Biomedical & Pharmacology Journal, June 2018. Vol. **11**(2), p. 609-620

Rhythm Versus Rate Control for Atrial Fibrillation: A Meta-analysis of Randomized Controlled Trials

Abdelrahman Ibrahim Abushouk[1,2‡], Aya Ashraf Ali[3,4‡], Ahmed Abdou Mohamed[3,4‡], Loalo'a El-Sherif[3,4], Menna Abdelsamed[4,5], Mohamed Kamal[4,5], Merhan Kamal Sayed[3,4], Nehal Alaa Mohamed[3,4], Ahmed Abdelbaset Osman[3,4], Sameh M Shaheen[1] and Mohamed M. Abdel-Daim[6]

[1]Faculty of Medicine, Ain Shams University, Cairo, Egypt.
[2]NovaMed Medical Research Association, Cairo, Egypt.
[3]Faculty of Medicine, Minia University, Minia, Egypt.
[4]Minia Medical Research Society, Minia University, Minia, Egypt.
[5]Faculty of Pharmacy, Minia University, Minia, Egypt.
[6]Faculty of Veterinary Medicine, Suez Canal University, Ismailia, Egypt.
[‡]these members contributed equally.
*Correspondence author E-mail: Abdeldaim.m@vet.suez.edu.eg

http://dx.doi.org/10.13005/bpj/1413

(Received: 09 April 2018; accepted: 22 May 2018)

Atrial fibrillation (AF) is a common, sustained tachyarrhythmia, associated with an increased risk of mortality and thromboembolic events. We performed this meta-analysis to compare the clinical efficacy of rate and rhythm control strategies in patients with AF in a meta-analysis framework. A comprehensive search of PubMed, OVID, Cochrane-CENTRAL, EMBASE, Scopus, and Web of Science was conducted, using relevant keywords. Dichotomous data on mortality and other clinical events were extracted and pooled as risk ratios (RRs), with their 95% confidence-interval (CI), using RevMan software (version 5.3). Twelve studies (8451 patients) were pooled in the final analysis. The overall effect-estimate did not favor rate or rhythm control strategies in terms of all-cause mortality (RR= 1.13, 95% CI [0.88, 1.45]), stroke (RR= 0.97, 95% CI [0.79, 1.20]), thromboembolism (RR= 1.06, 95% CI [0.64, 1.76]), and major bleeding (RR= 1.10, 95% CI [0.90, 1.35]) rates. These findings were consistent in AF patients with concomitant heart failure (HF). The rate of rehospitalization was significantly higher (RR= 0.72, 95% CI [0.57, 0.92]) in the rhythm control group, compared to the rate control group. In younger patients (<65 years), rhythm control was superior to rate control in terms of lowering the risk of all-cause mortality (p=0.0003), HF (p=0.003) and major bleeding (p=0.02). In older AF patients and those with concomitant HF, both rate and rhythm control strategies have similar rates of mortality and major clinical outcomes; therefore, choosing an appropriate strategy should consider individual variations, such as patient preferences, comorbidities, and treatment cost.

Keywords: Atrial Fibrillation; Meta-analysis; Rate Control; Rhythm Control.

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, affecting more than 5% of the worldwide population[1]. It is associated with a high risk of thromboembolic events, including stroke, which occurs in about 23% of AF patients, older than 80 years[2,3]. Over the last decade, it accounted for about one third of hospital admissions for cardiac arrhythmias[4,5]

with an increasing prevalence in patients with cardiovascular problems, such as valvular heart disease, heart failure (HF), and coronary artery disease (CAD)[6,7].

The pharmacological management of AF targets either rate control (maintaining the heart rate at normal levels, using pharmacological agents, such as beta-blockers, non-dihydropyridine calcium-channel blocker, and cardiac glycosides) or rhythm control (restoration of sinus rhythm, using electrical cardioversion and/or antiarrhythmic agents, such as sodium channel blockers and potassium channel blockers)[8]. In the past few years, several randomized controlled trials (RCTs) have investigated whether rhythm control is superior to rate control with respect to mortality and cerebrovascular accidents[9–22].

Besides the controversial results of these trials, former meta-analyses showed conflicting results, suggesting that rate control is either similar or superior to rhythm control in terms of mortality and stroke rates[23,24]. Moreover, recent trials have compared both strategies in different groups of AF patients, including younger and those with concomitant HF[9,12]. Therefore, we conducted this systematic review and meta-analysis to update the evidence regarding the optimal control approach for AF.

METHODS

This study was conducted following the guidelines of the Cochrane handbook of systematic reviews of interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[25,26]. All steps have been prespecified in a published protocol on the PROSPERO register of systematic reviews (CRD42016049648).

Literature Search strategy

We performed a comprehensive search of PubMed, Scopus, Web of Science (ISI), Embase, OVID and Cochrane Central register of controlled clinical trials (CENTRAL), during September 2016, to identify relevant studies. We developed the search strategy for each database using the following terms: "Atrial fibrillation", "Rate control", "Beta blockers", "Calcium channel blockers", "Antiarrhythmic", "Cardioversion", and "Rhythm control" (*Supplementary file 1*). No publication period or language restrictions were applied during literature search. We also checked the bibliography of included studies and searched the clinical trials registry (Clinicaltrials.gov) for any ongoing trials.

Eligibility Criteria and Study Selection

We included all RCTs that compared the efficacy of rate control versus rhythm control strategies, including non-invasive procedures of electrical cardioversion, in AF patients. We excluded trials on other types of atrial arrhythmia, such as atrial flutter, reviews, non-randomized trials, observational, and studies from which data could not be reliably extracted.

Three reviewers independently screened the retrieved titles and abstracts for matching our criteria. Then, the eligible abstracts underwent further full-text screening for eligibility to meta-analysis. Unrelated or duplicate reports were removed and multiple reports for the same trial were linked together as one study. All disagreements were solved by discussion between the reviewers.

