days and < 2 years	LVEF ≤ 35%, symptoms of CHF and history of paroxysmal or persistent AF for < 1 year	Paroxysmal and persistent AF for < 1 year	Persistent AF with chronic HF and NYHA ≥ II
No. of pts	252	522	4060	200	205	1376	823	61
Mean age (SD)	61 (10)	68 (9)	70 (9)	66 (9)	61 (11)	67	64.8 (11)	72 (7)
Men (%)	73	63.4	60.7	63.5	65.4	82	69.3	84
Hypertension (%)	48.8	50	50.8	62.5	64.3	48	42.8	70
Valvular disease (%)	16.2	17	4.9	13	15.1	5	5.6	N/A
HF (%)	N/A	50	23.1	55.5 (NYHA ≥ II)	70	100	3.6	100
CHD (%)	23.4	27	26.1	43.5	43.9	48	7.4	50
Recommended anticoagulation	All pts anticoagulated (INR 2—3)	Acenocoumarol or fenprocoumon 4 weeks before and after electrical cardioversion. Rate arm anticoagulated if age > 65 years or cardiac disease	Both arms anticoagulated; if sinus rhythm restored after 4 to 12 weeks with antiarrhythmic agents, anticoagulation could be stopped	ACCP guidelines	ACCP guidelines	Recommended for all pts: ACC/AHA/ESC 2006 AF guidelines	Modified AFFIRM protocol for non-valvular AF; Japanese guidelines on AF management for valvular AF	Recommended for all pts: warfarin (INR 2—3)
Anticoagulated pts: rate vs rhythm (%)	N/A	96 vs 86	> 85 vs 70	N/A	74.3 vs 15.6	90 pts received oral anticoagulant	59.4 vs 60.1	98

Table 1 (*Continued*)

	PIAF [11]	RACE [16,18]	AFFIRM [17,19]	STAF [10]	HOT CAFÉ [13]	AF-CHF [14]	J-RHYTHM [12]	CAFÉ-II [15]
Rate intervention	Diltiazem as initial drug	Digitalis, non-dihydropyridine calcium-channel blocker and beta-blocker	Beta-blocker, non-dihydropyridine calcium-channel blocker and digoxin	Beta-blocker, digitalis and calcium-channel blocker; AV nodal ablation or modification ± pacemaker	Beta-blocker, non-dihydropyridine calcium-channel blocker and digoxin; cardioversion or AV nodal ablation and pacemaker	Beta-blocker and digoxin; AV nodal ablation and pacemaker	Beta-blocker, calcium-channel blocker or digitalis	Digoxin and beta-blocker
Beta-blocker in rate control (%)	N/A	41	68.1	N/A	89.1	N/A	51.5	90
Rhythm intervention	Amiodarone or electrical cardioversion followed by amiodarone	Electrical cardioversion and sotalol, flecainide, propafenone or amiodarone	Many antiarrhythmic agents and/or electrical cardioversion	Electrical cardioversion and class I antiarrhythmic agents or sotalol; CHD or LV dysfunction, amiodarone	Electrical cardioversion and disopyramide, propafenone, sotalol or amiodarone	Electrical cardioversion and amiodarone (or sotalol or dofetilide)	Electrical cardioversion and antiarrhythmic agents (pilsicainide, cibenzoline, propafenone, disopyramide)	Amiodarone and electrical cardioversion
Amiodarone in rhythm control (%)	100	N/A	62.8	42	56.7	82	0.5	80
Mean years of follow-up (SD)	1	2.3 (0.6)	3.5	1.6 (0.7)	1.7 (0.4)	3.1 (1.6)	1.58	1.2[a]
PEDro score	6	7	6	7	7	6	6	7

ACC: American College of Cardiology; ACCP: American College of Chest Physicians; AF: atrial fibrillation; AFFIRM: Atrial Fibrillation Follow-up Investigation of Rhythm Management study; AF-CHF: Atrial Fibrillation and Congestive Heart Failure study; AHA: American Heart Association; AV: atrioventricular; CAFÉ-II: controlled study of rate versus rhythm control in patients with chronic AF and HF; CHD: coronary heart disease; CHF: congestive heart failure; ESC: European Society of Cardiology; HF: heart failure; HOT CAFÉ: How to Treat Chronic Atrial Fibrillation study; INR: international normalized ratio; J-RHYTHM: Japanese Rhythm Management Trial for Atrial Fibrillation; LV: left ventricular; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; N/A: not available; PIAF: Pharmacological Intervention in Atrial Fibrillation study; pts: patients; RACE: Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation study; SD: standard deviation; STAF: Strategies of Treatment of Atrial Fibrillation study.
[a] Median.

Table 2 Data and results from individual studies.

