Spontaneous Conversion and Maintenance of Sinus Rhythm by Amiodarone in Patients With Heart Failure and Atrial Fibrillation

Observations from the Veterans Affairs Congestive Heart Failure Survival Trial of Antiarrhythmic Therapy (CHF-STAT)

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Background—In a multicenter, double-blind, placebo-controlled study, the long-term effects of amiodarone on morbidity and mortality in patients with congestive heart failure (CHF) and atrial fibrillation (AF) were evaluated during a 4-year period.

Methods and Results—Of 667 patients with CHF, 103 (15%) had AF at baseline. Of these, 51 were randomized to amiodarone and 52 to placebo. The group with sinus rhythm and the group in AF were comparable except for a higher proportion of AF in patients with nonischemic versus ischemic cardiomyopathy (41% versus 27%, P<0.005). The mean ventricular response (VR) during AF over 24 hours was reduced by amiodarone at 2 weeks (20%, P=0.001), at 6 months (18%, P=0.001), and at 12 months (16%, P=0.006). Maximal VR was reduced 22% (P=0.001) at 2 weeks, 19% (P=0.001) at 6 months, and 14% (P=0.001) at 12 months. Sixteen of 51 patients on amiodarone and 4 of 52 on placebo converted to sinus rhythm during the study (χ²=9.23, P=0.002). During follow-up, 11 of 268 patients in sinus rhythm on amiodarone at baseline and 22 of the 263 in sinus rhythm on placebo developed AF; the difference was significant (χ²=12.88, P=0.005). Analysis of total mortality during follow-up showed a significantly lower mortality rate (P=0.04) in patients in AF at baseline who subsequently converted to sinus rhythm on amiodarone than in those who did not convert to sinus rhythm on the drug.

Conclusions—In patients with CHF, amiodarone has a significant potential to spontaneously convert patients in AF to sinus rhythm, with patients who convert having a lower mortality rate than those who do not. The drug prevented the development of new-onset AF and significantly reduced the VR in those with persistent AF. (Circulation. 1998;98:2574-2579.)

Key Words: fibrillation, atrial ■ heart failure ■ drugs ■ survival

Atrial fibrillation (AF) has emerged as the most common cardiac arrhythmia requiring treatment for significant morbidity and possibly mortality associated with the arrhythmia.1–4 There are 2 fundamental therapeutic approaches: restoration and maintenance of sinus rhythm and antiaggregation to reduce thromboembolism and control ventricular rate to alleviate symptoms.5–7 The relative therapeutic merits of these 2 lines of treatment have not been clearly defined, but the issue is under investigation in a number of controlled clinical trials.5–7

It is known that the incidence of AF increases with age and as ventricular function declines, especially with the onset of congestive cardiac failure.2,3 For example, the prevalence of AF increases from 10% in patients with NYHA class II symptoms to 40% in patients with NYHA class IV symptoms.8 However, the prognostic significance of AF in the setting of congestive heart failure is controversial, and it is not clear whether restoration of sinus rhythm will improve survival in patients with heart failure.

Barring digoxin,9 conventional antiarrhythmic drug therapy for rate control or for maintaining sinus rhythm in patients with AF in the setting of congestive heart failure is associated with an increased risk of potentially fatal proarrhythmia or aggravation of heart failure caused by
negative inotropic effects. In this context, the multifaceted pharmacological profile of amiodarone is of particular interest. Among class III agents, it has been shown to exhibit the lowest proarrhythmic potential and it does not appear to exert a potent negative inotropic effect in heart failure. Indeed, it has been found to increase left ventricular ejection fraction (LVEF). A number of nonrandomized trials of low-dose amiodarone for AF have reported high efficacy for maintaining stability of sinus rhythm and relatively low incidence of toxicity in patients who are refractory to treatment with multiple conventional antiarrhythmic drugs. However, the potential of the drug for controlling AF in patients with congestive heart failure is not clearly defined.

