

Rate-control vs. rhythm-control in patients with atrial fibrillation: a meta-analysis

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KEYWORDS

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Aims To systematically assess the risk/benefit ratio of a rate-control strategy vs. a rhythm-control strategy in patients with first or recurrent atrial fibrillation (AF).

Methods and results We searched Medline, CENTRAL, and other sources up to September 2004 for randomized trials. Individual and pooled random-effect odd ratios (OR) and 95% confidence intervals (CI) [OR (95% CI)] were calculated for the combined endpoint of all cause death and thromboembolic stroke (CEP), major bleeds (intra and extracranial), and systemic embolism. Number needed to treat (NNT) to avoid one CEP and heterogeneity were also assessed. Five studies enrolling 5239 patients with AF compared rate-control vs. rhythm-control. Average follow-up ranged from 1 to 3.5 years. A rate-control strategy compared with a rhythm-control approach was associated with a significantly reduced risk of CEP [OR 0.84 (0.73, 0.98), $P=0.02$], and with a trend towards a reduced risk of death [OR 0.87 (0.74, 1.02), $P=0.09$] and thromboembolic stroke [OR 0.80 (0.6, 1.07), $P=0.14$]. NNT to save one CEP was 50. There was no significant difference in the risk of major bleeds [OR 1.14 (0.9, 1.45), $P=0.28$] and systemic embolism [OR 0.93 (0.43, 2.02), $P=0.90$]. No significant heterogeneity was found in any of the analyses ($P>0.1$).

Conclusion This meta-analysis of 5239 patients with AF indicates that an initial rate-control strategy compared with a rhythm-control one is associated with a better prognosis, thus representing the standard treatment against which to test new therapeutic approaches.

Introduction

AF is the most common sustained rhythm disturbance and its prevalence is increasing worldwide because of progressive aging of the population.¹ AF can occur in the presence or in the absence of structural heart diseases. Notably, myocarditis confined to atria was demonstrated in some cases of 'lone AF'.²

Morbidity, mortality, and management costs are related to haemodynamic impairment and to thromboembolic events. In particular, a two- to three-fold increase of stroke has been observed with each decade of age.³ Thus, the goal of treatment is to reduce symptoms and risk of thromboembolic events and to avoid tachycardia-induced unfavourable myocardial remodelling. Some authors propose that regaining sinus rhythm may reduce the risk of bleeding associated with anticoagulation and re-establish a physiologic cardiac function. On the other hand, advocates of a simple rate-control approach associated with an accurate antithrombotic regimen propose that such a strategy may avoid the pro-arrhythmic risk of antiarrhythmic drugs.

The present meta-analysis was conducted to systematically assess the risk/benefit ratio of a rhythm-control strategy vs. a rate-control approach in patients with AF.

Methods

Search strategy

BioMedCentral, CENTRAL, Current Contents, MEDLINE, and mRCT were searched up to January 2005 for eligible studies, using the terms 'rate', 'rhythm', 'control', and 'AF'. MEDLINE was queried according to established methods,⁴ and no language restriction was applied. Pertinent reviews^{5–8} were manually sought for data not available in the original papers.

Selection criteria

Inclusion criteria for retrieved studies were (i) comparison of a ventricular rate-control strategy by means of pharmacologic therapy vs. restoration and maintenance of sinus rhythm by pharmacologic or electrophysiologic means, (ii) randomized treatment allocation, and (iii) inclusion of patients with first or recurrent AF, and (iv) intention-to-treat analysis. Exclusion criteria were (i) equivocal treatment allocation process, (ii) severe imbalances in major baseline characteristics among study groups, and (iii) incomplete (<80%) follow-up.

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Data abstraction and validity assessment

Data abstraction was independently performed by two unblinded reviewers (L.T., G.G.L.B.Z.). Divergences were resolved by consensus. The outcomes of interest were (i) the combined rate of all cause death or thromboembolic stroke, (ii) the rate of all cause death and thromboembolic stroke taken individually, (iii) the rate of major bleeds (intracranial or extracranial), and (iv) the rate of systemic embolism. Endpoint definitions were those of the individual studies included in the final analysis.

