Rate vs Rhythm Control in Patients With Atrial Fibrillation

A Meta-analysis

Simon de Denus, MSc; Cynthia A. Sanoski, PharmD; Jörg Carlsson, MD; Grzegorz Opolski, MD; Sarah A. Spinler, PharmD

Background: The 2 fundamental approaches to the management of atrial fibrillation (AF) are reestablishing and maintaining sinus rhythm (rhythm control) and controlling ventricular rate with atroventricular node blocking agents (rate control). We performed a meta-analysis of randomized controlled trials comparing these strategies in patients with AF to add precision to the relative merits of both strategies on the risk of all-cause mortality and to evaluate the consistency of the results between trials.

Methods: We performed a literature search in MEDLINE (1966 to May 2003), the Cochrane Controlled Trial Registry (first quarter of 2003), and International Pharmaceutical Abstracts (1970 to May 2003). Eligible trials were randomized controlled trials comparing pharmacologic rhythm and rate control strategies as first-line therapy in patients with AF.

Results: Five trials were identified that included a total of 5239 patients with persistent AF or AF that was considered likely to be recurrent. No significant difference was observed between the rate and the rhythm control arms regarding all-cause mortality, although a strong trend in favor of a rate control approach was observed (13.0% vs 14.6%; odds ratio, 0.87; 95% confidence interval, 0.74-1.02; P = .09). No heterogeneity was apparent between the trials (Q value = 2.97; P = .56).

Conclusions: In patients with persistent AF or with AF that is likely to be recurrent, a strategy of ventricular rate control, in combination with anticoagulation in appropriate patients, appears to be at least equivalent to a strategy of maintaining sinus rhythm by using currently available antiarrhythmic drugs in preventing clinical outcomes.

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Atrial fibrillation (AF) is the most frequently encountered sustained arrhythmia in clinical practice. It affects approximately 2.3 million individuals in the United States. Because the incidence of AF increases with age, it is expected that by 2030, more than 4 million individuals will be afflicted with this disease. This has enormous implications, as patients with AF have a 4- to 5-fold increased risk of stroke and a 2-fold increase in the risk of death.1,2

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The 2 fundamental approaches to the management of AF are reestablishing and maintaining sinus rhythm (rhythm control) and controlling ventricular rate with atroventricular nodal blocking agents (rate control).2 In the first strategy, electrical or pharmacologic cardioversion is followed by the use of antiarrhythmic agents to maintain sinus rhythm. In the latter strategy, atroventricular nodal blocking agents are given, generally with anticoagulation, to prevent thromboembolic events such as ischemic strokes. Maintaining sinus rhythm with the use of antiarrhythmic agents has several theoretical advantages over rate control, including a decrease in symptoms, an increase in exercise tolerance, a reduced risk of thromboembolic events, a reduced need for anticoagulants, and a reduced risk of death.3 On the other hand, the use of antiarrhythmic agents is not without risk, because these agents have proarrhythmic effects and many, such as amiodarone, have significant noncardiac toxicity.3

Nonetheless, despite these theoretical advantages of a rhythm control strategy over a rate control strategy and the overwhelming health problem that AF poses, data from randomized controlled clinical trials comparing these strategies have been scarce until recently.2 Because a number of such trials have recently been published,4,8 we conducted a meta-analysis to add precision to the relative merits of both
strategies and to evaluate the consistency of the results between trials. We hypothesized that rhythm control provides no significant survival benefit over rate control in the management of AF.

METHODS

TRIAL SEARCH STRATEGY

We performed a literature search in MEDLINE (1966 to May 2003), the Cochrane Controlled Trial Registry (first quarter of 2003), and International Pharmaceutical Abstracts (1970 to May 2003) by using the key words atrial fibrillation and randomized trial. We also searched the abstract books from the American Heart Association, American College of Cardiology, and European Heart Journal for 2001 and 2002. We extended our search to the references of the identified clinical studies and of published reviews and clinical guidelines. The search was conducted independently by 2 investigators to identify all eligible trials. Finally, international experts who had conducted prospective randomized trials comparing rate and rhythm control strategies were contacted to identify additional, published or unpublished, trials comparing such strategies.

In studies for which data of interest were missing, the primary investigator of the study was contacted to try to obtain this information. In addition, the US Food and Drug Administration's and the European Medicines Agency's Web sites were searched for additional unpublished data from these trials. Finally, pharmaceutical companies that sponsored trials for which data were unavailable were contacted.