Trial	Population	Rate control (n)	Rhythm control (n)	Primary outcome	Conclusions
PIAF	New-onset AF present for ≥ 7 days and < 1 year	125	127	Improvement in AF-related symptoms (palpitations and frequency of dyspnoea or dizziness)	No differences in primary outcome and quality of life; rhythm control better in exercise tolerance
RACE	Recurrent persistent AF or flutter for < 1 year	256	266	Composite of cardiovascular death, heart failure, embolism, bleeding, pacemaker implantation and severe adverse effects of drugs	No statistically significant differences in primary outcome; rate superior to rhythm control in women and hypertensive subgroups
AFFIRM	Likely to be recurrent AF in pts aged > 65 years with risk factors for stroke or death	2027	2033	All-cause mortality	No differences in primary outcome; rate control prevented mortality in age > 65 years, coronary artery disease and no HF group[s?]; rate control also better at reducing hospitalization
STAF	Recurrent and persistent AF present for > 4 weeks and < 2 years with ≥ 1 previous cardioversion	100	100	Composite of all-cause mortality, cerebrovascular events, embolism and cardiopulmonary resuscitation	No primary outcome advantage with rate or rhythm control; quality of life improved in two topics with rhythm control and five topics with rate control
HOT CAFÉ	AF present for ≥ 7 days and < 2 years	101	104	Composite of all-cause mortality and thromboembolic and major bleeding complications	No significant differences in primary outcome; hospitalizations lower in rate control
AF-CHF	LVEF $\leq 35\%$, symptoms of CHF and history of paroxysmal or persistent AF for < 1 year	694	682	Cardiovascular death	Primary outcome similar with both interventions; hospitalizations more frequent in rhythm control
J-RHYTHM	Paroxysmal and persistent AF for < 1 year	404	419	Composite of total mortality, symptomatic cerebral infarction, systemic embolism, major bleeding, hospitalization for heart failure and physical/psychological disabilities	Rhythm control reduced the incidence of the primary outcome and improved the frequency of symptoms score