Data Extraction

Data was extracted from included studies by one reviewer and checked by another one. The extracted data included the following: a) baseline characteristics of enrolled patients, b) risk of bias assessment domains, and c) main outcomes including the incidence of all-cause mortality, cardiovascular mortality, arrhythmic mortality, stoke or transient ischemic attack (TIA), systemic embolism, HF or worsening of HF, major or life threatening bleeding, re-hospitalization and subsequent myocardial infarction (MI).

Risk of Bias Assessment

Two independent reviewers assessed the risk of bias in included trials, using the Cochrane risk of bias (ROB) assessment tool[25]. This tool is designed to detect six types of bias: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other potential sources of bias. The authors classified the included studies in each domain as of low, high, or unclear risk of bias. The risk of publication bias was assessed, using funnel plot-based methods, whenever 10 or more studies reported on the same outcome[27].

Data synthesis

The statistical analyses were performed using the RevMan software (version 5.3 for windows), provided by the Cochrane Collaboration.

Under the fixed-effect model, dichotomous data were pooled as risk ratios (RRs) with their 95% confidence interval (CI), using the Mantel-Haenszel (M-H) method. The existence of heterogeneity was assessed by Chi-square test and its extent was measured by I-square test. In case of significant heterogeneity (Chi-square $p < 0.1$), the analysis was conducted under the random-effects model. Sensitivity analysis was performed to resolve significant heterogeneity and to ensure that our results were not affected by the weights of individual studies. We also conducted subgroup analyses to compare both strategies in patients with HF or under 65 years of age (by pooling studies in which the mean age was less than 65 years).

RESULTS

Literature search and screening process

A comprehensive database search retrieved 3879 unique records. Following title and abstract screening, 74 full-text articles were retrieved for assessment of eligibility to meta-analysis. Finally, we included 12 RCTs (14 full text articles: 8451 patients) that compared rate control to rhythm control in AF patients (9–22) (*Figure 1*). *Table 1* displays a summary of the used drugs and main findings of included studies and *Table 2* shows baseline characteristics of enrolled patients in these studies.

Risk of Bias Assessment

All included studies had a low risk of selection (random sequence generation), attrition, and reporting biases, except for the AFFIRM trial[20,21] (which did not clarify their randomization method), as well as CAFÉ II (16) and RACE[15,22] trials (which had an unclear risk of reporting bias). None of the included studies achieved or reported on blinding of patients and personnel or the blinding of outcome assessors. *Figure 2* shows a summary of the results of ROB assessment for each included study and the details of authors' judgements are illustrated in *Supplementary file 2*.

Clinical Outcomes

All-Cause Mortality

The pooled effect estimate of 12 studies (8451 patients)[9–22], under the random-effects model, showed no significant difference between rate and rhythm control group (RR = 1.13, 95% CI [0.88, 1.45], p = 0.32) in terms of all-cause mortality. Pooled studies were heterogeneous ($p = 0.04$, $I^2 = 46\%$) *Figure 3a*. Heterogeneity was best resolved ($p = 0.21$, $I^2 = 24\%$) by excluding the study by Okcun *et al* (2004), while the overall estimate remained non-significant (p = 1). A symmetrical funnel plot showed no evidence of publication bias.

Cardiovascular Mortality

The pooled effect estimate of seven studies (6676 patients) (9,11,12,15,16,19,20) showed comparable rates of cardiovascular mortality (RR = 1, 95% CI [0.88, 1.14], p = 0.97) between both groups. Pooled studies were homogenous ($p = 0.69$, $I^2 = 0\%$); *Figure 3b*.

Arrhythmic Mortality

The pooled effect estimate of five studies (6410 patients) (9,12,15,19,20) showed

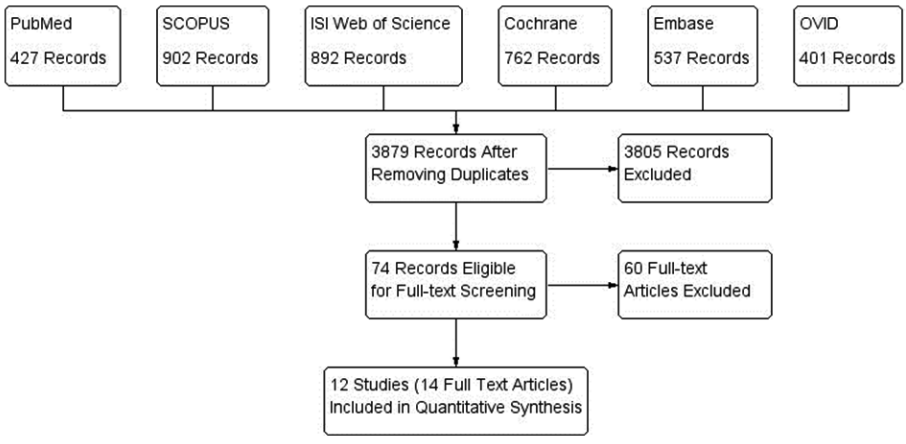

Fig. 1. PRISMA flow diagram of literature search and study selection

no significant difference (RR = 1.12, 95% CI [0.91, 1.38], p = 0.28) between both groups in terms of arrhythmic mortality. Pooled studies were homogenous (p = 0.80, I^2 = 0%); *Figure 3c*.

Stoke/TIA

The overall risk ratio of 10 included studies (8138 patients) (9–15,17,18,20–22) did not favor either of the two groups (RR = 0.97, 95% CI [0.79, 1.20], p = 0.77) in terms of the incidence of stroke/TIA. Pooled studies were homogenous (p = 0.27, I^2 = 19%). A symmetrical funnel plot showed no evidence of publication bias; *Figure 4a*.

