Electrophysiology

Clinical factors that influence response to treatment strategies in atrial fibrillation: The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Study

The AFFIRM Investigators*

Background  The AFFIRM Study was a randomized multicenter comparison of 2 treatment strategies, rate-control versus rhythm-control, in high-risk patients with atrial fibrillation (AF). The primary outcome of the trial showed no overall difference in survival between strategies. However, there may be important patient subgroups for which there are identifiable differences in outcome with 1 of the 2 strategies.

Methods and Results  Subgroups that were prespecified for analysis from the main AFFIRM Study were age, sex, coronary artery disease (CAD), hypertension, congestive heart failure (CHF), left ventricular ejection fraction (LVEF), rhythm at randomization, first episode of AF, and duration of the qualifying episode of AF. Baseline characteristics were analyzed for each subgroup. Adjusted hazard ratios for each subgroup and for each stratum were generated using Cox models, and these models were used to determine whether treatment strategy affected overall survival differentially by subgroup.

Adjusted survival was worse for patients ≥65 years and for patients with a history of CHF, CAD, or an abnormal LVEF. In the adjusted analyses, the effect of treatment strategy was similar within all of the prespecified subgroups. When each subgroup stratum was analyzed separately, patients ≥65 years and patients without a history of CHF had significantly better outcome with rate-control therapy (each P < .01).

Conclusions  Overall, treatment effect for rate control versus rhythm control was the same within each subgroup. However, certain selected patient categories may have better survival with one particular strategy for management of AF. (Am Heart J 2005;149:645-9.)

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia seen in the adult population. It is an independent predictor of mortality and is associated with a high morbidity, in particular, stroke. The natural history of AF is dominated by its association with older age. Moreover, age has a major impact upon treatment options because the elderly are more prone not only to the complications of thromboembolism but also to the risk of bleeding on anticoagulants.

The recently reported AFFIRM Study was a randomized multicenter comparison of rate-control versus rhythm-control treatment strategies in patients with AF requiring therapy who had a high risk of stroke or death, excluding those patients with permanent AF. The primary outcome of the trial was that there was no significant difference in overall survival with either strategy, although there was a trend toward increased survival in the rate-control group (P = .08).

Although there may be no overall difference in survival outcome with either a rate-control or a rhythm-control strategy for these patients with AF, there may be important patient subgroups, for example, the elderly or patients with congestive heart failure (CHF), for which one or the other strategy is superior. Patients with CHF (either with or without left ventricular systolic dysfunction) are an important subgroup because there is considerable evidence that sinus rhythm may be associated with a favorable outcome. The goal of this study was to examine the major subgroups in the AFFIRM Study that were prespecified at the beginning of
the study and determine whether there were any differences in outcome with either rate-control or rhythm-control treatment strategies.

**Methods**

The design of the AFFIRM Study and the baseline characteristics of the patients enrolled have been previously reported.\(^{19-20}\) Patients in the trial had AF and at least 1 risk factor for stroke or death. Patients were randomized to 1 of 2 treatment strategies, either rate control with anticoagulation or rhythm control with anticoagulation. The primary end point of the trial was total mortality. Each local site’s institutional review board approved the protocol, and each patient gave informed written consent.

Four thousand sixty patients enrolled in the trial and were followed up for a mean of 3.5 years.\(^8\) Subgroups that were prespecified for analysis from the main AFFIRM Study were age, sex, coronary artery disease (CAD), hypertension, CHF, left ventricular ejection fraction (LVEF), rhythm at randomization, first episode of AF, and duration of the qualifying episode of AF. Baseline characteristics were analyzed for each subgroup.

**Statistical analysis**

Baseline comparisons between the prespecified subgroups were based on the Student t test for continuous variables and the \(\chi^2\) test for categorical variables. When the assumptions of the \(\chi^2\) test were not met because of low expected cell counts, Fisher exact test was used to compare the 2 groups.

Cox proportional hazards models included covariates of all prespecified subgroup variables, as well as the variables of a history of smoking, prior stroke, and diabetes. To assess subgroup differences in treatment effect, 2-way interactions of treatment arm by subgroup were assessed after forcing all main effect subgroup covariates into the Cox model. In addition, within each subgroup, stratified Cox models including all other covariates were used to generate adjusted hazard ratio estimates associated with treatment assignment. These analyses correspond to those presented in Figure 2 in the article presenting the AFFIRM results,\(^8\) except that the analyses here reflect hazard ratios after adjustment for baseline covariates.

All statistical tests were 2-tailed, using a significance level of \(P < .01\) because of the large number of statistical tests performed.