CAFÉ-II	Persistent AF with chronic HF and NYHA $\geq$ II	31	30	QoL SF-36vII at 1 year	Rhythm control improved the primary outcome

AF: atrial fibrillation; AFFIRM: Atrial Fibrillation Follow-up Investigation of Rhythm Management study; AF: atrial fibrillation; AF-CHF: Atrial Fibrillation and Congestive Heart Failure study; CAFÉ-II: controlled study of rate versus rhythm control in patients with chronic AF and HF; CHF: congestive heart failure; HF: heart failure; HOT CAFÉ: How to Treat Chronic Atrial Fibrillation study; J-RHYTHM: Japanese Rhythm Management Trial for Atrial Fibrillation; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association class; PIAF: Pharmacological Intervention in Atrial Fibrillation study; pts: patients; QoL SF-36vII: Quality of Life Short Form-36 version II; RACE: Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation study; STAF: Strategies of Treatment of Atrial Fibrillation study.
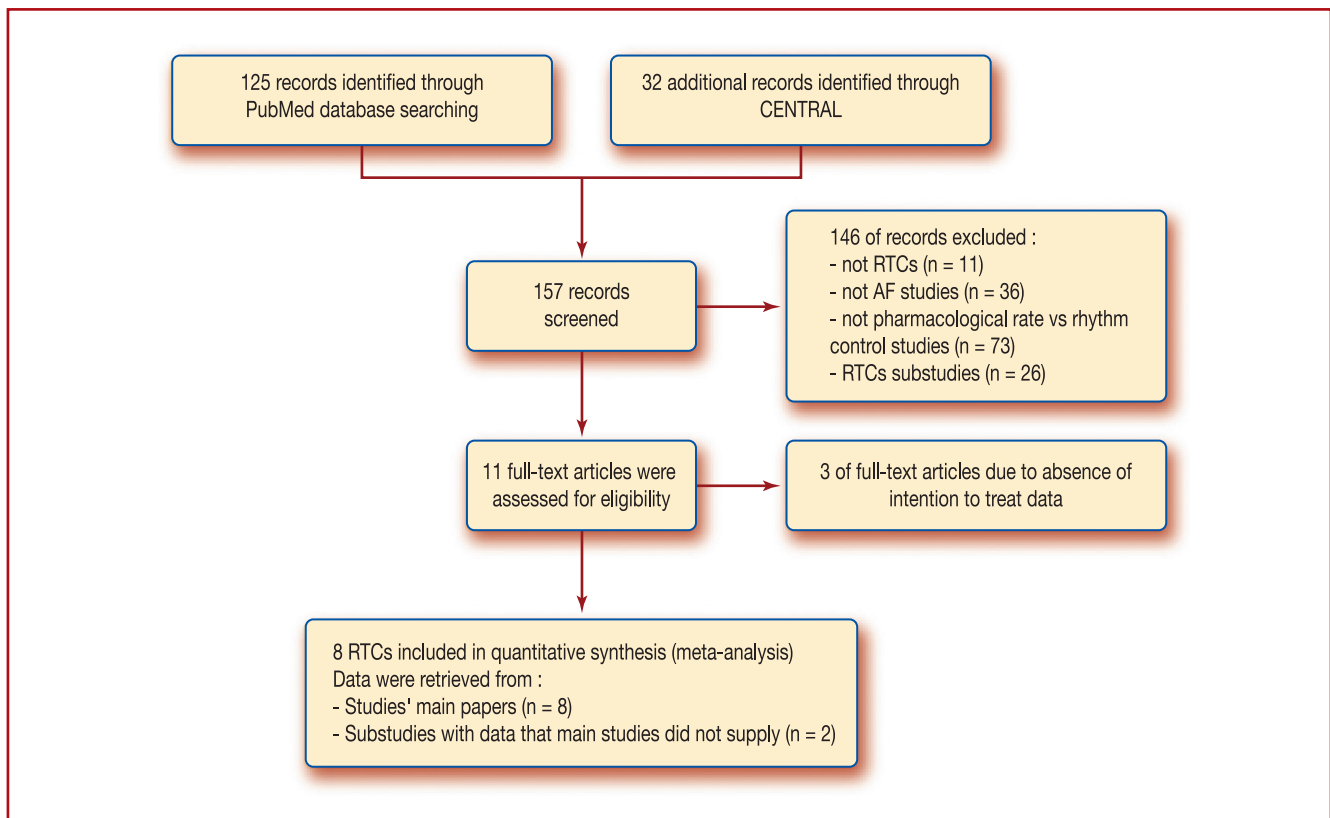
Figure 1.	Flowchart of study selection for meta-analysis. AF: atrial fibrillation; CENTRAL: Cochrane Central Register of Controlled Trials; RCTs: randomized controlled trials.
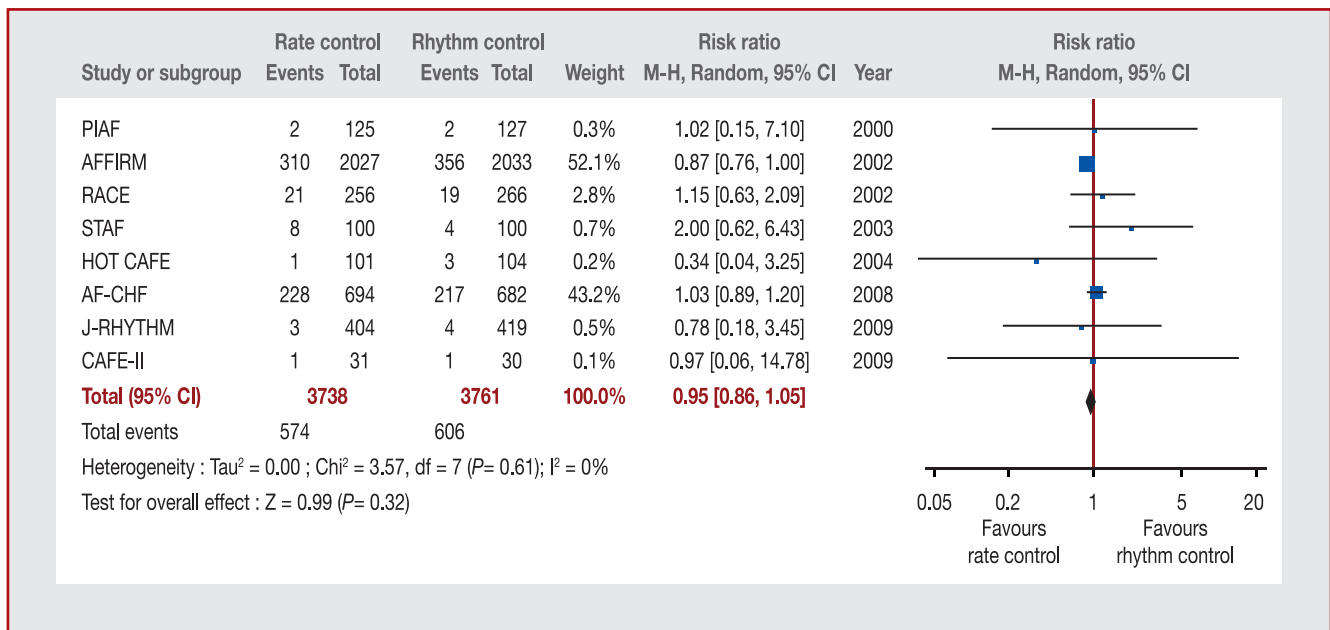
Figure 2.	Forest plot for all-cause mortality. AFFIRM: Atrial Fibrillation Follow-up Investigation of Rhythm Management study; AF-CHF: Atrial Fibrillation and Congestive Heart Failure study; CAFÉ-II: controlled study of rate versus rhythm control in patients with chronic atrial fibrillation and heart failure; CI: confidence interval; HOT CAFÉ: How to Treat Chronic Atrial Fibrillation study; J-RHYTHM: Japanese Rhythm Management Trial for Atrial Fibrillation; M-H: Mantel-Haenszel; PIAF: Pharmacological Intervention in Atrial Fibrillation study; RACE: Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation study; STAF: Strategies of Treatment of Atrial Fibrillation study.