Data analysis and synthesis

Random effect OR and 95% confidence intervals (CI) [OR (95% CI)] were obtained for the combined endpoint of all cause death and thromboembolic stroke (CEP), for major bleeds (intracranial and extracranial) and for the single endpoints of all cause death, thromboembolic stroke, intracranial bleeds, extracranial bleeds, and systemic embolism. Power and number needed to treat (NNT, with 95% CI) were extrapolated from pooled random effect risk differences. Statistical analysis was performed using the RevMan 4.2 freeware package.⁹ Review Manager is a comprehensive statistical and reviewing program, developed and maintained by the Cochrane Collaboration, which includes *ad hoc* statistical tools for pooled estimate calculations, according to several methods.⁹ Binary outcomes from individual studies were combined with the Der Simonian and Laird random effect model.¹⁰ To assess dispersion of estimates 95% CI were also used as summary statistics.¹⁰

We also carried out the 'z' test with $z = \text{estimated effect size} / \text{standard error of the estimated effect size}$, and the OR considered on the log scale.¹⁰ As $\log(\text{OR})$ has a unimodal distribution, the reported z values were analysed to obtain a two-tailed 'P', and hypothesis testing results were considered statistically significant at the 0.05 level.¹⁰

Heterogeneity was assessed by means of Cochran Q heterogeneity test and considered significant when $P < 0.10$.¹¹ Inconsistency (I^2) was also ascertained, where I^2 represents an estimate of the degree of inconsistency among studies with scores of 25, 50, and 75% representing, respectively, low, moderate, or high inconsistency.¹¹

This study is inspired by good practice guidelines,^{12,13} including those from the Cochrane Collaboration, and the Quality of Reporting of Meta-analyses (QUORUM) statement.¹⁴

Results

Search results and study selection

Database searches retrieved 319 citations. Most papers were excluded because of non-randomized design, duplicate reporting or still ongoing.^{15,16} We finally identified five eligible randomized trials¹⁷⁻²¹ which were appraised for data abstraction. Quality assessment according to the Cochrane Collaboration approach was largely non-contributory (one study²⁰ with A grade and four studies^{17-19,21} with B and C grades), mostly because of study design limitations inherent to a comparison of therapeutic strategies which cannot be conducted blindly.

Study characteristics

The eligible studies randomized a total of 5239 patients with first or recurrent AF involving 16 207 patient-years.

The Pharmacological Intervention in AF (PIAF) trial¹⁷ enrolled 252 patients with persistent AF lasting up to 360 days. Exclusion criteria were NYHA Class IV heart failure, unstable angina, acute myocardial infarction within 30 days, ventricular rate < 50 b.p.m in AF, sick sinus syndrome,

Wolf Parkinson White (WPW) syndrome, coronary artery bypass grafting or valve replacement within 3 months, intracardiac thrombi, central or peripheral embolization within 6 months, dysthyroidism, previously implanted pacemaker, contraindications to oral anticoagulants, and pregnancy. In the rate-control arm, diltiazem was used while restoration and maintenance of sinus rhythm was obtained using amiodarone or electrical cardioversion as first intervention, followed by various other antiarrhythmic drugs. The length of follow-up was 1 year. The primary endpoint of the study was improvement in symptoms related to AF.

The Strategies of Treatment of AF (STAF) study¹⁸ enrolled 200 patients with persistent AF. Exclusion criteria were permanent AF lasting over 2 years, ≥ 70 mm left atrial size, left ventricular ejection fraction (LVEF) $< 20\%$, paroxysmal AF, WPW syndrome, and prior atrioventricular node ablation. In the rate-control arm beta-blockers, digitalis, calcium antagonists, or atrioventricular node ablation/modification with or without pacemaker implantation were used. In the rhythm-control arm, patients were to be cardioverted by external or internal cardioversion; after restoration of sinus rhythm, prophylaxis was performed with class I antiarrhythmic drugs or sotalol, in the absence of coronary artery disease (CAD) and in the presence of normal LVEF, whereas in the presence of impaired ventricular function or CAD, beta-blockers or amiodarone were used. Follow-up was of 1.7 ± 0.7 years. Primary endpoint was the combined rate of death, cardiopulmonary resuscitation, cerebrovascular events, and systemic embolism.

