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

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

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. Moreover, recent trials have compared both strategies in different groups of AF patients, including younger and those with concomitant HF. 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. 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, stroke 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. 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.

**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
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, I² = 3%); Figure 4c.

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, I² = 42%). Heterogeneity was best resolved (p = 0.41, I² = 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 = 0.37) 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, I² = 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, I² = 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 [0.59, 1.28]), 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](image-url)
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
Table 1. Shows a summary of the used drugs and main findings of included trials

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Sample Size</th>
<th>Rate control arm</th>
<th>Rhythm control arm</th>
<th>Patient inclusion criteria</th>
<th>Follow up</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF CHF</td>
<td>1376</td>
<td>Beta-blockers (²B) and digoxis</td>
<td>Electrical cardioversion, amiodarone and either sotalol or dofetilide</td>
<td>Patients with left ventricular (LV) ejection of ≤35%, a history of symptomatic heart failure (HF) [NYHA class II or IV] within the past 6 months.</td>
<td>19±37 months</td>
<td>Rhythm control does not reduce cardiovascular mortality, as compared with a rate-control strategy.</td>
</tr>
<tr>
<td>AFFIRM</td>
<td>4060</td>
<td>²B, digoxis, and calcium-channel blockers (CCB)</td>
<td>Amiodarone or sotalol</td>
<td>Patients with recurrent AF who were at least 65 years of age or who had other risk factors for stroke or death.</td>
<td>6 years</td>
<td>Rhythm-control strategy offers no survival advantage over the rate-control strategy which has a lower risk of adverse drug effects.</td>
</tr>
<tr>
<td>CAFÉ II</td>
<td>61</td>
<td>Digoxin and ²B</td>
<td>Amiodarone</td>
<td>Patients aged &gt;18 years of age with persistent AF and chronic symptomatic HF with evidence of systolic dysfunction on echocardiography.</td>
<td>14 months</td>
<td>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.</td>
</tr>
<tr>
<td>CRAFT</td>
<td>144</td>
<td>Diltiazem</td>
<td>Amiodarone</td>
<td>All patients with rheumatic heart disease who had AF.</td>
<td>12 months</td>
<td>In patients with rheumatic AF, rhythm-control is superior to rate control in improving exercise capacity, QoL, and possibly mortality.</td>
</tr>
<tr>
<td>Gillinov et al. 2016</td>
<td>523</td>
<td>²B, CCB, or both</td>
<td>Amiodarone</td>
<td>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).</td>
<td>60 days</td>
<td>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.</td>
</tr>
<tr>
<td>HOT CAFE</td>
<td>205</td>
<td>²B, nondihydropyridine CCB; digoxin</td>
<td>Propafenone, disopyramide, or sotalol</td>
<td>AF patients, aged 50 to 75 years of age, known to have AF for at least 7 days, but not for 2 years.</td>
<td>1.7 ± 0.4 years</td>
<td>There were no significant differences in major clinical endpoints between rate and rhythm control groups.</td>
</tr>
<tr>
<td>J-RHYTHM</td>
<td>885</td>
<td>²B, CCB, and digitalis</td>
<td>Propafenone, disopyramide, flecainide, aprindine, pirmenol, bepridil, and amiodarone</td>
<td>Patients with persistent AF with no contraindications to anticoagulation.</td>
<td>578 days</td>
<td>Rhythm control was associated with fewer adverse events than rate control. However, no difference was showed with respect to mortality and cardiovascular morbidity.</td>
</tr>
<tr>
<td>Ockun et al. 2004</td>
<td>154</td>
<td>Digoxin and metoprolol</td>
<td>Cardioversion and amiodarone</td>
<td>Patients ≥ 18 years of age who had persistent AF lasting more than 48 hours</td>
<td>3 years</td>
<td>Rhythm-control is preferable in patients with non-ischemic HF and AF with lower</td>
</tr>
<tr>
<td>Study</td>
<td>Patients</td>
<td>Treatment</td>
<td>Duration</td>
<td>Outcomes</td>
<td></td>
<td></td>
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<tr>
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<td></td>
</tr>
<tr>