Study or subgroup	Rate control		Rhythm control		Weight	Risk ratio M-H, Random, 95% CI	Year	Risk ratio M-H, Random, 95% CI
	Events	Total	Events	Total				
PIAF	2	125	2	127	0.5%	1.02 [0.15, 7.10]	2000	
AFFIRM	167	2027	164	2033	40.2%	1.02 [0.83, 1.26]	2002	
RACE	18	256	18	266	4.3%	1.04 [0.55, 1.95]	2002	
STAF	8	100	3	100	1.0%	2.67 [0.73, 9.76]	2003	
HOT CAFE	0	101	2	104	0.2%	0.21 [0.01, 4.24]	2004	
AF-CHF	175	694	182	682	53.7%	0.94 [0.79, 1.13]	2008	
CAFE-II	1	31	0	30	0.2%	2.91 [0.12, 68.66]	2009	
Total (95% CI)		3334		3342	100.0%	0.99 [0.87, 1.13]		
Total events	371		371					

Heterogeneity : Tau^2 = 0.00 ; Chi^2 = 4.10, df = 6 (P= 0.66); I^2 = 0%

Test for overall effect : Z = 0.17 (P= 0.86)

Figure 3. Forest plot for cardiovascular mortality. AFFIRM: Atrial Fibrillation Follow-up Investigation of Rhythm Management study; AF-CHF: Atrial Fibrillation and Congestive Heart Failure study; CAFÉ-II: controlled study of rate versus rhythm control in patients with chronic atrial fibrillation and heart failure; CI: confidence interval; HOT CAFÉ: How to Treat Chronic Atrial Fibrillation study; M-H: Mantel-Haenszel; PIAF: Pharmacological Intervention in Atrial Fibrillation study; RACE: Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation study; STAF: Strategies of Treatment of Atrial Fibrillation study.
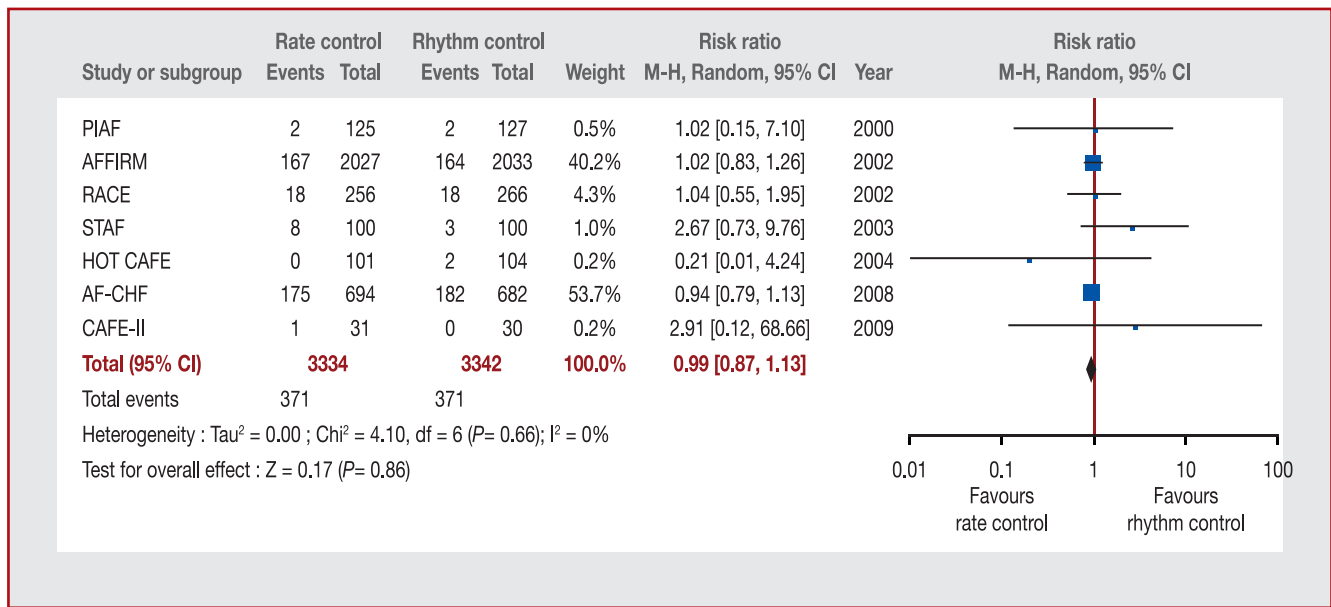
The arrhythmic/sudden death RR was 1.12 (95% CI: 0.91–1.38) among 6410 patients in five studies (Fig. 4). Ischaemic stroke data was retrieved from four trials with a total of 5288 patients, with a pooled analysis RR of 0.89 (95% CI: 0.52–1.53) (Fig. 5). Six trials with 6062 patients evaluated systemic embolism (which included ischaemic strokes and other systemic embolic events) and the RR was 0.89 (95% CI: 0.69–1.14) (Fig. 6). Major bleeding also showed no significant differences in results pooled from five RCTs that enrolled 5810 patients; the RR was 1.10 (95%

CI: 0.89–1.36) (Fig. 7). Table 3 presents a summary of the findings.

A sensitivity analysis was done according to variables such as heart failure, mean age, anticoagulation treatment, mean follow-up period and study size, as shown in Table 4. Pooled systemic embolic events were significantly less frequent with rate control when trials with more than 50% of patients with heart failure were analysed. The PIAF, AFFIRM and J-RHYTHM studies were excluded for this reason. The RR was 0.43 (95% CI: 0.21–0.89).

Study or subgroup	Rate control		Rhythm control		Weight	Risk ratio M-H, Random, 95% CI	Year	Risk ratio M-H, Random, 95% CI
	Events	Total	Events	Total				
PIAF	0	125	1	127	0.4%	0.34 [0.01, 8.23]	2000	
RACE	8	256	8	266	4.5%	1.04 [0.40, 2.73]	2002	
AFFIRM	79	2027	77	2033	44.7%	1.03 [0.76, 1.40]	2002	
STAF	4	100	2	100	1.5%	2.00 [0.37, 10.67]	2003	
AF-CHF	88	694	71	682	48.9%	1.22 [0.91, 1.63]	2008	
Total (95% CI)		3202		3208	100.0%	1.12 [0.91, 1.38]		
Total events	179		159					

Heterogeneity : Tau^2 = 0.00 ; Chi^2 = 1.63, df = 4 (P= 0.80); I^2 = 0%

Test for overall effect : Z = 1.11 (P= 0.27)

Figure 4. Forest plot for arrhythmic/sudden death mortality. AFFIRM: Atrial Fibrillation Follow-up Investigation of Rhythm Management study; AF-CHF: Atrial Fibrillation and Congestive Heart Failure study; CI: confidence interval; M-H: Mantel-Haenszel; PIAF: Pharmacological Intervention in Atrial Fibrillation study; RACE: Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation study; STAF: Strategies of Treatment of Atrial Fibrillation study.

Table 3   Summary of findings.