The RACE study¹⁹ enrolled 522 patients with persistent AF after an initial attempt of electrical cardioversion. Exclusion criteria were transient AF or lasting > 1 year, NYHA Class IV heart failure, previously implanted pacemaker, severe systemic disease, and past therapy with amiodarone. Rate-control was achieved using digitalis, calcium antagonists, and beta-blockers alone or in combination. Rhythm-control was obtained with electrical cardioversion without previous treatment with antiarrhythmic drugs. Thereafter, sotalol was used for prophylaxis. At the first recurrence of AF, electrical cardioversion was repeated and sotalol replaced by flecainide. In the presence of a recurrence within 6 months, another cardioversion was performed and flecainide replaced by amiodarone. Follow-up length was 2.3 ± 0.6 years. The primary endpoint was a composite of cardiovascular death, heart failure, thromboembolic complications, bleeding, implantation of a pacemaker, and severe adverse effects of drugs.

The AFFIRM study²⁰ enrolled 4060 patients with first or recurrent, paroxysmal or persistent, AF at high risk for stroke. Risk factors for stroke were hypertension, diabetes mellitus, congestive heart failure, prior transient ischaemic attack, cerebrovascular accident, prior systemic embolism, left atrial size of ≥ 50 mm, and LVEF $< 40\%$. Patients with contraindications to oral anticoagulant therapy were excluded. Digitalis, calcium antagonists, and beta-blockers alone or in combination were the drugs accepted in the rate-control arm; the goal was a heart rate not higher than 80 b.p.m at rest and 110 b.p.m during the 6-min walk test. In the rhythm-control arm the antiarrhythmic drug was chosen by the treating physician; acceptable drugs were amiodarone, disopyramide, flecainide, moricizine, procainamide, propafenone, quinidine, sotalol, and their combination according to an imposed protocol; attempts

Table 1 Study characteristics

	No. of pts	Rate-control strategy	Rhythm-control strategy	Mean age (years)	Male sex (%)	Individual study end points	Follow-up (years)	Drugs in rhythm-control arm
PIAF ²³	252	125	127	61.5	73	Improved symptoms	1	Amiodarone
STAF ²⁴	200	100	100	65.8	63.5	All cause death, cerebrovascular events, cardiopulmonary resuscitation, systemic embolism	1.7	Sotalol, amiodarone, class I antiarrhythmic drugs
RACE ²⁵	522	256	266	68	63.5	Cardiovascular death, hospitalisation for heart failure, thromboembolic complications, major bleeding, pacemaker implantation, severe adverse effect of therapy	2.3	Flecainide, propafenone, amiodarone
AFFIRM ²⁶	4060	2027	2033	69.7	61.3	Overall mortality	3.5	Amiodarone, disopyramide, flecainide, moricizine, procainamide, propafenone, quinidine, sotalol and their combination
HOT CAFÉ ²⁷	205	101	104	60.8	65.3	Overall mortality, thromboembolic stroke, bleeds, exercise tolerability, re-hospitalization, complications due to drugs,	1	Amiodarone

to maintain rhythm-control could include cardioversion. Mean follow-up length was 3.5 years. The primary endpoint was overall mortality, but several other clinical endpoints were reported.

The HOT CAFÉ study²¹ enrolled 205 patients with a mean duration of AF of 273 ± 112.4 days. Exclusion criteria were contraindications to treatment with antiarrhythmic drugs, arrhythmias associated with a reversible condition, thyroid dysfunction, pregnancy or lactation, myocardial infarction within 3 months, acute myocarditis, cardiac surgery, NYHA Class IV heart failure, severe systemic hypertension not responding to treatment, hypotension, history of transient ischaemic attack, haemorrhagic or ischaemic stroke, any mitral stenosis or other valve disease suitable for surgical intervention, R-R intervals exceeding 3 s, ventricular response to AF <90 b.p.m (unrelated to drugs used to reduce ventricular rate), bundle branch block or QT interval prolongation, alcoholism, contraindications to anticoagulation therapy, liver, kidney or central nervous system damage, advanced chronic lung disease or any non-cardiac illness associated with a life expectancy of <1 year, and participation in other studies. In the rate-control arm, beta-blockers, calcium antagonists, and digoxin alone or in combination were allowed. All patients randomized to rhythm-control strategy were treated with electrical cardioversion and subsequent antiarrhythmic drugs. Follow-up length was 1.7 ± 0.4 years. The primary endpoint was a composite of death from any cause, thromboembolic complications (especially disabling stroke), and intracranial or other major haemorrhages.