INCLUSION AND EXCLUSION CRITERIA

Trials were included in the meta-analysis if they were randomized controlled trials comparing pharmacologic rhythm and rate control strategies as first-line therapy in patients with AF. Open trials were included because these trials were expected to compare, in many cases, complex multidrug strategies and because it was expected that one arm would include electrical cardioversion, which cannot be blinded. Trials conducted in patients after surgery or those evaluating invasive or surgical interventions (eg, atroventricular nodal ablation) as a primary strategy were excluded.

DATA EXTRACTION

Two of the investigators (S.D. and C.A.S.) independently identified and selected trials for inclusion. Differences regarding the inclusion of studies were identified and resolved by consensus or, as needed, with a third investigator. Data for each trial were abstracted by an investigator and confirmed by a second investigator. Any discrepancies were identified and resolved by consensus or, as needed, with a third investigator.

DATA QUALITY

Data quality of the trials was assessed on the basis of criteria put forward by Schulz and collaborators: (1) concealment of treatment allocation schedule, (2) generation of allocation sequence, (3) inclusion in the analysis of all randomized patients, and (4) double-blinding. Three quality categories were created: (A) low risk of bias (all quality criteria were met), (B) moderate risk of bias (at least 1 quality criterion was only partly met), and (C) high risk of bias (at least 1 criterion was not met).

OBJECTIVE AND DESIGN

The primary objective of this meta-analysis was to add precision to the effects of a rhythm control strategy compared with a rate control strategy on all-cause mortality. We believe this end point to be superior to cardiovascular mortality because it takes into consideration the possible adverse outcomes induced by noncardiac toxic effects of several of the commonly used antiarrhythmic agents. The all-cause mortality end point has been reported in all published trials except for the Rate Control vs Electrical Cardioversion for Persistent Atrial Fibrillation Study (RACE), in which cardiovascular mortality was reported. In this trial, all deaths were considered cardiovascular deaths unless proved otherwise, and no noncardiovascular deaths were reported. Therefore, we included the results of the cardiovascular mortality end point from this trial into our analysis of all-cause mortality. The secondary objective of this analysis was to evaluate the effect of both treatment strategies on the incidence of ischemic stroke.

STATISTICAL ANALYSIS

The meta-analyses were performed by computing odds ratios (ORs) in a random-effects model. Odds ratios were calculated by means of the Mantel-Haenszel technique for both all-cause mortality and ischemic stroke. For all ORs, the 95% confidence intervals (CIs) were calculated and graphic representations of the results were computed. The Q test was used to test for homogeneity of groupings. P < .05 was considered significant for the detection of heterogeneity and comparison between groups. All analyses were performed with Comprehensive Meta-analysis software, version 1.01.2 (Biostat, Englewood, NJ).

RESULTS

A total of 2856 citations were obtained in our search (Figure 1). We identified a total of 6 trials that compared rate and rhythm control strategies. Of these, 1 was excluded because it included patients who were in the period immediately after heart surgery. Therefore, only 5 trials met inclusion and exclusion criteria and were included. The trial acronyms and patient and study details are presented in the Table. As expected, all trials were given a grade of C because of their open design. Nonetheless, in all trials, data analyses were performed by intention to treat.

A total of 5239 patients were included in these 5 trials, of whom 38% were female, with a mean age of 69 years. Furthermore, approximately 67% had a history of hypertension and 28% had a history of heart failure. The follow-up period for each trial ranged from 1 to 3.5 years. The all-cause mortality end point was reported in 3 trials with a median follow-up period of 2 years. As expected, patients in rhythm control arm had a lower risk of death compared with patients in rate control arm (relative risk of death 0.67; 95% CI, 0.50-0.94; P = .02). For ischemic stroke, in the 3 trials in which data were available, the incidence of ischemic stroke was lower in the rhythm control arm compared with rate control arm (GEE odds ratio 0.36; 95% CI, 0.15-0.82; P = .02).
years. All trials included patients with persistent AF or AF that was considered likely to be recurrent. In the small trials (RACE, Strategies of Treatment of Atrial Fibrillation [STAF], Pharmacological Intervention in Atrial Fibrillation [PIAF], and How to Treat Chronic Atrial Fibrillation [HOT CAFE]), AF lasted from 110 days to 12.1 months before enrollment,\textsuperscript{4,6-8,13} while 69.2\% in the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial had the qualifying episode of AF for at least 2 days.\textsuperscript{5,12}