Outcome	Studies	Total patients (n)	Rate control patients (n)	Rhythm control patients (n)	Random effects (RR [95% CI])	Fixed-effects (RR [95% CI])	Heterogeneity I² (%)
All-cause mortality	8	7499	3738	3761	0.95 [0.86—1.05]	0.94 [0.84—1.04]	0
Cardiovascular mortality	7	6676	3334	3342	0.99 [0.87—1.13]	0.99 [0.87—1.13]	0
Arrhythmic/sudden death	5	6410	3202	3208	1.12 [0.91—1.38]	1.12 [0.91—1.38]	0
Ischaemic stroke	4	5288	2632	2656	0.89 [0.52—1.53]	0.92 [0.70—1.23]	26
Systemic embolism	6	6062	3013	3049	0.89 [0.69—1.14]	0.88 [0.68—1.12]	0
Major bleeding	5	5810	2888	2922	1.10 [0.89—1.36]	1.10 [0.89—1.36]	0

CI: confidence interval; RR: risk ratio.

Table 4   Sensitivity analysis.

Subgroup	Risk ratio [95% CI]				
	Mortality	Cardiovascular mortality	Ischaemic stroke	Systemic embolism	Major bleeding
≥ 50% of patients with HF [10,13—16]	1.04 [0.90—1.21]	0.97 [0.82—1.15]	0.18 [0.03—1.01]	0.43 [0.21—0.89]	1.01 [0.54—1.90]
Exclusively patients with HF [14,15]	1.03 [0.89—1.20]	0.95 [0.79—1.13]	N/A	N/A	N/A
Mean age ≥ 65 years [10,14—17]	0.96 [0.85—1.08]	0.99 [0.87—1.13]	0.63 [0.16—2.49]	0.71 [0.40—1.26]	1.11 [0.89—1.37]
Mean age < 65 years [11—13]	0.70 [0.25—2.00]	0.64 [0.12—3.27]	0.69 [0.10—4.78]	1.06 [0.52—2.18]	0.52 [0.05—5.70]
Recommended anticoagulation for all patients [11,14,15]	1.03 [0.89—1.20]	0.95 [0.79—1.13]	N/A	N/A	N/A
Follow-up ≥ 2 years [14,16,17]	0.96 [0.83—1.10]	0.98 [0.86—1.12]	N/A	0.74 [0.37—1.47]	1.14 [0.91—1.42]
< 200 patients per arm [10,11,13,15]	1.25 [0.53—2.97]	1.63 [0.62—4.29]	0.18 [0.03—1.01]	0.52 [0.17—1.53]	0.73 [0.31—1.73]
≥ 200 patients per arm [12,14,16,17]	0.95 [0.86—1.05]	0.98 [0.86—1.12]	0.99 [0.74—1.33]	0.87 [0.57—1.34]	1.13 [0.91—1.41]
Excluding AFFIRM and AF-CHF	1.13 [0.71—1.81]	1.19 [0.70—2.01]	0.50 [0.11—2.30]	0.70 [0.42—1.19]	0.97 [0.54—1.75]

AFFIRM: Atrial Fibrillation Follow-up Investigation of Rhythm Management study; AF-CHF: Atrial Fibrillation and Congestive Heart Failure study; CI: confidence interval; HF: heart failure; N/A: not available.
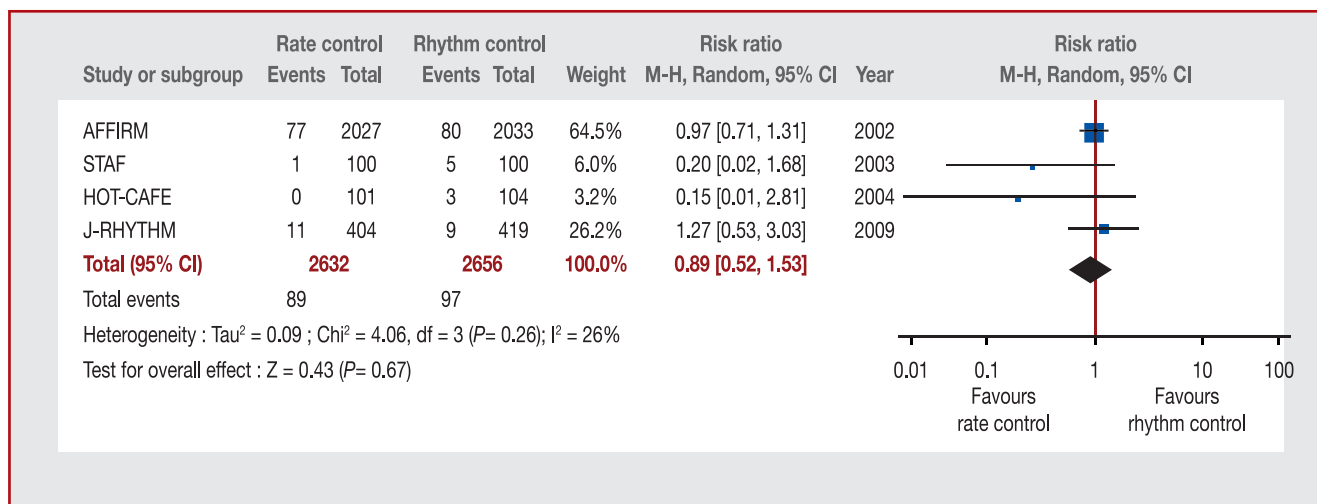
Study or subgroup	Rate control Events	Total	Rhythm control Events	Total	Weight	Risk ratio M-H, Random, 95% CI	Year
AFFIRM	77	2027	80	2033	64.5%	0.97 [0.71, 1.31]	2002
STAF	1	100	5	100	6.0%	0.20 [0.02, 1.68]	2003
HOT-CAFE	0	101	3	104	3.2%	0.15 [0.01, 2.81]	2004
J-RHYTHM	11	404	9	419	26.2%	1.27 [0.53, 3.03]	2009
Total (95% CI)		**2632**		**2656**	**100.0%**	**0.89 [0.52, 1.53]**	
Total events	89		97				