**Results**

**Baseline comparisons**

Consistent with the enrollment criterion that stated that a patient <65 years needed to have another risk factor for stroke or death, important differences existed within the age (<65 vs \(\geq 65\)) subgroup (data not shown). Among patients <65 years old, significantly more patients were men, were members of minority groups, and had a history of hypertension, diabetes, or an abnormal LVEF. Younger patients were less likely to have a history of CAD and more likely to have abnormal left atrial size or a history of CHF. Initial therapy and characteristics of AF were similar in both age groups, except for a lower percentage of younger patients with AF at the time of randomization.

With regard to sex differences, men enrolled in the AFFIRM Study were, on average, younger than women. Men were less often members of minority groups, had a higher prevalence of CAD, and had a lower prevalence of hypertension. Men more often had an abnormal LVEF or left atrial size, compared with women, and more often had AF at the time of randomization. Men less often had the qualifying episode of AF lasting <2 days, and both the prior medication exposure and the initial medications used in AFFIRM were different.

For the other prespecified subgroups, baseline differences were consistent with known risk factors for cardiac disease. For example, patients with CHF at baseline were more likely to be a minority and to have a history of CAD, abnormal LVEF, abnormal left atrial size, hypertension, or diabetes. Patients with CHF were also more likely to be presenting with their first episode of AF, to have AF at randomization, and to have duration of the qualifying episode of AF \(\geq 2\) days than patients without CHF. Digoxin was the drug most commonly initially prescribed or continued in the rate-control group among patients with CHF, whereas \(\beta\)-blockers and digoxin were both prescribed as initial therapy in 38% of patients without CHF. Amiodarone was the most commonly prescribed initial therapy among CHF patients in the rhythm-control group, whereas amiodarone and sotalol were used equally often in patients without CHF in the rhythm-control arm.

Outcomes in patients with AF may depend on the ability to maintain a patient on antiarrhythmic drugs and to maintain sinus rhythm. In this regard, discontinuation of any antiarrhythmic drug occurred in 43% of older patients randomized to the rhythm-control arm versus 41% among younger rhythm-control patients (for amio-
Table II. Adjusted hazard ratios for overall survival in prespecified subgroups

<table>
<thead>
<tr>
<th>Subgroup strata</th>
<th>Adjusted hazard ratio*</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;65</td>
<td>0.81</td>
<td>.06</td>
</tr>
<tr>
<td>Age ≥65</td>
<td>1.32</td>
<td>.06</td>
</tr>
<tr>
<td>History of CHF</td>
<td>0.94</td>
<td>.06</td>
</tr>
<tr>
<td>No history of CHF</td>
<td>1.44</td>
<td>.94</td>
</tr>
<tr>
<td>Men</td>
<td>1.20</td>
<td>.71</td>
</tr>
<tr>
<td>Women</td>
<td>1.30</td>
<td>.38</td>
</tr>
<tr>
<td>CAD</td>
<td>1.22</td>
<td>.21</td>
</tr>
<tr>
<td>No CAD</td>
<td>1.25</td>
<td>.26</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.31</td>
<td>.08</td>
</tr>
<tr>
<td>No hypertension</td>
<td>1.08</td>
<td>.42</td>
</tr>
<tr>
<td>LVEF abnormal</td>
<td>1.05</td>
<td>.85</td>
</tr>
<tr>
<td>LVEF normal</td>
<td>1.33</td>
<td>.33</td>
</tr>
<tr>
<td>AF at randomization</td>
<td>1.16</td>
<td>.42</td>
</tr>
<tr>
<td>Sinus rhythm at randomization</td>
<td>1.31</td>
<td>.08</td>
</tr>
<tr>
<td>First AF episode</td>
<td>1.23</td>
<td>.80</td>
</tr>
<tr>
<td>Recurrent AF episode</td>
<td>1.23</td>
<td>.95</td>
</tr>
<tr>
<td>Duration of AF &lt;2 days</td>
<td>1.10</td>
<td>.85</td>
</tr>
<tr>
<td>No CAD</td>
<td>1.29</td>
<td>.01</td>
</tr>
</tbody>
</table>

*From stratified analysis, adjusted for all other subgroup variables and diabetes, stroke, and smoking histories. Hazard ratio reflects comparison of rhythm-control to rate-control with values >1, indicating increased risk of death in the rhythm-control arm.
†P value for interaction of subgroup with treatment arm.
‡P < .01 in stratified analyses.

Darazone, the discontinuation rates were 27% vs 28%, respectively, both P = NS). Regarding the maintenance of sinus rhythm, older rhythm-control patients were no more likely to remain continuously in sinus rhythm over the course of the study than younger patients (37% vs 32%, P = NS).

Cox proportional hazards models and multivariate analyses

The overall outcome of the study continued to show no significant survival difference between treatment strategies (hazard ratio 1.23, range 0.96-1.57) (Table I) when adjusted for differences in baseline variables.