Overall results

The baseline study characteristics are summarized in *Table 1*. Average age across all studies was 65.1 years, 65.3% of patients were male, 29.9% of patients had history of coronary artery disease, and 52.7% of patients had arterial hypertension. The mean duration of follow-up was 1.9 years. Not all studies reported the exact number of patients with previous cerebrovascular accident or history of diabetes mellitus.

Although the funnel plot (*Figure 1*) might suggest a possible publication bias [given the greater standard error (log OR) for OR farthest from 1] no individual study achieved

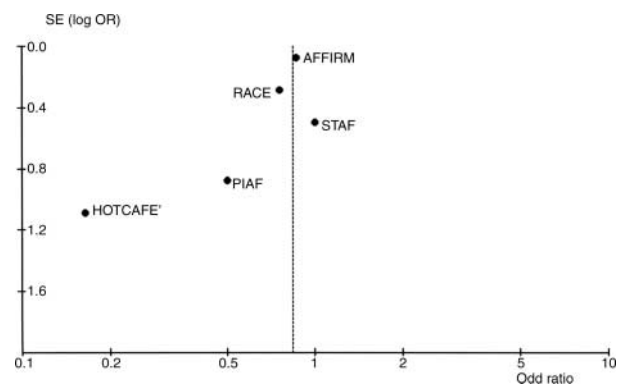


Figure 1 Funnel plot of included studies for the CEP. Although the funnel plot might suggest a possible publication bias [given the greater Standard Error (log OR) for OR farthest from 1], none of the individual studies achieved statistical significance for the CEP, thus excluding the possibility of publication bias.

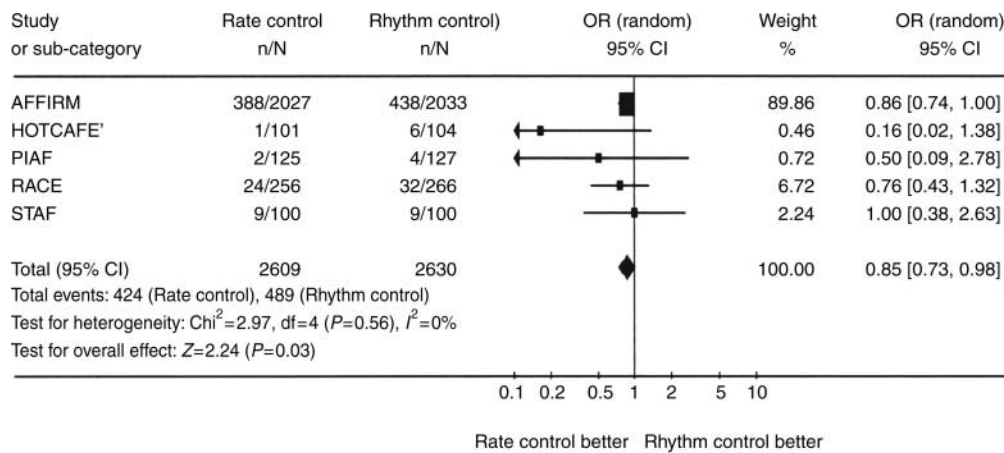


Figure 2 Single and pooled OR for the CEP. The rate-control approach is associated with a statistically significant lower rate of the combined endpoint compared with the rhythm-control strategy.