Heterogeneity : Tau^2 = 0.09 ; Chi^2 = 4.06, df = 3 (P= 0.26); I^2 = 26%

Test for overall effect : Z = 0.43 (P= 0.67)

Figure 5. Forest plot for ischaemic stroke. AFFIRM: Atrial Fibrillation Follow-up Investigation of Rhythm Management study; CI: confidence interval; HOT CAFÉ: How to Treat Chronic Atrial Fibrillation study; J-RHYTHM: Japanese Rhythm Management Trial for Atrial Fibrillation; M-H: Mantel-Haenszel; STAF: Strategies of Treatment of Atrial Fibrillation study.

Discussion

This systematic review with meta-analysis was done to assess the direction, size and consistency of effects across RCTs comparing rate versus rhythm control in AF.

In a previous meta-analysis, rate and rhythm control strategies were not significantly different in terms of mortality but a trend towards rate control was observed in patient survival (odds ratio 0.87 [95% CI: 0.74—1.02]; P= 0.09) [21]. Statistically significant results favouring rate control with regard to a mortality-stroke composite have been reported in another meta-analysis (odds ratio 0.84 [95% CI: 0.73—0.98]; P= 0.02) [22]. Under these circumstances and with new RCTs, it is important to clarify which is the best treatment strategy according to the best available evidence. Our meta-analysis included these new RCTs and provides updated results that answer with more powered information whether rate or rhythm control is better for treating these patients.

None of the strategies showed superiority in the outcomes assessed. Although the results of individual studies did not show clear differences, the performance of the meta-analysis ensured the consistency of findings for a large population, especially when approaching very important clinical outcomes.
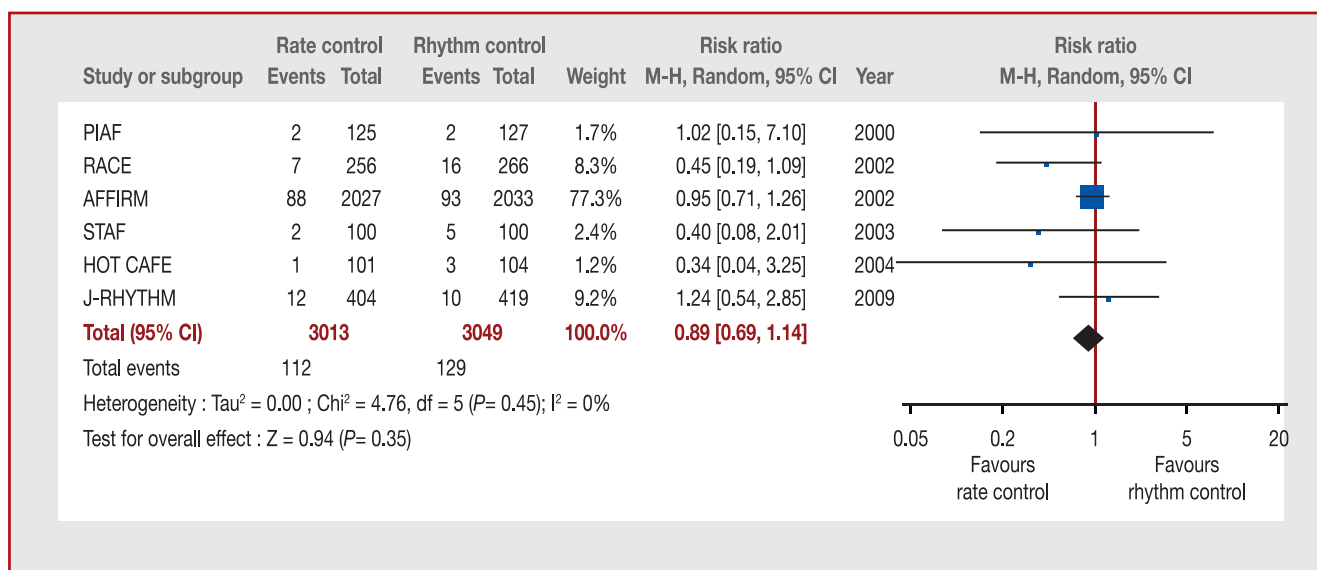

Study or subgroup	Rate control Events	Total	Rhythm control Events	Total	Weight	Risk ratio M-H, Random, 95% CI	Year
PIAF	2	125	2	127	1.7%	1.02 [0.15, 7.10]	2000
RACE	7	256	16	266	8.3%	0.45 [0.19, 1.09]	2002
AFFIRM	88	2027	93	2033	77.3%	0.95 [0.71, 1.26]	2002
STAF	2	100	5	100	2.4%	0.40 [0.08, 2.01]	2003
HOT CAFE	1	101	3	104	1.2%	0.34 [0.04, 3.25]	2004
J-RHYTHM	12	404	10	419	9.2%	1.24 [0.54, 2.85]	2009
Total (95% CI)		**3013**		**3049**	**100.0%**	**0.89 [0.69, 1.14]**	
Total events	112		129				