Amiodarone was the most frequently used antiarrhythmic in most trials, while the selection of atrioventricular nodal blocking agents varied between trials. In the small trials, the proportion of patients assigned to the rhythm control group who were in sinus rhythm at the end of the study varied greatly, from 38\% to 63.5\%. In AFFIRM, sinus rhythm was maintained in 73.3\% and 62.6\% after 3 and 5 years, respectively, in the rhythm control group. As expected, the proportion of patients in sinus rhythm was much lower in patients allocated to the rate control strategy in all of the trials.

Data for all-cause mortality were available from all trials, while data regarding ischemic strokes were available only from the AFFIRM,\textsuperscript{7} STAF,\textsuperscript{6} and HOT CAFE\textsuperscript{4} trials.

\textbf{MORTALITY}

No differences in all-cause mortality were observed between the rate and rhythm control groups in any of the individual trials. When the results of the trials were pooled (Figure 2),

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|c|}
\hline
Trial & AFFIRM\textsuperscript{4,12} & RACE\textsuperscript{3} & STAF\textsuperscript{6} & PIAF\textsuperscript{4,12} & HOT CAFE\textsuperscript{4} \\
\hline
No. of patients & 4060 & 522 & 200 & 252 & 205 \\
\hline
Duration of AF before randomization & NA (69.2\% had AF \geq 2 d for the qualifying episode) & 327 d (median) & 10.4 mo (mean) & 1.6 (Mean) & 1.7 (Mean) \\
\hline
Follow-up, y & 3.5 (Mean) & 2.3 (Mean) & 3.7 mo (mean) & 16.5 & Persistent AF \\
\hline
AF population & Age \geq 65 y or other risk factors for stroke or death; AF likely to be recurrent & Recurrent persistent AF or atrial flutter & Persistent AF with moderate to high risk of recurrence & Persistent, symptomatic AF & Persistent AF \\
\hline
Patient details & Mean age, y & 68 & 65.8 & 60.5 & 60.8 \\
\hline
 & Female, \% & 36.6 & 36.5 & 27 & 34.8 \\
\hline
 & HTN, \% & 49 & 62.5 & 50 & 64.4 \\
\hline
 & IHD, \% & 27 & 55.5 & 16.5 & 62 \\
\hline
Anticoagulation & Rate: required & 43.5 & 23 & 43.9 \\
\hline
 & Rhythm: physician discretion if sinus rhythm maintained & NS & ACCP guidelines & All patients & Rhythm: physician discretion if sinus rhythm maintained \\
\hline
AV blocking agents used in the rate control group, \% & Digoxin, 70.6 & \textsuperscript{*}β-Blocker, 45 & \textsuperscript{β}-Blocker, 9 & \textsuperscript{β}-Blocker, 89.1 & \textsuperscript{β}-Blocker, 9 \\
\hline
 & Diltiazem hydrochloride, 46.1 & Calcium channel blocker,\textsuperscript{†} 22 & Digoxin, 75 & Calcium channel blocker,\textsuperscript{†} 7.9 & Digoxin, 42.6 \\
\hline
 & Verapamil hydrochloride, 16.8 \\
\hline
AA agents most frequently used in the rhythm control group, \% & Amiodarone hydrochloride, 62.8 & Sotalol as initial agent, followed by other agents if necessary & Amiodarone, 42 & Amiodarone, 100 & Amiodarone, 56.7 \\
\hline
 & Sotalol hydrochloride, 41.4 & Class I, 12 & Sotalol, 22 & Sotalol, 24.0 & Propafenone, 36.5 \\
\hline
 & Propafenone hydrochloride, 14.5 & \\
\hline
Patients in sinus rhythm at end of study, \% & Rhythm & 39 & 38 & 56 & 63.5 \\
\hline
 & Rate & 10 & 9 & 10 & NS \\
\hline
Trial weight, \% & 39.3 & 23 & 14.6 & 16.8 \\
\hline
All-cause mortality & 27 & 55.5 & 16.5 & 62 & 6 \\
\hline
Ischemic strokes & 27 & 55.5 & 16.5 & 62 & 6 \\
\hline
\end{tabular}
\caption{Trials Comparing Rate and Rhythm Control Strategies in Patients With Atrial Fibrillation}
\end{table}

Abbreviations: AA, antiarrhythmic agent; ACCP, American College of Chest Physicians; AF, atrial fibrillation; AFFIRM, Atrial Fibrillation Follow-up Investigation of Rhythm Management; AV, atrioventricular; HTN, hypertension; IHD, ischemic heart disease; NA, not applicable; NS, not specified; PIAF, Pharmacological Intervention in Atrial Fibrillation; RACE, Rate Control vs Electrical Cardioversion for Persistent Atrial Fibrillation Study; STAF, Strategies of Treatment of Atrial Fibrillation.