<td>PIAF</td>
<td>252</td>
<td>Diltiazem</td>
<td>Amiodarone</td>
<td>1 year</td>
<td>Rhythm-control improved exercise capacity.</td>
<td></td>
</tr>
<tr>
<td>RACE</td>
<td>522</td>
<td>Digitalis, a nondihydropyridine CCB, and a 'B alone or in combination</td>
<td>Sotalol, class IC antiarrhythmic drugs and amiodarone</td>
<td>2.4 years</td>
<td>Rhythm control strategy is associated with increased cardiovascular morbidity and mortality in persistent AF patients.</td>
<td></td>
</tr>
<tr>
<td>STAF</td>
<td>200</td>
<td>'B, digitalis, CCB, or ablation + pacemaker implantation atrioventricular node</td>
<td>Class I antiarrhythmic agents or sotalol, 'B and/or amiodarone</td>
<td>12 to 36 months</td>
<td>No differences between the two treatment strategies were recorded in all clinical endpoints, except for rehospitalizations.</td>
<td></td>
</tr>
<tr>
<td>Yildiz et al. 2008</td>
<td>221</td>
<td>Digoxin, verapamil</td>
<td>Amiodarone</td>
<td>21 ± 39 in rate control group and 40 ± 19 in rhythm control group</td>
<td>Rate control is an acceptable strategy in hypertensive AF patients although rhythm control has beneficial effect on exercise capacity. Both strategies have similar rates of mortality and embolic events.</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Study Arm</th>
<th>Sample size (N)</th>
<th>Age (Mean ± SD)</th>
<th>Males (%)</th>
<th>Hypertension N (%)</th>
<th>Comorbidities</th>
<th>Coronary Heart Disease</th>
<th>Anticoagulation</th>
<th>Patients in sinus rhythm at the end</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rhythm Control</td>
<td>694</td>
<td>67 ± 11</td>
<td>85</td>
<td>319 (46%)</td>
<td>215 (31%)</td>
<td>34 (5%)</td>
<td>333 (48%)</td>
<td>624 (90%)</td>
</tr>
<tr>
<td>AF CHF</td>
<td>Rate Control</td>
<td>682</td>
<td>66 ± 11</td>
<td>78</td>
<td>334 (49%)</td>
<td>218 (32%)</td>
<td>34 (5%)</td>
<td>327 (48%)</td>
<td>586 (86%)</td>
</tr>
<tr>
<td></td>
<td>Rhythm Control</td>
<td>2027</td>
<td>69.8 ± 8.9</td>
<td>56.4</td>
<td>1045 (51.6%)</td>
<td>475 (23.4%)</td>
<td>98 (4.8%)</td>
<td>497 (24.5%)</td>
<td>1722 (85%)</td>
</tr>
<tr>
<td>AFFIRM</td>
<td>Rate Control</td>
<td>2033</td>
<td>69.7 ± 9</td>
<td>72.1</td>
<td>1018 (50.1%)</td>
<td>464 (22.8%)</td>
<td>100 (4.9%)</td>
<td>562 (27.6%)</td>
<td>1423 (70%)</td>
</tr>
<tr>
<td>CAFÉ II</td>
<td>Rate Control</td>
<td>31</td>
<td>72.2 ± 8.3</td>
<td>81</td>
<td>22 (72%)</td>
<td>31 (100%)</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>Rhythm Control</td>
<td>2027</td>
<td>69.2 ± 9.8</td>
<td>75.2</td>
<td>193 (73.7%)</td>
<td>35 (13.4%)</td>
<td>140 (53.4%)</td>
<td>50 (19.1%)</td>
<td>112 (42.7%)</td>
</tr>
<tr>
<td>Gillinov et al. 2016</td>
<td>Rate Control</td>
<td>261</td>
<td>68.4 ± 8.4</td>
<td>76.2</td>
<td>198 (75.9%)</td>
<td>33 (12.6%)</td>
<td>148 (56.7%)</td>
<td>48 (18.4%)</td>
<td>113 (43.3%)</td>
</tr>
<tr>
<td></td>
<td>Rhythm Control</td>
<td>102</td>
<td>61.4 ± 17.6</td>
<td>62.4</td>
<td>60 (59.4%)</td>
<td>53 (52.4%)</td>
<td>15 (14.8%)</td>
<td>38 (37.6%)</td>
<td>74.30%</td>
</tr>
<tr>
<td>HOT CAFÉ</td>
<td>Rhythm Control</td>
<td>1044</td>
<td>60.4 ± 7.9</td>
<td>68.3</td>
<td>72 (69.2%)</td>
<td>74 (71.4%)</td>
<td>16 (15.4%)</td>
<td>52 (50%)</td>
<td>15.60%</td>
</tr>
<tr>
<td>J-RHYTHM</td>
<td>Rate Control</td>
<td>402</td>
<td>69.2 ± 10.3</td>
<td>69</td>
<td>187 (44.6%)</td>
<td>14 (3.3%)</td>
<td>20 (4.8%)</td>
<td>252 (60.1%)</td>
<td>305 (72.7%)</td>
</tr>
<tr>
<td>Ockun et al. 2004</td>
<td>Rate Control</td>
<td>84</td>
<td>58 ± 12</td>
<td>68</td>
<td>45 (54%)</td>
<td>---</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>100 (100%)</td>
</tr>
<tr>
<td>PIAF</td>
<td>Rate Control</td>
<td>125</td>
<td>61 ± 9</td>
<td>74</td>
<td>67 (54%)</td>
<td>---</td>
<td>19 (15%)</td>
<td>33 (26%)</td>
<td>125 (100%)</td>
</tr>
<tr>
<td>RACE</td>
<td>Rate Control</td>
<td>127</td>
<td>60 ± 10</td>
<td>72</td>
<td>56 (46%)</td>
<td>---</td>
<td>22 (17%)</td>
<td>26 (20%)</td>
<td>127 (100%)</td>
</tr>
<tr>
<td>STAF</td>
<td>Rate Control</td>
<td>66</td>
<td>57 ± 11</td>
<td>50</td>
<td>66 (100%)</td>
<td>---</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>---</td>
</tr>
<tr>
<td>Yidiz et al. 2008</td>
<td>Rate Control</td>
<td>155</td>
<td>61 ± 9</td>
<td>48.3</td>
<td>155 (100%)</td>
<td>---</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>---</td>
</tr>
</tbody>
</table>

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.
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.

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