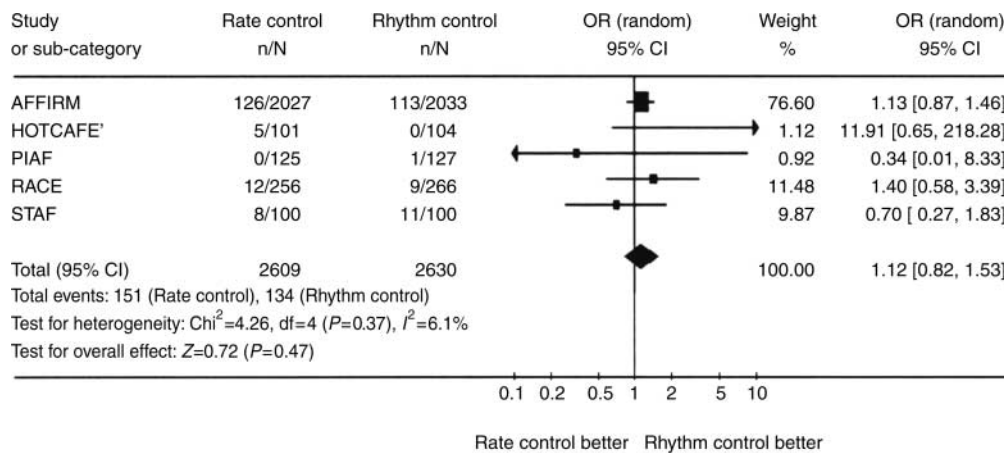


Figure 3 Single and pooled OR for major bleeds (intracranial and extracranial). There is no significant difference between the two strategies for the risk of major bleeds.

statistical significance for the CEP. A rate-control strategy compared with a rhythm-control approach was associated with a significantly lower risk of the CEP [OR 0.85 (0.73, 0.98), $P=0.03$] (Figure 2). There was a non-significant trend towards a reduced risk of the single endpoint of death [OR 0.87 (0.74, 1.02), $P=0.09$] and thromboembolic stroke [OR 0.8 (0.6, 1.07), $P=0.14$]. Rate-control vs. rhythm-control yielded a favourable risk difference for the CEP of -0.02 [$(-0.04, -0.01)$, $P=0.006$], resulting in an NNT of 50. NNT to avoid one death was 50 and to avoid one thromboembolic stroke 100. These findings imply that allocation of 1000 patients to a rate-control approach vs. a rhythm-control strategy, would avoid 20 deaths and 10 thromboembolic strokes per year.

Rate- and rhythm-control strategies were associated with similar rates of major bleeds [OR 1.12 (0.82, 1.53), $P=0.47$] (Figure 3), intracranial bleed [OR 1.16 (0.64, 2.10), $P=0.6$], extracranial bleed [OR 1.09 (0.94, 1.41), $P=0.5$], and systemic embolism [OR 0.93 (0.43, 2.02), $P=0.90$].

No significant heterogeneity was found in any of the analyses ($P > 0.17$), thus confirming the robustness and validity of the present quantitative overview. Moreover, no relevant

inconsistency ($I^2 < 25\%$) was found in all of the present analyses except for the endpoint of thromboembolic stroke, which showed moderate inconsistency ($I^2 > 50\%$).

In the three studies enrolling patients with a mean age ≥ 65 ¹⁸⁻²⁰ and in the two studies with a mean follow-up ≥ 20 months and a mean age ≥ 65 ,^{19,20} the rate-control strategy was associated with a significant reduction in the risk of the CEP, with an OR of 0.86 [0.74, 0.99], ($P=0.04$, NNT = 50, Figure 4) and an OR of 0.85 (0.74, 0.99) ($P=0.04$, NNT = 50, Figure 5), respectively, in the absence of a significant increase in the risk of major bleeds.

Notably, in the three studies with a mean follow-up < 20 months,^{17,18,21} independently of age, rate-control strategy is associated to a strikingly lower risk of thromboembolic stroke [OR 0.18 (0.04, 0.82), $P=0.03$] with an NNT of 33 (Figure 6).