\textsuperscript{†}Diltiazem or verapamil.

\textsuperscript{*}Heart failure was defined as history of congestive HF in AFFIRM, history of HF in RACE, New York Heart Association class greater than I in STAF, and New York Heart Association class greater than I in HOT CAFE.
ISCHEMIC STROKES

The majority of ischemic strokes occurred in the AFFIRM trial. When the results of AFFIRM, STAF, and HOT CAFE were pooled, the proportion of patients experiencing an ischemic stroke was similar between the rate control and rhythm control groups (3.5% vs 3.9%, respectively; OR, 0.50; 95% CI, 0.14-1.83; P = .30), with no evidence of heterogeneity between trials (Q value = 3.6; P = .16) (Figure 3).

COMMENT

The results of our meta-analysis suggest that in most patient populations with persistent AF or a high risk of recurrent AF, a strategy of maintaining rhythm control does not translate into significant benefit on survival compared with a strategy of rate control in combination with anticoagulation in patients at risk of experiencing a thromboembolic event. The trend we observed suggests that the use of antiarrhythmic agents to maintain sinus rhythm may not be equivalent to a rate control strategy but, in fact, may be inferior as a therapeutic option with regard to survival.14 The 1.6% absolute difference in mortality observed could translate into a nonnegligible number needed to harm of 63. Clinically, this would clearly make rhythm control with antiarrhythmic agents a second-line therapy, limited to patients in whom rate control fails and who show symptomatic improvement after the restoration of sinus rhythm. Nonetheless, because this result did not reach statistical significance, additional data are required to clearly establish whether this trend would become statistically significant with sufficient power.

Although we observed no statistically significant heterogeneity between the clinical trials, its is important to underscore that this does not necessarily rule out heterogeneity, given the small number of trials. This is particularly evident when the results from each trial are evaluated qualitatively. While 2 of the trials suggested a benefit for the rate control strategy over the rhythm control strategy (AFFIRM and HOT CAFE), one suggested opposite results (STAF), and 2 demonstrated no difference (PIAF and RACE). Furthermore, when only the small trials were considered separately, the 2 strategies appeared to be equivalent. Whether these discrepancies reflect the small number of deaths in the small trials or other factors is unclear, but differences in the strategies used in each trial could have contributed to these apparent differences.

Although the results of our meta-analysis appear to contradict the common perception that maintenance of sinus rhythm is superior to ventricular rate control, there are several possible reasons to explain them. One possible explanation is that, although maintenance of sinus rhythm may provide a survival benefit, this benefit may be negated by the potential proarrhythmic effects and noncardiac toxicities of antiarrhythmic agents. Consistent with this hypothesis, in AFFIRM, the rate of torsades de pointes and cardiac arrest due to bradycardia or pulseless electrical activity was significantly higher in the rhythm control group. Such results were observed despite a high rate of use of amiodarone, which is considered to have a low risk of proarrhythmia, but a significant risk of noncardiac toxicities.3 Tolerance-related problems with antiarrhythmic agents were also highlighted in the RACE trial, in which rates of severe adverse effects were significantly higher in the rhythm control group.7 Similarly, in the PIAF trial, in which amiodarone was used in all patients, a higher rate of adverse effects occurred in the rhythm control group, which led to a higher rate of early drug discontinuation.4

Table 2. Odds ratios (ORs) for the end point of all-cause mortality for individual trials and the combined analysis. HOT CAFE indicates How to Treat Chronic Atrial Fibrillation; PIAF, Pharmacological Intervention in Atrial Fibrillation; RACE, Rate Control vs Electrical Cardioversion for Persistent Atrial Fibrillation Study; STAF, Strategies of Treatment of Atrial Fibrillation; AFFIRM, Atrial Fibrillation Follow-up Investigation of Rhythm Management; and CI, confidence interval.