In the Veterans Affairs (VA) Congestive Heart Failure Survival Trial of Antiarrhythmic Therapy (CHF-STAT), long-term treatment with amiodarone therapy was compared with placebo in a group of 667 patients with dilated cardiomyopathy, decreased ejection fraction, and NYHA class II to IV symptoms of heart failure. One hundred three of these patients at baseline were in AF. The effects of amiodarone versus placebo in these patients on conversion to and maintenance of sinus rhythm relative to survival patterns form the basis of the present report.

Methods

Study Design and Patient Population

The details of the study design and baseline characteristics of the patients enrolled in the study have been described previously. In brief, patients with an established history of heart failure (≥3 months) and NYHA functional class II, III, or IV were enrolled at 25 VA Medical Centers in the US. All patients were required to have LVEF ≤40% as measured by radionuclide angiography and evidence of dilated cardiomyopathy as denoted by either a cardiothoracic ratio >0.50 on chest x-ray or left ventricular end-diastolic dimension ≥55 mm. In addition, all patients were required to have dyspnea on exertion or history of paroxysmal nocturnal dyspnea. Patients were also required to have frequent ventricular premature beats (≥10 per hour averaged over a 24-hour period) on 24-hour Holter monitoring, but they were excluded if they had evidence of sustained ventricular tachycardia or symptomatic arrhythmia. Although patients could be given digoxin and diuretic as needed by their primary care physicians, all patients were required to be on an angiotensin-converting enzyme inhibitor or another effective vasodilator regimen such as hydralazine and an oral nitrate.

Exclusion criteria included women of childbearing age; myocardial infarction or revascularization within 3 months; heart failure due to uncorrected primary valvular disease or restrictive or infiltrative cardiomyopathy; a history of aborted sudden death, symptomatic ventricular arrhythmia, or need for continuing antiarrhythmic therapy; QRS duration of ≥180 milliseconds or QTc of ≥500 milliseconds; active drug or alcohol abuse; uncontrolled thyroid disease; noncardiac conditions or malignancy that was likely to be fatal within 3 years; and symptomatic hypotension or systolic blood pressure of <90 mm Hg. Treatment with β-blockers or investigational medications was not permitted.

The protocol was approved by the institutional review board of each participating medical center and by the Human Rights Committee of the Hines VA Cooperative Studies Program Coordinating Center. The conduct of the study was monitored by the executive committee and by an external data and safety monitoring board. All participants provided written informed consent before entering the study.

Study Enrollment and Follow-up

Patient enrollment began in September 1989 and continued for 3.5 years, with a minimum follow-up period of 1 year for all patients. During the initial baseline phase, medical therapy for heart failure was optimized, drug compliance was tested, and radionuclide angiography and 24-hour Holter monitoring were performed. Patients fulfilling the enrollment criteria were randomly assigned to amiodarone or placebo by the use of a stratification scheme for cause of heart failure (ischemic or nonischemic), LVEF (≥30% versus <30%), and participating medical center. The cause of heart failure was classified as ischemic if patient had a history or EKG evidence of myocardial infarction, current or previous history of angina pectoris, positive stress test, or angiographic evidence of coronary artery disease. The remaining patients were classified as having nonischemic cause.

Treatment with amiodarone or matching placebo began on an outpatient basis at a total daily dose of 800 mg for the first 2 weeks, 400 mg QD for the next 50 weeks, and 300 mg QD for the remainder of the 4.5-year trial. Dose reduction or temporary discontinuation was permitted if limiting side effects occurred, but reinstitution of the protocol-stipulated therapy was encouraged. Patients who permanently discontinued the study drug were followed to the end of the trial and analyzed by the intention-to-treat principle. Clinic visits were scheduled after 2 weeks and monthly thereafter; these visits included an interim history and complete cardiovascular examination. Laboratory testing was performed at appropriate intervals.