In the adjusted Cox models of the subgroups, decreased survival was associated with age ≥65 years, a history of CHF, a history of CAD, and having an abnormal LVEF (Table I).

There were no significant differences in treatment effect within any of the subgroups based on analyses assessing all subgroup by treatment interactions (Table II). For example, the hazard ratio (rhythm-control to rate-control) for men was 1.20, not significantly different from the hazard ratio for women (1.30, P = .94).

However, individual patient groups in some categories showed suggestive differences between rate-control and rhythm control in adjusted analyses. In older patients (≥65 years) and in patients with no history of CHF, adjusted Cox models indicated that overall survival was significantly better in the rate-control arm (P < .01). In all other subgroups, there were no significant treatment differences in overall survival (Table II).

Discussion

The results of this subgroup analysis confirm the primary result of the AFFIRM Study: overall survival is not statistically different between a rate-control and rhythm-control treatment strategy in the treatment for patients with AF, with no significant differences in survival within prespecified subgroups. The effect of treatment arm (rate-control or rhythm-control) was not different between the 2 strata within any subgroup. However, when each subgroup stratum was analyzed individually, some possible treatment effects seemed to emerge. Older patients and patients without a history of CHF fared significantly better with rate-control.

There are several potential explanations for the finding in older patients. Older patients may have more adverse effects from antiarrhythmic drugs, offsetting any potential benefits to remain in sinus rhythm. Alternatively, they may be less likely to stay in sinus rhythm with antiarrhythmic drugs, thus experiencing the risks of the drugs without receiving any potential benefit. In this regard, we found that discontinuation of antiarrhythmic drugs and the likelihood of remaining in sinus rhythm were equally common in older and younger patients randomized to rhythm-control, and therefore other explanations need to be considered.

Prior studies have demonstrated that AF is associated with adverse hemodynamic changes that could theoretically result in an increase in the detrimental neurohormonal milieu of CHF.21 Several prior studies on registry populations and subsets of patients entered into randomized controlled trials have suggested that AF is associated with a worse prognosis in patients with heart failure.6,9-18,22,23 Thus, the presence of sinus rhythm in patients with left ventricular dysfunction who have a history of AF appears to be associated with an improved outcome, although it may simply be the result of sinus rhythm being a marker for good outcome, rather than being the causative mechanism.24

Similar results were reported in the DIAMOND Study, in which all patients had ejection fractions of ≤35%.11 On the other hand, in the RACE Study, which showed no difference in the outcome with a rate-control or a rhythm-control strategy, there was likewise no difference in the outcome according to whether patients were in sinus rhythm or AF at the end of follow-up.25

The AFFIRM Study did not require a diagnosis of hypertension in patients <65 years; rather, at least 1 risk factor for stroke was required in those <65 years, of which hypertension was one such risk factor, whereas age alone was sufficient for inclusion in the trial in patients ≥65 years. This difference led to a higher proportion of patients <65 years who had hypertension...
compared with those $\geq 65$ (82% vs 67%, $P < .0001$). If the value of rate-control related primarily to its effect on undertreated hypertension, one might have expected the rate-control strategy to be more beneficial in patients $<65$ who more often had hypertension. We found the opposite, and thus the benefit of a rate-control strategy cannot simply be a direct effect of rate-control agents on blood pressure.

This study has demonstrated a few subgroups in which one treatment strategy might seem to be superior to another. Hazard ratios $>1.0$ (indicating superiority of the rate-control strategy) were seen for patients $\geq 65$ years and patients without a history of CHF (both $P < .01$). Hazard ratios $<1.0$ (indicating superiority of the rhythm-control strategy) were seen only for patients $<65$ years and for patients with a history of CHF, although neither was significant. The latter patients are the subject of an ongoing clinical trial of rate-control versus rhythm-control in the setting of CHF.26

Limitations

The data presented are subgroup analyses of the main trial; thus, the results should be interpreted with caution and be considered to be only hypothesis-generating, despite the fact that these were prespecified analyses. Numerous comparisons performed in these analyses may lead to spurious results, even at a significance level of .01. Conversely, an observed lack of statistical significance in a subgroup may be a result of lack of power rather than absence of a relationship.

The design of the AFFIRM Study may also have influenced the results of subgroup analyses, because patients $<65$ years had to have at least 1 risk factor for stroke or death. This criterion for inclusion in the AFFIRM study population made the younger and older patients more comparable in regards to overall survival but may bias the comparison of the younger to older age groups. However, treatment comparisons within an age subgroup should not be biased by the AFFIRM study design, as long as conclusions are based on the population studied.

Conclusions

For most AFFIRM patient subgroups, rate control is associated with similar survival compared with rhythm-control. The observation that older patients and patients with no history of CHF had significantly better survival with the rate-control strategy is an intriguing observation, and it suggests avenues for further studies.

References


Appendix

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