<table>
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<td>2/127</td>
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<td></td>
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<td>4/100</td>
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<td>356/2033</td>
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Figure 2. Odds ratios (ORs) for the end point of all-cause mortality for individual trials and the combined analysis. HOT CAFE indicates How to Treat Chronic Atrial Fibrillation; PIAF, Pharmacological Intervention in Atrial Fibrillation; RACE, Rate Control vs Electrical Cardioversion for Persistent Atrial Fibrillation Study; STAF, Strategies of Treatment of Atrial Fibrillation; AFFIRM, Atrial Fibrillation Follow-up Investigation of Rhythm Management; and CI, confidence interval.

Figure 3. Odds ratios (ORs) for the end point of ischemic strokes for individual trials and the combined analysis. HOT CAFE indicates How to Treat Chronic Atrial Fibrillation; STAF, Strategies of Treatment of Atrial Fibrillation; AFFIRM, Atrial Fibrillation Follow-up Investigation of Rhythm Management; and CI, confidence interval.
Another possible reason for the lack of benefit in the rhythm control group is the difficulty of maintaining sinus rhythm (Table). The efficacy of antiarrhythmic drugs in the rhythm control group may be overestimated, as previous reports have suggested that a significant number of patients experience asymptomatic paroxysmal AF, which would decrease the apparent benefit of maintaining sinus rhythm. Finally, discontinuation of warfarin sodium in some patients who were believed to be in sinus rhythm could also have contributed to the results observed.

Taken together, these results highlight the low efficacy and high frequency of toxic effects of using antiarrhythmic agents to maintain sinus rhythm. Maintenance of sinus rhythm could become a more attractive treatment strategy with the eventual development of safer and more effective agents or ablation procedures. From our meta-analyses also suggest that a rhythm control strategy has no impact on the risk of experiencing an ischemic stroke compared with a rate control strategy when patients at risk of thromboembolic events are receiving anticoagulation, although complete data were available for only 3 of the 5 included trials. Whether such an observation applies to patients at lower risk of ischemic stroke or those who have a contraindication to anticoagulation therapy cannot be extrapolated from our results. Furthermore, because a large proportion of ischemic strokes (113 of 157 in AFFIRM; 2 of 6 in STAF) and embolic events (29 of 35 in RACE) occurred in patients in whom anticoagulation had been stopped or had a subtherapeutic international normalized ratio, it appears that the appropriate use of anticoagulation is the key factor in preventing embolic events in patients with atrial fibrillation.

Our results should be interpreted in light of the population studied. In general, the patients included in these 5 trials were those with persistent AF or high risk of recurrence who were at high risk of thromboembolic events and receiving anticoagulation therapy. Therefore, these results should not be extrapolated to patients with paroxysmal AF at low risk of recurrence, patients at low risk of thromboembolic events, or patients with heart failure. The ongoing Atrial Fibrillation and Congestive Heart Failure study will provide further insight into the comparative efficacy and safety of rate and rhythm control in this patient population.

Finally, as is inherent in any meta-analysis, it is important to underline that our results are dependent on the quality of the trials conducted and the publication or availability of their results. First, because all the trials included were open trials, possible bias cannot be excluded. Because of the complexity of the strategies evaluated in most of these trials and the fact that cardioversion is an integrated part of the rhythm control strategy and cannot be blinded, it appears virtually impossible to conduct a double-blind trial to compare these strategies. Furthermore, publication bias affecting our findings cannot be completely ruled out. This is particularly relevant given the possibility that one strategy may prove to be inferior to the other.

In conclusion, the results of this meta-analysis suggest that in patients with persistent AF or with AF that is likely to be recurrent, a strategy of ventricular rate control, in combination with anticoagulation in patients at risk of thromboembolic events, appears to be at least equivalent to a strategy of maintaining sinus rhythm with currently available antiarrhythmic drugs and may, in fact, prove to be superior. Although a rhythm control strategy may be appropriate in selected patients, it should not be considered the preferred strategy in all patients.

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Correspondence: Sarah A. Spinler, PharmD, Department of Pharmacy Practice and Pharmacy Administration, Philadelphia College of Pharmacy, University of the Sciences in Philadelphia, 600 S 43rd St, Philadelphia, PA 19103-4495 (s.spinle@usp.edu).

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