Discussion

This meta-analysis shows that, in patients with first or recurrent AF, a rate-control strategy compared with a rhythm-control approach, ensures a reduction of the combined rate of all cause death and thromboembolic stroke with an

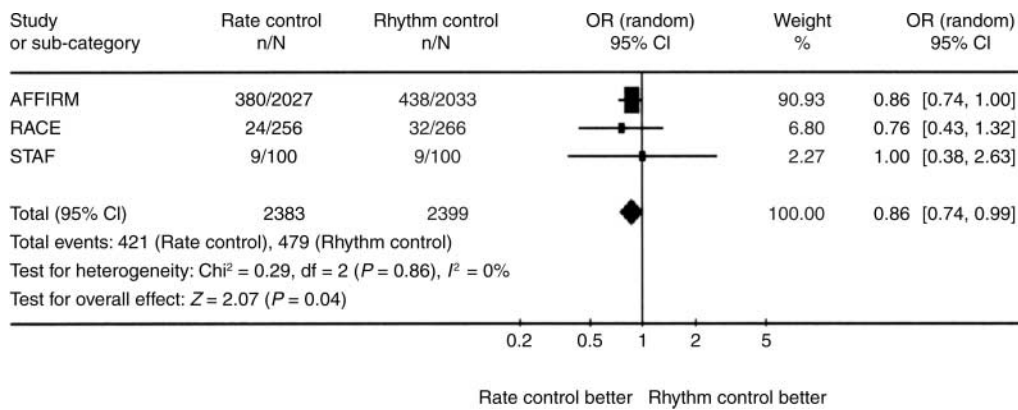


Figure 4 Single and pooled OR for the CEP in the three studies with a mean age ≥ 65 years. The rate-control approach confirms its superiority in reducing the risk of the combined endpoint.

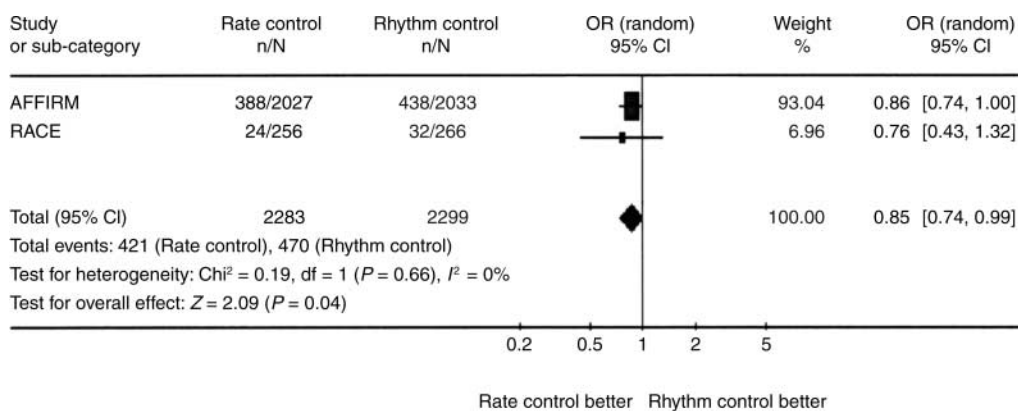


Figure 5 Single and pooled OR for the CEP in the two studies with a follow-up ≥ 20 months and a mean age ≥ 65 years. The rate-control approach shows a reduced risk of the combined endpoint.