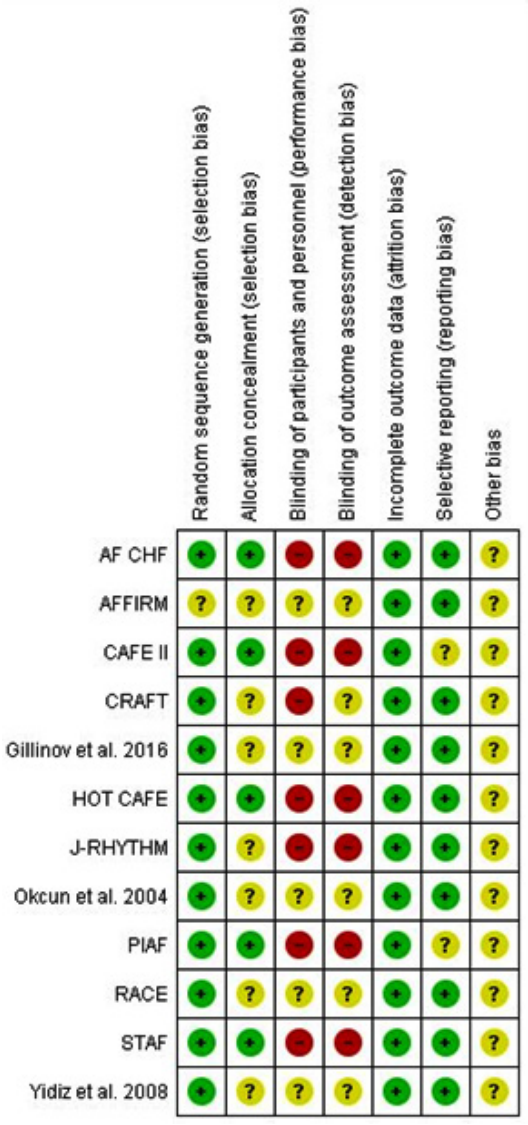

Fig. 2. Risk of bias summary for included randomized trials

Systemic Embolism

The overall risk ratio of nine studies (6929 patients) (9–11,13–15,18–20) showed no significant difference (RR = 1.06, 95% CI [0.64, 1.76], p = 0.83) between both groups regarding the risk of systemic embolism. Pooled studies were homogenous (p = 0.41, I^2 = 3%); *Figure 4b*.

Heart failure/Worsening of heart failure

The pooled risk ratio of nine included studies (7933 patients) (9,10,12–15,17,18,20), under the random-effects model, showed no significant difference (RR = 1.04, 95% CI [0.79, 1.38], p = 0.76) between both groups in terms of development or worsening of HF. Pooled studies were heterogeneous (p = 0.09, I^2 = 42%). Heterogeneity was best resolved (p = 0.41, I^2 = 3%) by excluding the study by Okcun *et al* (2004), while the pooled estimate remained non-significant (p = 0.78); *Figure 4c*.

Major/Life threatening bleeding

A pooled analysis of 10 included studies (8138 patients) (9–15,17,18,20–22) did not favor either of the two groups (RR = 1.10, 95% CI [0.90, 1.35], p = 37) in terms of major bleeding. Pooled studies were homogenous (p = 0.37, I2 = 7%). A symmetrical funnel plot showed no evidence of publication bias.

Rehospitalization

A pooled analysis of seven included studies (6701 patients) (9–12,17,19,20) showed that rehospitalization rates were significantly lower in the rate control group (RR = 0.72, 95% CI [0.57, 0.92], p = 0.009), compared to the rhythm control group. Pooled studies were significantly heterogeneous (p < 0.00001, I^2 = 88%) that removal of any included study by the Leave-One-Out method could not resolve such heterogeneity.

Subsequent Myocardial Infarction

Pooling data from two RCTs (5436 patients) (12,20,21) showed no significant difference (RR = 0.86, 95% CI [0.64, 1.17], p = 0.34) between rate and rhythm control groups regarding the risk of subsequent MI. Pooled studies were homogenous (p = 0.34, I^2 = 0%).

Subgroup analysis

Heart failure patients (Grade II – IV)

Subgroup analysis of data from three trials (1637 patients) (9,12,16), collected from patients with grade II to IV HF, showed no significant difference between both groups in terms of

all-cause mortality (RR = 1.05, 95% CI [0.90, 1.22]), cardiovascular mortality (RR = 0.99, 95% CI [0.83, 1.18]), stroke/TIA (RR = 0.85, 95% CI [039, 1.82]), development/worsening of HF (RR = 0.98, 95% CI [0.87, 1.11]), and rehospitalization rates (RR = 0.72, 95% CI [0.34, 1.49]). Except for rehospitalization (Chi-square p = 0.0002), pooled studies were homogenous in all outcomes (p > 0.1).

Age under 65 years old

Interestingly, when pooling data from younger patients (four studies, 681 patients) (14,17–19), the overall risk ratio showed a higher risk of all-cause mortality (RR = 3.18, 95% CI [1.71, 5.92]), HF (RR = 3.84, 95% CI [1.57, 9.37]), and major bleeding (RR = 5.07, 95% CI [1.29, 19.90]) in the rate control group, compared to the rhythm control group. However, both groups were comparable in terms of stroke (RR = 1.26, 95% CI [0.61, 2.85]) and systemic embolism rates (RR = 2.90, 95% CI [0.71, 11.89]). Pooled studies in all outcomes were homogenous (p > 0.1).

Sensitivity analysis

All the effect-estimates remained robust when we removed the two largest studies (AF CHF and AFFIRM), except for all-cause mortality. Upon removal of AF CHF and AFFIRM trials, which reported a non-significant increase in all-cause mortality in the rhythm control group, the