Heterogeneity : Tau^2 = 0.00 ; Chi^2 = 4.76, df = 5 (P= 0.45); I^2 = 0%

Test for overall effect : Z = 0.94 (P= 0.35)

Figure 6. Forest plot for systemic embolism. AFFIRM: Atrial Fibrillation Follow-up Investigation of Rhythm Management study; AF-CHF: Atrial Fibrillation and Congestive Heart Failure study; CI: confidence interval; HOT CAFÉ: How to Treat Chronic Atrial Fibrillation study; J-RHYTHM: Japanese Rhythm Management Trial for Atrial Fibrillation; M-H: Mantel-Haenszel; PIAF: Pharmacological Intervention in Atrial Fibrillation study; RACE: Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation study; STAF: Strategies of Treatment of Atrial Fibrillation study.
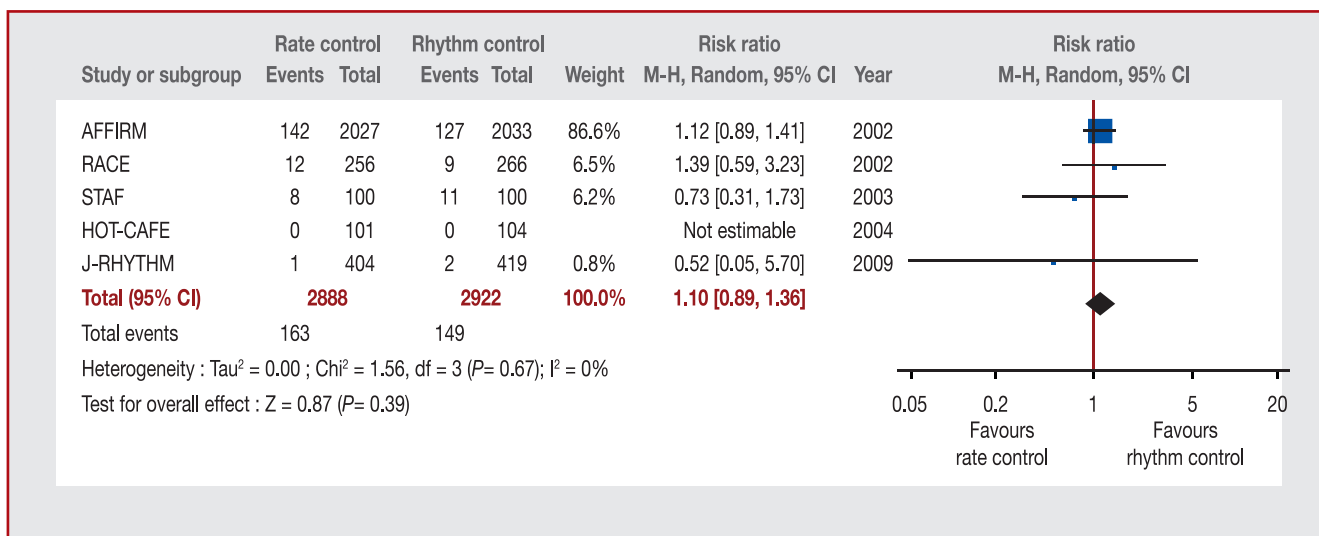
Study or subgroup	Rate control Events	Total	Rhythm control Events	Total	Weight	Risk ratio M-H, Random, 95% CI	Year	Risk ratio M-H, Random, 95% CI
AFFIRM	142	2027	127	2033	86.6%	1.12 [0.89, 1.41]	2002	
RACE	12	256	9	266	6.5%	1.39 [0.59, 3.23]	2002	
STAF	8	100	11	100	6.2%	0.73 [0.31, 1.73]	2003	
HOT-CAFE	0	101	0	104		Not estimable	2004	
J-RHYTHM	1	404	2	419	0.8%	0.52 [0.05, 5.70]	2009	
Total (95% CI)		2888		2922	100.0%	1.10 [0.89, 1.36]		
Total events	163		149					

Heterogeneity : Tau² = 0.00 ; Chi² = 1.56, df = 3 (P= 0.67); I² = 0%

Test for overall effect : Z = 0.87 (P= 0.39)

Favours rate control   Favours rhythm control

0.05   0.2   1   5   20

Figure 7.   Forest plot for major bleeding. AFFIRM: Atrial Fibrillation Follow-up Investigation of Rhythm Management study; CI: confidence interval; HOT CAFÉ: How to Treat Chronic Atrial Fibrillation study; J-RHYTHM: Japanese Rhythm Management Trial for Atrial Fibrillation; M-H: Mantel-Haenszel; RACE: Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation study; STAF: Strategies of Treatment of Atrial Fibrillation study.

Despite the cardiovascular consequences of AF, we considered it important to assess all-cause mortality to include possible non-cardiovascular deaths caused by antiarrhythmic drugs. Amiodarone, which can induce pulmonary toxicity, was prescribed to most patients in four of the six trials that reported data on antiarrhythmic agent use (Table 1). In the AFFIRM analysis of cause-specific mortality, non-cardiovascular deaths were mainly due to pulmonary diseases and lung cancer. Pneumonia was the most common cause of pulmonary death in both interventions. Pulmonary toxicity of amiodarone was the cause of death in only three of 39 patients in the rhythm intervention who died due to lung diseases [19]. The incidence of this effect may be more important, as AF needs to be treated longer than the mean follow-up of this study and the long-term incidence of amiodarone toxicity events is likely to be higher.