Twelve-lead EKGs and 24-hour Holter monitoring were repeated at 2 weeks, 3 months, 6 months, 12 months, and 24 months after randomization. To evaluate the effects of amiodarone versus placebo on AF in the present study, we identified all patients who had AF on baseline 12-lead EKG and 24-hour Holter recordings. Of those identified as having AF, 14% and 13% of the amiodarone and placebo patients, respectively, had intermittent AF on 24-hour Holter monitoring. On subsequent visits at 2 weeks, 6 months, and 12 months, 12-lead EKGs were evaluated for the presence or absence of AF, and, when AF was present, average ventricular rate was calculated. In addition, for patients with AF, we evaluated the average ventricular rate, minimum ventricular rate, and maximum ventricular rate during the 24-hour period from Holter recordings obtained at baseline and at 2 weeks and 6 months after randomization to the study medications. We specifically evaluated the effects of amiodarone versus placebo on rate control versus conversion to sinus rhythm in patients who had AF detected on baseline 12-lead EKG and during 24-hour recording sessions. Because patients with CHF have a tendency to frequently go into AF, we also evaluated the occurrence of new AF in patients who were in sinus rhythm at baseline. In addition, we compared the survival patterns in AF patients who converted to sinus rhythm to those who remained in AF during the follow-up period.

Statistical Analysis

Differences between treatment groups in categorical and continuous variables were detected with χ² test and Student’s t test, respectively. Changes in ventricular response rates between the treatment groups over time were examined based on application of Student’s t test to the difference in ventricular rate from baseline to the time point of interest. Kaplan-Meier survival techniques were used to examine differences between various groups in time from randomization to cardiac death. Patients not experiencing the event were censored at the date of last follow-up visit or the date of death from another cause. In all cases, a 2-sided α level of 0.05 was considered statistically significant. Data are presented as mean±SD.

Results

Of the total 667 patients enrolled in the study, 103 patients (15%) had AF at baseline evaluation. In the study as a
whole, there was no significant difference between patients randomized to amiodarone versus those assigned to placebo. Table 1 displays the comparison of baseline clinical variables in patients with AF at baseline who were randomized to amiodarone (n = 51) versus those randomized to placebo (n = 52). These results suggest that the 2 drug groups were comparable at baseline. Ninety-five percent of patients with AF were on digoxin at baseline.

Rate Control
Figure 1 shows the average ventricular rate in patients with AF on 12-lead EKG at baseline and at 2 weeks, 6 months, and 12 months after randomization. Although at baseline the average ventricular rate was comparable in the amiodarone and the placebo groups, at 2 weeks the average ventricular rate in the amiodarone group was significantly lower than in the placebo group. The beneficial effect of amiodarone on rate control was sustained throughout the evaluation periods at 6 months and 1 year. In contrast, there was no significant change in the average ventricular rate at any point of evaluation in the placebo group.

Spontaneous Conversion to Sinus Rhythm
All patients with AF at baseline and those in sinus rhythm were evaluated at 2 weeks, 6 months, and yearly thereafter for any changes in the rhythm. In the amiodarone group, there were 51 patients who had AF at entry and, of these, 16 (31%) had converted to sinus rhythm and remained in sinus rhythm for the duration of the study (Table 2). In contrast, only 4 patients out of 52 in the placebo group had converted and remained in sinus rhythm for the duration of the study. The

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**TABLE 1.** Baseline Clinical Variables in Patients With AF Randomized to Amiodarone vs Placebo

<table>
<thead>
<tr>
<th></th>
<th>Amiodarone (n = 51)</th>
<th>Placebo (n = 52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y</td>
<td>67 ± 7</td>
<td>67 ± 8</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>61</td>
<td>57</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>27</td>
<td>33</td>
</tr>
<tr>
<td>Active tobacco use, %</td>
<td>18</td>
<td>23</td>
</tr>
<tr>
<td>Current alcohol use, %</td>
<td>25</td>
<td>27</td>
</tr>
<tr>
<td>Prior MI, %</td>
<td>45</td>
<td>50</td>
</tr>
<tr>
<td>Cause of CHF, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>61</td>
<td>58</td>
</tr>
<tr>
<td>Nonischemic</td>
<td>39</td>
<td>42</td>
</tr>
<tr>
<td>Mean LVEF, %</td>
<td>25 ± 8.4</td>
<td>26 ± 8.1</td>
</tr>
</tbody>
</table>

MI indicates myocardial infarction.

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**Figure 1.** Mean VR in bpm in patients in persistent AF computed from 12-lead EKG recordings obtained at baseline at 2 weeks, 6 weeks, and 12 months after randomization. Numbers at the bottom of each bar indicate sample size at each point of evaluation. Note that compared with placebo, amiodarone reduced mean VR significantly after 2 weeks of drug therapy, an effect that was subsequently maintained. See text for further details.