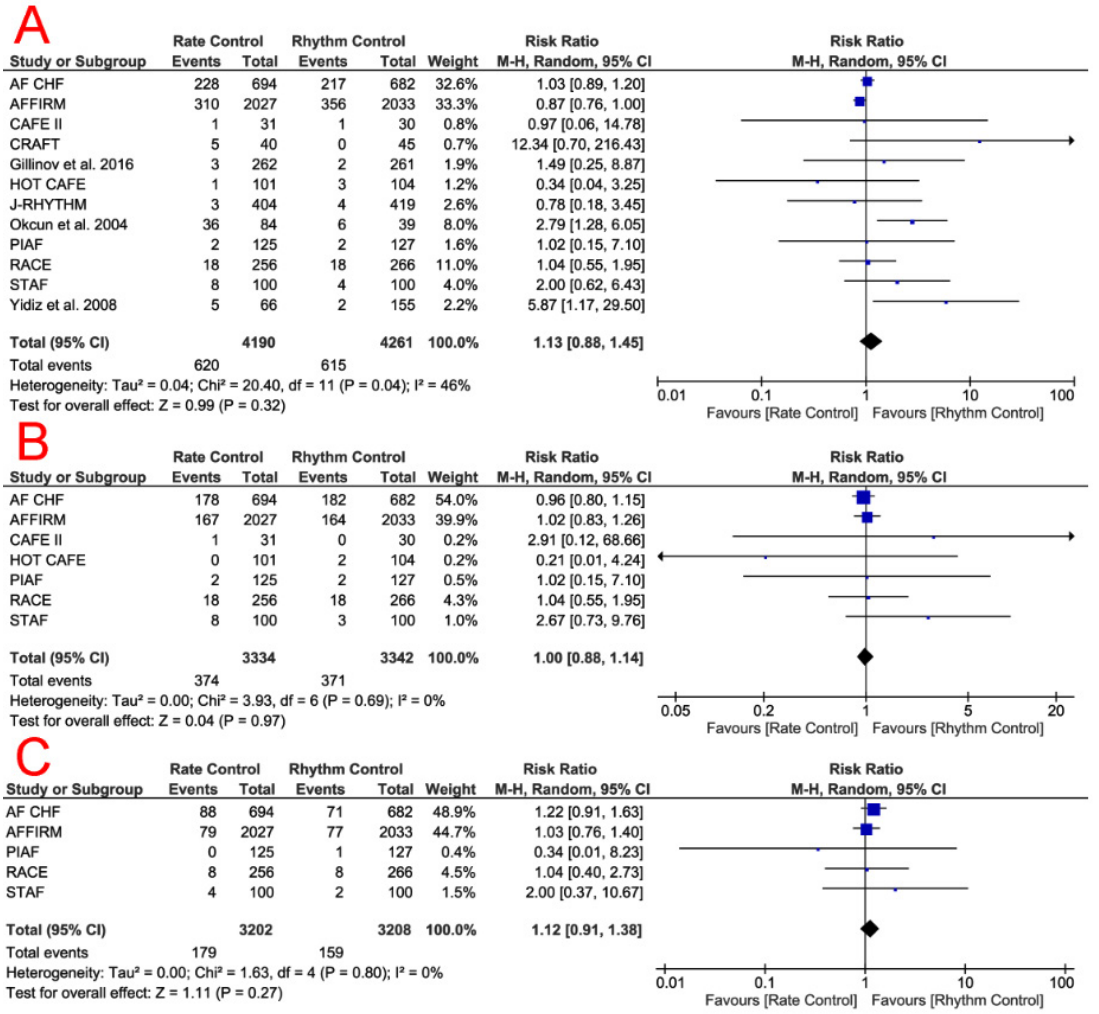

Fig. 3. Forest plots of risk ratios for A) All-cause mortality, B) Cardiovascular mortality, and C) Arrhythmic mortality

effect estimate favored rate control over rhythm control (RR = 1.66, 95% CI [1.15, 2.39], p = 0.006) regarding this particular outcome. The detailed results of sensitivity analysis are shown in *Table 3*.

DISCUSSION

Our meta-analysis of 12 studies showed no significant difference between rate and rhythm control groups in terms of mortality rates and other major clinical outcomes (including bleeding and thromboembolic events), except for rehospitalization rate, which was significantly higher in the rhythm control group. Across the five studies (9,12,15,19,20) that investigated arrhythmic, cardiovascular, and all-cause mortality, cardiovascular mortality represented 63.8% of all-cause mortality, while arrhythmic death represented 45.5% of cardiovascular and 29% of all-cause mortality.

Although restoring a physiological cardiac rhythm is hypothesized to lower the risk of