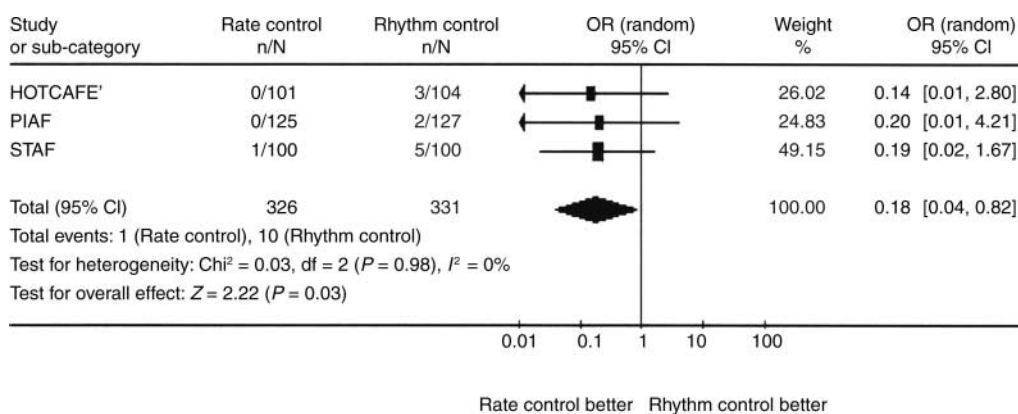


Figure 6 Single and pooled OR for stroke in the two studies with a mean follow-up < 20 months, independently of age. The rate-control approach strikingly reduces the risk of thromboembolic stroke.

NNT of 50. More specifically, the NNT by rate-control to save one all cause death was 50 and to save one thromboembolic stroke was 100, in the absence of significant heterogeneity and inconsistency. A rate-control strategy confirmed its superiority in the studies with older patient or longer follow-up.

The present analysis refers to patients with a mean age superior to 60, thus our findings cannot be extrapolated to younger patients. Furthermore, the available data from

included studies do not include patients with WPW syndrome, those who had previously undergone heart surgery, or those with NYHA Class IV heart failure. Of note, one study²⁰ enrolled $\sim 80\%$ of the total population examined in this meta-analysis; this study²⁰ failed to demonstrate that the superiority of one over the other strategy in reducing the CEP.

AF is a growing public health problem and its increasing prevalence in industrialized countries imposes an every

growing economic burden. Although there are clear guidelines for the acute management of symptomatic AF,¹ the best long-term approach for patients with first or recurrent AF is still debated with regard to quality of life,^{22,23} risk of new hospitalizations, and possible disabling complications, such as thromboembolic stroke, major bleeds, and death.

Two *post hoc* analyses of the AFFIRM study's population explored, respectively, the cause specific mortality,²⁴ and the relation among sinus rhythm, treatment, and survival.²⁵ In the first analysis, the investigators reported that the trend toward a lower total mortality in the rate-control vs. the rhythm-control group was entirely explained by non-cardiovascular deaths.²⁴ At multivariate analysis, significant predictors of non-cardiovascular death were rhythm-control strategy, age, male gender, previous smoking history, heart failure, and coronary heart disease. In the second, the authors analysed the time dependent predictors of all cause death. The presence of sinus rhythm and warfarin therapy were inversely associated, whereas digoxin and antiarrhythmic drugs were directly associated, with increased mortality after adjustment for other covariates.²⁵ Taken together, the findings of these analyses suggest that antiarrhythmic drugs may improve prognosis if they succeed in pursuing sinus rhythm, but this potential advantage has to be weighted against various non-cardiovascular adverse effects.

Notably, the most common drug used in the rhythm-control strategy was amiodarone¹⁷⁻²¹ which some studies found to be associated with an increased risk of non-cardiac mortality²⁶⁻²⁸ although other studies failed to confirm this association.^{29,30} On the other hand, warfarin (more frequently and constantly used in patients randomized to a rate-control strategy) has been found to have an unexpected beneficial effect on the extent of metastatic spread and on the hypercoagulable state often associated with malignancies.³¹ Furthermore, oral anticoagulants might allow an earlier detection of cancer by facilitating cancer-related bleeding.³¹

The trend towards a reduction of thromboembolic stroke in patients randomized to a rate-control strategy is probably related to a more frequent and prolonged utilization of oral anticoagulants. Moreover, the risk of stroke associated with electrical cardioversion is not entirely abolished by anticoagulation, which might explain the early striking excess of stroke in patients randomized to a rhythm-control strategy. It is conceivable that new and safer antiarrhythmic agents, associated with careful and prolonged anticoagulation, may, in future, show superiority of a rhythm-control strategy when compared with rate-control approach, especially if these agents are more effective than the currently available ones in improving cardiac performance through sinus rhythm restoration. Nonetheless, based on current evidence, our study suggests that a rate-control strategy represents the standard strategy against which to test new therapies, such as circumferential pulmonary vein ablation associated or not with oral anticoagulants.³²

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