**Figure 2.** Effects of chronic amiodarone therapy on the minimal, mean, and maximal VR in patients with persistent AF. Data were obtained from serial Holter recordings. Numbers below each group of bars indicate sample size at each point of evaluation. Amiodarone had no significant effect on the lowest heart rate during 24 hours of recording but significantly reduced both average and maximal heart rate. See text for details.

**TABLE 2.** Spontaneous Conversion to Sinus Rhythm and Onset of New AF With Amiodarone vs Placebo During 4-Year Follow-Up

<table>
<thead>
<tr>
<th></th>
<th>Amiodarone (n = 330)</th>
<th>Placebo (n = 337)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinus rhythm</td>
<td>268</td>
<td>263</td>
</tr>
<tr>
<td>AF at randomization</td>
<td>51</td>
<td>52</td>
</tr>
<tr>
<td>AF Always</td>
<td>35</td>
<td>48</td>
</tr>
<tr>
<td>Converted to NSR</td>
<td>16</td>
<td>4*</td>
</tr>
<tr>
<td>AF New-onset</td>
<td>11</td>
<td>22†</td>
</tr>
</tbody>
</table>

NSR indicates normal sinus rhythm.

* $x^2 = 9.23$ (P = 0.002).

† $x^2 = 12.88$ (P = 0.005).
rate of conversion to sinus rhythm was significantly better ($\chi^2 = 9, P = 0.002$) with amiodarone therapy (Table 2).

**New-Onset AF**

Because patients with heart failure are known to be at increased risk of developing new-onset AF, we also evaluated the emergence of AF in patients who were in sinus rhythm at baseline evaluation. A total of 268 patients in the amiodarone group were in sinus rhythm at randomization. During the follow-up period, 11 of the 268 (4%) patients developed new-onset AF. In contrast, of the 263 placebo patients with sinus rhythm, twice as many, 22 (8%), developed new-onset AF. There was a significant difference between the 2 groups ($\chi^2 = 13, P = 0.005$) in the rate of development of new AF among patients who were in sinus rhythm at baseline (Table 2).

**Effects of Conversion to Sinus Rhythm on Survival**

Overall, there was no significant difference in survival of patients with AF at baseline between the drug groups ($P = 0.83$). The long-term effects of treatment with amiodarone on the survival rates in patients with AF were assessed by Kaplan-Meier survival analyses based on conversion to sinus rhythm versus continued AF in the 2 groups. As shown in Figure 3, the amiodarone patients who spontaneously converted to sinus rhythm and maintained it during the follow-up period had significantly lower mortality compared with those who remained in AF.

**Predictors of Spontaneous Conversion to Sinus Rhythm**

To identify specific predictors that might be associated with spontaneous conversion of AF to sinus rhythm, we evaluated the role of well-known factors associated with AF. These included age, NYHA class, cause of CHF (ischemic versus nonischemic), change in LVEF, left atrial size, left ventricular end diastolic dimension on echo, and use of digitalis. Multivariate regression analyses revealed that none of these factors was a predictor of conversion to sinus rhythm. Of interest was the finding that, although in this study a significantly greater proportion of patients with AF had nonischemic cardiomyopathy, the cause of heart failure was also not an independent predictor of conversion to sinus rhythm.

**Discussion**

Numerous studies during the last 10 years have suggested that amiodarone exerts a powerful effect in maintaining stability of sinus rhythm in patients with paroxysmal and persistent AF. The drug has been shown to maintain stability of sinus rhythm in over 65% of patients for $\geq 1$ year after direct current conversion. Few direct, controlled comparisons have been made with other antifibrillatory compounds in common use. However, the overall efficacy of such agents rarely exceeds 50% at the end of the first year of treatment. The most commonly used agent to date has been quinidine, but its therapeutic effect may be associated with an increase in mortality, especially in patients with heart failure. Thus, the potential of amiodarone for maintaining stability of sinus rhythm in patients with AF in the setting of heart failure is of particular interest. In the atria, the drug has been shown to consistently increase the effective refractory period after chronic administration in experimental animals and in humans. The drug also exerts a noncompetitive antiadrenergic effect that might be expected to modulate the ventricular response during relapses to AF. Furthermore, the drug has little or no negative inotropic action. Indeed, in patients with cardiac failure and systolic dysfunction, it increases the LVEF and improves exercise capacity. For these reasons, amiodarone may be used with relative impunity in patients with varying levels of ventricular dysfunction. As reported earlier, amiodarone was well tolerated in the CHF-STAT study. In this substudy, 7 amiodarone patients compared with 1 placebo patient had discontinued the study drug.