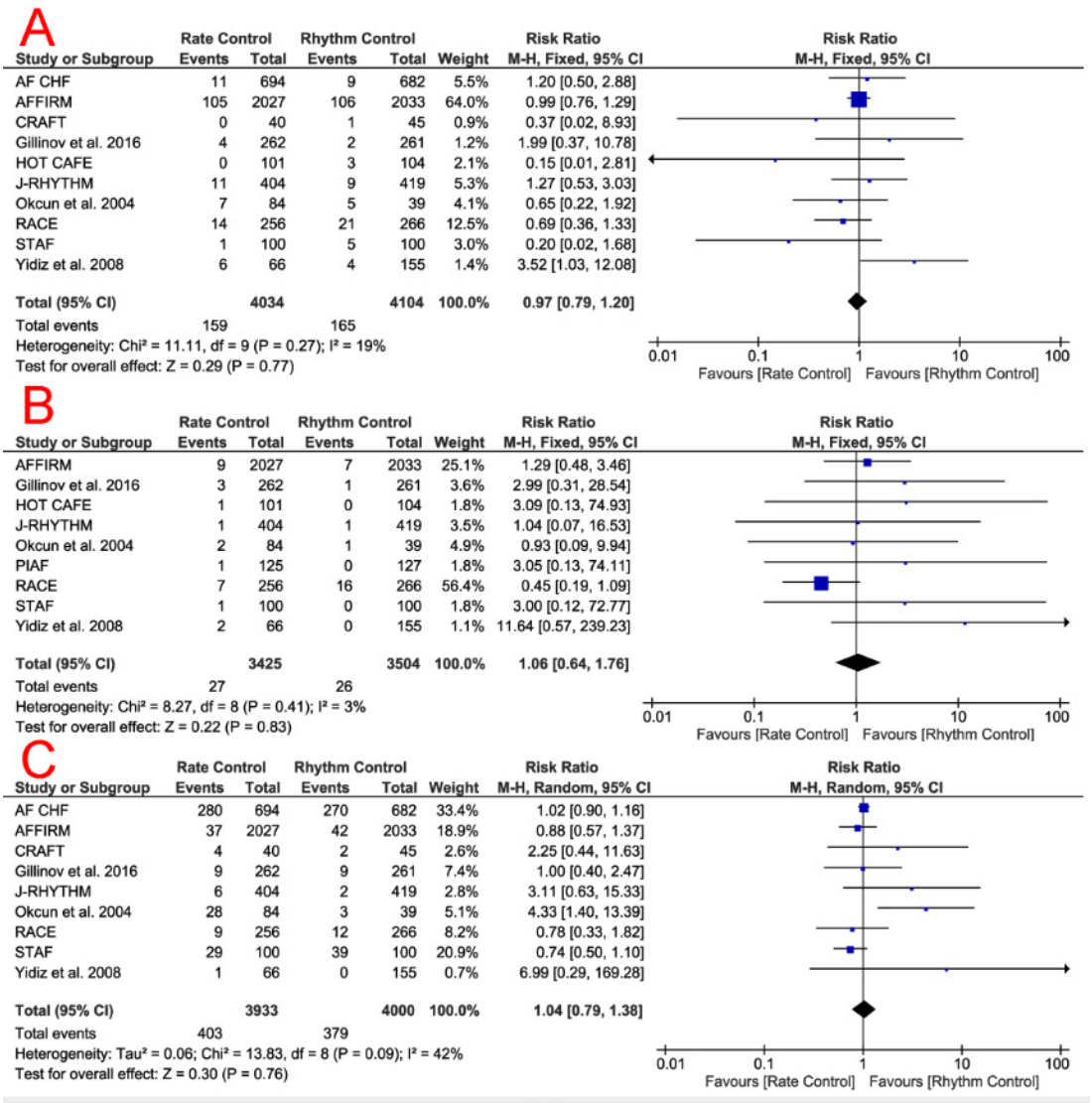

Fig. 4. Forest plot of risk ratios for A) Stroke/Transient Ischemic Attack, B) Systemic embolism, and C) Development or worsening of heart failure

Table 1. Shows a summary of the used drugs and main findings of included trials

Study ID	Sample Size	Rate control arm	Rhythm control arm	Patient inclusion criteria	Follow up	Conclusions duration
AF CHF	1376	Beta-blockers (²B) and digitalis	Electrical cardioversion, amiodarone and either sotalol or dofetilide	Patients with left ventricular (LV) ejection of d" 35%, a history of symptomatic heart failure (HF) [NYHA class II or IV] within the past 6 months.	19± 37 months	Rhythm control does not reduce cardiovascular mortality, as compared with a rate-control strategy.
AFFIRM	4060	²B, digitalis, and calcium-channel blockers (CCB)	Amiodarone or sotalol	Patients with recurrent AF who were at least 65 years of age or who had other risk factors for stroke or death.	6 years	Rhythm-control strategy offers no survival advantage over the rate-control strategy which has a lower risk of adverse drug effects.
CAFÉ II	61	Digoxin and ²B	Amiodarone	Patients aged >18 years of age with persistent AF and chronic symptomatic HF with evidence of systolic dysfunction on echocardiography.	14 months	Rhythm-control strategy in patients with AF and HF provides more improvement to quality of life (QoL) and LV function, when compared with rate control strategy.
CRAFT	144	Diltiazem	Amiodarone	All patients with rheumatic heart disease who had AF.	12 months	In patients with rheumatic AF, rhythm-control is superior to rate control in improving exercise capacity, QoL, and possibly mortality.
Gillinov et al. 2016	523	²B, CCB, or both	Amiodarone	Patients with postoperative AF that persisted for more than 60 minutes or recurrent episodes of AF during the index hospitalization (d"7 days after surgery).	60 days	Both rhythm and rate-control strategy are associated with similar complications and mortality rates, as well as comparable rates of persistent AF, 60 days after onset.
HOT CAFE	205	²B, nondihydropyridine CCB; digoxin	Propafenone, disopyramide, or sotalol	AF patients, aged 50 to 75 years of age, known to have AF for at least 7 days, but not for 2 years.	1.7 ± 0.4 years	There were no significant differences in major clinical endpoints between rate and rhythm control groups.
J-RHYTHM	885	²B, CCB, and digitalis	Propafenone, disopyramide, flecainide, aprindine, pirmenol, bepridil, and amiodarone	Patients with persistent AF with no contraindications to anticoagulation.	578 days	Rhythm control was associated with fewer adverse events than rate control. However, no difference was showed with respect to mortality and cardiovascular morbidity.
Ockun et al. 2004	154	Digoxin and metoprolol	Cardioversion and amiodarone	Patients e" 18 years of age who had persistent AF lasting more than 48 hours	3 years	Rhythm-control is preferable in patients with non-ischemic HF and AF with lower

				and nonischemic LV dysfunction diagnosed by echocardiography (EF < 50%).		mortality and improved exercise capacity.
PIAF	252	Diltiazem	Amiodarone	Patients, aged 18 to 75 years, presenting with symptomatic persistent AF of between 7 days and 360 days duration.	1 year	Rhythm-control improved exercise tolerance, yet with more frequent hospital admissions than rate-control. Otherwise, both strategies had similar clinical results.
RACE	522	Digitalis, a nondihydropyridine CCB, and a ²B alone or in combination	Sotalol, class IC antiarrhythmic drugs and amiodarone	Patients with recurrent persistent AF, in whom oral anticoagulation was not contraindicated.	2.4 years	Rhythm control strategy is associated with increased cardiovascular morbidity and mortality in persistent AF patients.
STAF	200	²B, digitalis, CCB, or ablation ± pacemaker implantation atrioventricular node	Class I antiarrhythmic agents or sotalol, ²B and/ or amiodarone.	Patients aged e" 18 years, with e" 1 of the following criteria: AF for 4 weeks; left atrial size e" 45 mm; LV ejection fraction d" 45%, or 1 prior cardioversion with arrhythmia recurrence.	12 to 36 months	No differences between the two treatment strategies were recorded in all clinical endpoints, except for rehospitalizations.
Yildiz et al. 2008	221	Digoxin, verapamil	Amiodarone	Patients aged e" 18 years who for > 48 hours.	21 ± 39 in rate control group and 40 ± 19 in rhythm control group	Rate control is an acceptable strategy in hypertensive AF patients although rhythm control has beneficial effect on exercise capicity. Both strategies have similar rates of mortality and embolic events.