Cardiovascular mortality was 63% of the total mortality of all trials and the incidence of this outcome was shown to be independent of the intervention strategy. In AFFIRM, arrhythmias were the main cause of cardiovascular mortality, probably due to the high incidence of atherosclerotic risk factors and ischaemic heart disease in patients with AF [19,23]. In a post-hoc analysis of the RACE trial, myocardial infarction history was the baseline characteristic more frequently associated with sudden deaths [18]. The two therapeutic strategies were not significantly different with regard to arrhythmic/sudden death, although there was a slight tendency favouring rhythm control; this was surprising because beta-blockers (used in 41% and 68.1% of RACE and AFFIRM rate control patients, respectively) have been shown to prevent sudden death in patients with previous myocardial infarction [24]. Nevertheless, AF subgroup analysis of the US Carvedilol Heart Failure Trials Program showed that these drugs had no advantage in reducing mortality in these patients [25]. Antiarrhythmics used to restore and maintain sinus rhythm have been shown previously to be ineffective in sudden death prevention [26,27]. However, an increase in arrhythmic/sudden death adverse effect was not observed and a trend towards rhythm control preventing this outcome was seen.

AF itself can be considered as a prothrombotic state and cumulative thrombotic risk factors play an important role in these patients [28,29]. Rate control groups had protocols that favoured the maintenance of anticoagulant therapy. At the end of all studies, with exception of J-RHYTHM, the rhythm control group had fewer anticoagulated patients than the rate control sample. Recurrence of AF and anticoagulation withdrawal may explain the trend favouring rate control in ischaemic stroke and systemic embolism outcomes. Vitamin K antagonists were the chosen drugs for anticoagulation. These drugs have a narrow therapeutic window with major bleeding incidence rates ranging from 1.4 to 13 per 100 patient-years [30]. Major bleeding incidence was not different between the interventions but there was a tendency favouring rhythm control; this was expected because anticoagulant therapy is a well-known risk factor for bleeding and rate control patients were more frequently treated with anticoagulants.

Sensitivity analysis showed that rate control was better at preventing embolic events in a pooled analysis of studies with more than 50% of patients with heart failure. Heart failure is a component of the CHADS$_2$ score and adequate anticoagulation may have produced this result favouring rate control. A pooled analysis of results from the HOT CAFÉ, STAF and RACE studies was done. None of these trials had both arms anticoagulated during study follow-up. In these studies, rhythm control patients were less likely to receive oral anticoagulation. As AF may have a structural origin and arrhythmia recurrence is frequent, premature or inadequate withdrawal of oral anticoagulants in the rhythm control arm could have predisposed towards thromboembolic events. More recently, AF-CHF, an RCT that exclusively analysed patients with heart failure with both rate and rhythm control arms under anticoagulation, showed that stroke was

similar between interventions (hazard ratio 0.74 [95% CI: 0.40–1.35]).

Eight RCTs were included in the meta-analysis, but most of the statistical weight came from AFFIRM and AF-CHF. A sensitivity analysis excluding these trials was done. A pooled analysis of the smaller studies showed the same result as the primary analysis (Table 4). It is interesting that when trials with a mean patient age less than 65 years were analysed, there was a trend towards rate control. The analysed population may not be sufficiently young to be representative of younger/middle-aged symptomatic patients, for whom the primary policy would be to restore and maintain sinus rhythm.

In the absence of a clear benefit for one intervention in the analysed outcomes, other factors should be considered for strategy choice, such as individual preferences, comorbidities, drug tolerance and cost issues; regarding this last factor, cost-effectiveness studies favoured the rate control strategy [31–33].

Implications for clinical practice and research

All-cause mortality and cardiovascular mortality analysis showed no trend towards either intervention and had small CIs. In the other outcomes, with larger CIs, there was a tendency for rate control to be better in the prevention of ischaemic stroke and systemic embolism, while prevention of arrhythmic/sudden death and major bleeding tended towards rhythm control. These last data were not statistically significant but can be clinically relevant when applied to the individual patient, tailoring the approach according to their characteristics.

Limitations

This review includes a meta-analysis of RCTs. Results were pooled from reported outcomes and not from individual patient data, which is a potential source of bias in this type of analysis.

Heterogeneity of clinical characteristics and interventions across the various studies are important limitations despite the random effects method used in quantitative analysis.

All RCTs included in this meta-analysis were unblinded. This may be explained by the physical nature of electrical cardioversion that is very distinct from rate control standard procedures. The use of fake electrical cardioversion for blinding would raise ethical issues and would interfere with other outcomes measured in some studies, such as quality of life and number of hospitalizations.

In the arrhythmic/sudden death outcome, we included presumable arrhythmic deaths from AF-CHF, arrhythmic deaths from AFFIRM and sudden deaths from the other trials.

For studies that did not supply data for systemic embolism, the information was calculated by adding ischaemic stroke to systemic embolism. Ischaemic stroke can be either embolic or thrombotic but most ischaemic strokes in AF patients have a cardiac embolic source [34].

Conclusion

In this review, rate and rhythm control options did not differ in terms of all-cause mortality, cardiovascular mortality, arrhythmic/sudden death, ischaemic stroke, systemic embolism and major bleeding. The large population of patients with AF from which quantitative data was obtained allowed us to robustly reinforce the conclusions that rate and rhythm control are similar in terms of clinical outcomes. This supports guidelines' class I recommendations for rate and rhythm control strategies [35,36]. Both are acceptable alternatives for patients with AF and the initial clinical choice should be individualized according to patient preferences, AF symptoms, AF recurrence risk, comorbidities, tolerance to antiarrhythmic drugs and expected costs.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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