Our current data on the effects of the drug in AF, although not derived prospectively in terms of a primary hypothesis with stratified randomization, are in line with the unique combination of the drug’s electrophysiological and pharmacological properties. The drug was not only more effective than placebo (31% versus 8%, $P = 0.002$) in converting patients with AF during the course of the study but also in preventing the development of new-onset AF during the course of the study, a difference that was highly statistically significant ($P = 0.005$) compared with placebo. Although the number of patients in which amiodarone was effective in converting AF to sinus rhythm was small, the Kaplan-Meier survival analysis indicated a significantly better survival in converters compared with the nonconverters. Moreover, amiodarone was uniformly effective in producing a sustained and significant slowing of the mean and maximal ventricular responses documented by 24-hour Holter recordings in patients who remained in AF while taking amiodarone. We believe this is the first report of a blinded, placebo-controlled study in which spontaneous conversion of AF to sinus rhythm and the prevention of new-onset AF on amiodarone in patients with heart failure have been documented during prolonged follow-up.
propensity to effectively modulate the ventricular rate control also found in this study, is clearly of therapeutic relevance.

Our results therefore raise the issue of whether chronic amiodarone therapy alone or in combination with digoxin might be the preferred first-line therapy in many patients with AF and heart failure. This is the setting in which most other antiarrhythmic medications (class IA, sotalol, or pure class III agents) or ventricular rate-controlling compounds (diltiazem, verapamil, and β-blockers) may be poorly tolerated. In heart failure, their use may be associated with serious proarrhythmic or negative inotropic actions. Neither of these adverse drug effects was noted in the CHF-STAT study13 from which our current data have been derived. For these reasons, the precise role of amiodarone for the control of AF in patients with heart failure should be defined in prospectively controlled, blinded, and randomized studies. It is of interest that a recent trial, albeit in a different subset of patients,32 provides further evidence of a strong antiarrhythmic protection against the development of AF when the drug is given prophylactically before and continued during the early postoperative phases of cardiac surgery. Postoperative AF developed in 16 of the 64 patients in the amiodarone group (24%) compared with the development of the arrhythmia in 32 of the 60 patients (53%; P = 0.003) in the placebo group.

Our data indicate that patients who converted to sinus rhythm during chronic amiodarone therapy tended to have a significantly better prognosis. Our observations in this regard are consistent with those of Middlekauff et al2 who also found that both total mortality and the risk of sudden death were lowered by conversion of AF to sinus rhythm in patients with heart failure. However, these data need to be interpreted with caution because they are observations that are not derived from prospectively randomized studies. An alternative explanation might be that patients with an intrinsically better prognosis are inherently likely to be those who might respond more favorably to the antiarrhythmic actions of amiodarone. Because of these limitations, our data neither prove nor exclude the possibility that amiodarone has the potential to improve survival in heart failure patients by decreasing the occurrence of new AF or conversion from existing AF. Rather, the data provide the rationale for a controlled study to examine this issue.

In summary, our data have shown that patients with AF in the setting of heart failure have a significantly greater tendency to spontaneously convert to sinus rhythm during chronic amiodarone therapy. Those with sinus rhythm at baseline are also less likely to develop new-onset AF, and if AF does supervene during chronic amiodarone administration, the ventricular response under those circumstances is significantly slower than it is in comparable patients on placebo. Such an aggregate of drug effects in a single agent raises the possibility that, in patients with congestive heart failure, amiodarone has the potential to be the first-line therapy in the pharmacological control of AF, a possibility that should be examined in prospectively designed, blinded, placebo-controlled trials.

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References
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