Abbreviations: AF: atrial fibrillation, AFFIRM: Atrial Fibrillation Follow-up Investigation of Rhythm Management study, AF CHF: Atrial Fibrillation and Congestive Heart Failure study, BB: Beta-Blockers, 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, NYHA: New York Heart Association, PIAF: Pharmacological Intervention in Atrial Fibrillation study, QoL: Quality of life, RACE: Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation study, RHD: rheumatic heart disease, STAF: Strategies of Treatment of Atrial Fibrillation study.

Table 2. Shows baseline characteristics of enrolled patients in included studies

Study ID	Study Arm	Sample size (N)	Age (Mean ± SD)	Males (%)	Comorbidities				Anticoagulation	Patients in sinus rhythm at the end
					Hypertension N (%)	Heart Failure (Class II-IV)	Valvular Disease	Coronary Heart Disease		
	Rate Control	694	67 ± 11	85	319 (46%)	215 (31%)	34 (5%)	333 (48%)	624 (90%)	—-
AF CHF	Rhythm Control	682	66 ± 11	78	334 (49%)	218 (32%)	34 (5%)	327 (48%)	586 (86%)	—-
	Rate Control	2027	69.8 ± 8.9	56.4	1045 (51.6%)	475 (23.4%)	98 (4.8%)	497 (24.5%)	1722 (85%)	701 (34.6%)
AFFIRM	Rhythm Control	2033	69.7 ± 9	72.1	1018 (50.1%)	464 (22.8%)	100 (4.9%)	562 (27.6%)	1423 (70%)	1272 (62.6%)
	Rate Control	31	72.2 ± 8.3	81	22 (72%)	31 (100%)	—-	17 (55%)	31 (100%)	27 (90%)
CAFÉ II	Rhythm Control	30	72 ± 5.4	87	20 (68%)	30 (100%)	—-	13 (44%)	30 (100%)	19 (66%)
	Rate Control	48	38.4	41.7	—-	34 (70.8%)	48 (100%)	—-	48 (100%)	—-
CRAFT	Rhythm Control	48	39.5	47.9	—-	37 (77%)	48 (100%)	—-	48 (100%)	29 (69.1%)
Gillinov	Rate Control	262	69.2 ± 9.8	75.2	193 (73.7%)	35 (13.4%)	140 (53.4%)	50 (19.1%)	112 (42.7%)	220 (84.2%)
et al. 2016	Rhythm Control	261	68.4 ± 8.4	76.2	198 (75.9%)	33 (12.6%)	148 (56.7%)	48 (18.4%)	113 (43.3%)	227 (86.9%)
	Rate Control	101	61.4 ± 17.6	62.4	60 (59.4%)	53 (52.4%)	15 (14.8%)	38 (37.6%)	74.30%	56 (53.8%)
HOT CAFÉ	Rhythm Control	104	60.4 ± 7.9	68.3	72 (69.2%)	74 (71.1%)	16 (15.4%)	52 (50%)	15.60%	66 (63.5%)
J-RHYTHM	Rate Control	404	64.5 ± 12.3	69.6	*165 (40.8%)*	*16 (4%)*	26 (6.4%)	*31 (7.7%)*	240 (59.4%)	177 (43.9%)
	Rhythm Control	419	64.9 ± 10.3	69	*187 (44.6%)*	*14 (3.3%)*	20 (4.8%)	*30 (7.2%)*	252 (60.1%)	305 (72.7%)
Ockun	Rate Control	84	58 ± 12	68	45 (54%)	—-	0 (0%)	0 (0%)	100 (100%)	36 (42.9%)
et al. 2004	Rhythm Control	74	61 ± 10	66	33 (47%)	—-	0 (0%)	0 (0%)	Discontinued after the 1st month of cardioversion.	33 (47%)
	Rate Control	125	61 ± 9	74	67 (54%)	—-	19 (15%)	33 (26%)	125 (100%)	9 (10%)
PIAF	Rhythm Control	127	60 ± 10	72	56 (46%)	—-	22 (17%)	26 (20%)	127 (100%)	45 (56%)
	Rate Control	256	68 ± 9	63	110 (43%)	131 (51%)	46 (18%)	74 (29%)	96%	26 (10%)
RACE	Rhythm Control	266	68 ± 8	64	146 (55%)	130 (49%)	43 (16%)	69 (26%)	86%	103 (39%)
	Rate Control	100	66.2 ± 7.6	68	62 (62%)	—-	16 (16%)	53 (53%)	100 (100%)	9 (9%)
STAF	Rhythm Control	100	65.3 ± 9.4	59	63 (63%)	—-	10 (10%)	34 (34%)	100 (100%)	38 (38%)
	Rate Control	66	57 ± 11	50	66 (100%)	—-	0 (0%)	0 (0%)	100 (100%)	0
Yidiz	Rhythm Control	155	61 ± 9	48.3	155 (100%)	—-	0 (0%)	0 (0%)	Discontinued after the 1st month of cardioversion	62 (40%)
et al. 2008										

Abbreviations: 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 AF and HF, HOT CAFÉ: How to Treat Chronic Atrial Fibrillation study, J RHYTHM: Japanese Rhythm Management Trial for Atrial Fibrillation, 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. Results of sensitivity analysis after excluding the largest two studies (AF CHF and AFFIRM)

Outcome	Risk Ratio	95% Confidence Interval	P value	Number of included studies	Chi-Square P value	I-Square
All-cause Mortality	1.66	[1.15, 2.39]	0.006	10	0.25	21%
Cardiovascular Mortality	1.18	[0.71, 1.98]	0.52	5	0.51	0%
Arrhythmic Mortality	1.12	[0.51, 2.46]	0.78	3	0.6	0%
Stroke/Transient ischemic attack	0.88	[0.60, 1.29}	0.51	8	0.15	35%
Systemic embolism	0.98	[0.54, 1.78]	0.95	8	0.34	12%
Heart Failure	1.14	[0.84, 1.53]	0.4	7	0.03	58%
Major Bleeding	1.27	[0.85, 1.89]	0.25	8	0.3	16%
Rehospitalization	0.62	[0.52, 0.73]	<0.00001	5	<0.00001	86%

Abbreviations: AFFIRM: Atrial Fibrillation Follow-up Investigation of Rhythm Management study, AF CHF: Atrial Fibrillation and Congestive Heart Failure study

mortality and embolic events, our analysis shows that neither strategy was superior to the other in these regards. A possible explanation is that the survival benefit of rhythm control is likely to be negated by the non-cardiac side-effects of anti-arrhythmic drugs (28,29).

The higher frequency of rehospitalization in the rhythm control group may be explained by the possible occurrence of dysrhythmias, as a complication of anti-arrhythmic drugs and the need to perform cardioversion in a monitored environment (20,30). This higher rate of rehospitalization can be translated to a higher treatment cost in the rhythm control group, which is confirmed by real-world data from observational studies (31–33).

We performed a subgroup analysis for AF patients with concomitant CHF because this comorbidity affects more than 50% of AF patients and its interaction with AF means that none of them can be optimally managed without treating the other (9,12). Except for rehospitalization rate, mortality and clinical outcomes' results were similar to those of the main analysis. This may be explained by the fact that these patients require frequent hospitalization for management of CHF, regardless the method of AF control.

Interestingly, rhythm control strategy was associated with lower rates of mortality, HF, and major bleeding than rate control in younger patients (mean age below 65 years), probably by delaying the progression to permanent AF, which has a higher rate of complications (23). This finding is supported by real life data from the RECORDAF registry (Registry on Cardiac Rhythm Disorders AF), established following the AFFIRM trial (34).

Postoperative AF occurs in 20% to 50% of patients following cardiac surgery (35,36). An included study by Gillinov *et al*. showed no significant difference between rate and rhythm control strategies in terms of mortality and complication rates in postoperative patients (10). Additionally, about 17 to 18% of rheumatic patients develop AF (8). The included CRAFT trial showed that rhythm control was superior to rate control in rheumatic heart patients in terms of reducing mortality and improving quality of life and exercise capacity (17).

Strength points

Compared to the formerly mentioned meta-analyses (23,24), our analysis included a larger number of trials, with a fairly higher sample size. We performed subgroup analyses for younger patients and those with HF and conducted a sensitivity analysis to ensure that our results were not affected by the weights of individual studies. Unlike previous meta-analyses, we performed a thorough risk of bias assessment and investigated for publication bias, whenever appropriate.

Limitations

All included trials were open-label studies because the nature of electric cardioversion in the rhythm control group prevents proper blinding and applying a fake electrical cardioversion protocol is ethically controversial and would interfere with the results of other outcomes, such as rehospitalization rate. The main weight of our analysis comes from the two largest trials (AF CHF and AFFIRM);

therefore, we performed a sensitivity analysis by excluding these trials to overcome this limitation. We did not assess the impact of either strategy on quality of life outcomes because these data were poorly reported in included studies. Future trials should further investigate the effect of other comorbidities, such as stroke and left ventricular dysfunction on the treatment outcomes. We are aware of few ongoing studies, comparing both strategies, in different categories of AF patients, such as AFARC-LVF trial (NCT02509754) and RAFT-AF trial (NCT01420393).

CONCLUSION

In older AF patients and those with concomitant CHF, both rate and rhythm control strategies have similar rates of mortality and major clinical outcomes; therefore, choosing an appropriate therapeutic strategy should consider individual variations such as patient preferences, comorbidities, and treatment cost. Future trials should compare both strategies in younger patients and those with other comorbidities such as stroke and left ventricular dysfunction.

REFERENCES

1. Heeringa J, van der Kuip DAM, Hofman A, Kors JA, van Herpen G, Stricker BHC, *et al*. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. *European heart journal.* **27**(8):949–53 (2006).
2. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation: a major contributor to stroke in the elderly. The Framingham Study. *Arch Intern Med.* 1987/09/01 ed.; **147**(9):1561–4 (1987).
3. Copley DJ, Hill KM. Atrial Fibrillation: A Review of Treatments and Current Guidelines. AACN Adv Crit Care. 2016/02/26 ed. **27**(1):120–8 (2016).
4. Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, *et al*. ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Circulation. 2006/08/16 ed.; **114**(7):e257–354 (2006).
5. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, *et al*. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. Circulation. 2013/12/19 ed.; **129**(8):837–47 (2014).
6. Furberg CD, Psaty BM, Manolio TA, Gardin JM, Smith VE, Rautaharju PM. Prevalence of atrial fibrillation in elderly subjects (the Cardiovascular Health Study). Am J Cardiol. 1994/08/01 ed. **74**(3):236–41 (1994).
7. Kannel WB, Wolf PA, Benjamin EJ, Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. Am J Cardiol. 1998/11/11 ed.; **82**(8a):2n–9n (1998).
8. Wyse DG. Pharmacologic approaches to rhythm versus rate control in atrial fibrillation—where are we now? Int J Cardiol. 2006/03/07 ed. ; **110**(3):301–12 (2006).
9. Carlsson J, Miketic S, Windeler J, Cuneo A, Haun S, Micus S, *et al*. Randomized trial of rate-control versus rhythm-control in persistent atrial fibrillation. *Journal of the American College of Cardiology.*; **41**(10):1690 (2003).
10. Gillinov AM, Bagiella E, Moskowitz AJ, Raiten JM, Groh MA, Bowdish ME, *et al*. Rate control versus rhythm control for atrial fibrillation after cardiac surgery. *New England Journal of Medicine.;* **374**(20):1911–21 (2016).
11. Opolski G, Torbicki A, Kosior DA, Szulc M, WozÌ B, KoÅ P, *et al*. Rate control vs rhythm control in patients with nonvalvular persistent atrial fibrillation: the results of the Polish How to Treat Chronic Atrial Fibrillation (HOT CAFE) Study. *CHEST Journal.;* **126**(2):476–86 (2004).
12. Roy D, Talajic M, Nattel S, Wyse DG, Dorian P, Lee KL, *et al*. Rhythm control versus rate control for atrial fibrillation and heart failure. *New England Journal of Medicine.;* **358**(25):2667–77 (2008).
13. Ogawa S, Yamashita T, Yamazaki T, Aizawa Y, Atarashi H, Inoue H, *et al*. Optimal treatment strategy for patients with paroxysmal atrial fibrillation. *Circulation Journal.;* **73**(2):242–8.
14. Ökçün B, Yigit Z, Arat A, Küçükoglu MS. Comparison of rate and rhythm control in patients with atrial fibrillation and nonischemic heart failure. *Japanese heart journal.;* **45**(4):591–601 (2004).
15. Rienstra M, Van Veldhuisen DJ, Crijns HJGM, Van Gelder IC. Enhanced cardiovascular morbidity and mortality during rhythm control treatment in persistent atrial fibrillation in hypertensives: data of the RACE study. *European*

heart journal (2007);
16. Shelton RJ, Clark AL, Goode K, Rigby AS, Houghton T, Kaye GC, *et al*. A randomised, controlled study of rate versus rhythm control in patients with chronic atrial fibrillation and heart failure:(CAFE-II Study). *Heart.;* **95**(11):924–30 (2009).
17. Vora A, Karnad D, Goyal V, Naik A, Gupta A, Lokhandwala Y, *et al*. Control of rate versus rhythm in rheumatic atrial fibrillation: a randomized study. *Indian heart journal.;* **56**(2):110–6 (2004).
18. Yildiz A, Yigit Z, Okcun B, Baskurt M, Ortak K, Kaya A, *et al*. Comparison of rate and rhythm control in hypertension patients with atrial fibrillation. *Circulation Journal.;* **72**(5):705–8 (2008).
19. Hohnloser SH, Kuck K-H, Lilienthal J, Investigators P. Rhythm or rate control in atrial fibrillation—Pharmacological Intervention in Atrial Fibrillation (PIAF): a randomised trial. *The Lancet*. **356**(9244):1789–94 (2000).
20. Investigators AFFI of RM. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med.* 2002(347):1825–33 (2002).
21. Steinberg JS, Sadaniantz A, Kron J, Krahn A, Denny DM, Daubert J, *et al*. Analysis of cause-specific mortality in the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study. *Circulation.* **109**(16):1973–80 (2004).
22. Van Gelder IC, Hagens VE, Bosker HA, Kingma JH, Kamp O, Kingma T, *et al*. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *New England Journal of Medicine.;* **347**(23):1834–40 (2002).
23. Chatterjee S, Sardar P, Lichstein E, Mukherjee D, Aikat S. Pharmacologic Rate versus Rhythm Control Strategies in Atrial Fibrillation: An Updated Comprehensive Review and Meta Analysis. *Pacing and Clinical Electrophysiology.* **36**(1):122–33 (2013).
24. De Denus S, Sanoski CA, Carlsson J, Opolski G, Spinler SA. Rate vs rhythm control in patients with atrial fibrillation: a meta-analysis. *Archives of Internal Medicine.;* **165**(3):258–62 (2005).
25. Higgins JP, Green S. Cochrane Handbook for Systematic Reviews of interventions. The Cochrane Collaboration. (2008).
26. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ (Clinical research ed.). *British Medical Journal Publishing Group;* **339**(17):b2535 (2009).
27. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ (Clinical research ed.).; **315**(7109):629–34 (1997).
28. Julian DG, Camm AJ, Frangin G, Janse MJ, Munoz A, Schwartz PJ, *et al*. Randomised trial of effect of amiodarone on mortality in patients with left-ventricular dysfunction after recent myocardial infarction: EMIAT. *The Lancet.;* **349**(9053):667–74 (1997).
29. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, *et al*. Amiodarone or an implantable cardioverter–defibrillator for congestive heart failure. *New England Journal of Medicine.;* **352**(3):225–37 (2005).
30. Cordina J, Mead GE. Pharmacological cardioversion for atrial fibrillation and flutter. The Cochrane Library. (2005);
31. Hagens VE, Vermeulen KM, TenVergert EM, Van Veldhuisen DJ, Bosker HA, Kamp O, *et al*. Rate control is more cost-effective than rhythm control for patients with persistent atrial fibrillation—results from the RAte Control versus Electrical cardioversion (RACE) study. *European heart journal.*; **25**(17):1542–9 (2004).
32. Marshall DA, Levy AR, Vidaillet H, Fenwick E, Slee A, Blackhouse G, *et al*. Cost-effectiveness of rhythm versus rate control in atrial fibrillation. *Annals of Internal Medicine.* **141**(9):653–61 (2004).
33. Pietrasik A, Kosior DA, Niewada M, Opolski G, Latek M, Kamiñski B. The cost comparison of rhythm and rate control strategies in persistent atrial fibrillation. *International journal of cardiology.* **118**(1):21–7 (2007).
34. Camm AJ, Breithardt G, Crijns H, Dorian P, Kowey P, Le Heuzey J-Y, *et al*. Real-life observations of clinical outcomes with rhythm- and rate-control therapies for atrial fibrillation: RECORDAF (Registry on Cardiac Rhythm Disorders Assessing the Control of Atrial Fibrillation). *Journal of the American College of Cardiology.* **58**(5):493–501 (2011).
35. Echahidi N, Pibarot P, O'Hara G, Mathieu P. Mechanisms, prevention, and treatment of atrial fibrillation after cardiac surgery. *Journal of the American College of Cardiology.* **51**(8):793–801 (2008).
36. Nair SG. Atrial fibrillation after cardiac surgery. *Annals of cardiac anaesthesia.*; **13**(3):196 (2010).