Analysis of Cause-Specific Mortality in the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Study

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Background—Expectations that reestablishing and maintaining sinus rhythm in patients with atrial fibrillation might improve survival were disproved in the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study. This report describes the cause-specific modes of death in the AFFIRM treatment groups.

Methods and Results—All deaths in patients enrolled in AFFIRM underwent blinded review by the AFFIRM Events Committee, and a mode of death was assigned. In AFFIRM, 2033 patients were randomized to a rhythm-control strategy and 2027 patients to a rate-control strategy. During a mean follow-up of 3.5 years, there were 356 deaths in the rhythm-control patients and 310 deaths in the rate-control patients (P=0.07). In the rhythm-control group, 129 patients (9%) died of a cardiac cause, and in the rate-control group, 130 patients (10%) died (P=0.95). Both groups had similar rates of arrhythmic and nonarrhythmic cardiac deaths. The numbers of vascular deaths were similar in the 2 groups: 35 (3%) in the rhythm-control group and 37 (3%) in the rate-control group (P=0.82). There were no differences in the rates of ischemic stroke and central nervous system hemorrhage. In the rhythm-control group, there were 169 noncardiovascular deaths (47.5% of the total number of deaths), whereas in the rate-control arm, there were 113 noncardiovascular deaths (36.5% of the total number of deaths) (P=0.0008). Differences in noncardiovascular death rates were due to pulmonary and cancer-related deaths.

Conclusions—Management of atrial fibrillation with a rhythm-control strategy conferred no advantage over a rate-control strategy in cardiac or vascular mortality and may be associated with an increased noncardiovascular death rate. (Circulation. 2004;109:1973-1980.)

Key Words: atrium • fibrillation • antiarrhythmia agents • survival

Atrial fibrillation (AF) is associated with increased morbidity and mortality,1 is common among the elderly, and often requires medical treatment. Anticoagulation therapy is recommended to prevent stroke and other thromboembolic events in high-risk patients,2 but an accepted algorithm for control of rate and/or rhythm for patients with AF had not been defined previously. Reestablishing and maintaining sinus rhythm has been presumed to reduce symptoms, lower stroke risk, and enhance survival.

Recently, a large prospective study comparing treatment strategies designed to achieve either rate or rhythm control in high-risk patients with AF, the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study, was completed, and final results were reported.3 Patients randomized to the rhythm-control arm did not have lower all-cause mortality than those randomized to a rate-control approach. There was a trend toward a higher death rate in the rhythm-control arm (356 [24%] versus 310 [21%], Kaplan-Meier estimates at 5 years, P=0.08). In this report, we describe the cause-specific modes of death in the AFFIRM study by treatment approach.

Methods

The design and the primary results of the AFFIRM study have been reported.3–4 AFFIRM was a randomized, multicenter comparison of...
treatment strategies for AF in patients who were at least 65 years of age or who had other risk factors for either stroke or death. Patients were randomized to either (1) a rhythm-control strategy, in which antiarrhythmic drug therapy (including amiodarone, sotalol, propafenone, procarbazone, quinidine, flecainide, disopyramide, moricizine, and dofetilide and combinations thereof) selected by the treating physician was used to achieve and attempt to maintain sinus rhythm; or (2) a rate-control strategy, in which ativoventricular nodal blocking drugs (digoxin, β-adrenergic–blocking drugs, and/or calcium channel–blocking drugs, verapamil and diltiazem) were used to attempt to achieve a maximum heart rate during AF of ≤80 bpm at rest and ≤110 bpm during a 6-minute walk test. Both treatment arms included innovative therapy if conventional therapy was unsuccessful. A total of 4060 patients were enrolled in AFFIRM. There were no differences in clinical characteristics between the 2 groups.

**Death Events Adjudication**

All patient deaths in AFFIRM during follow-up underwent blinded review by the AFFIRM Events Committee. A mode of death was assigned for each patient. For each death, the Principal Investigator at the local site submitted a narrative, with supportive material (paramedic and emergency room reports, hospital notes, admission/discharge summaries, autopsy reports, outpatient records, laboratory tests, ECGs, etc), that characterized the death and surrounding events in as much detail as possible. Each death was assigned to a notator of the Events Committee, who filled out a form further characterizing the death. The records were submitted to the committee member only after all references to the randomized therapy had been removed. If the Principal Investigator’s and the Events Committee member’s conclusions about category of death were in agreement, the adjudication was complete. If there was disagreement, the records were forwarded to the entire committee, and the final adjudication was decided by consensus of the committee during a meeting or conference call. For the total number of adjudicated deaths, there was a 91% rate of agreement between the local Principal Investigator and Events Committee member for the major category of cause of death.

Data on the death review form included the date and time of clinical death (if unwitnessed, the time the patient was found). The cause of death was that which initiated the terminal event and was not necessarily the event most proximate to the death. Emphasis was placed on identifying the primary cause of death, especially when other intermediate events preceded the actual cessation of respiration and circulation. Major categories of cause of death were specified as cardiac, vascular, noncardiovascular, and uncertain mechanism.

For cardiac death, the following characterizing descriptors were considered and tabulated: evidence of ischemia (symptoms, ECG changes, cardiac enzymes); premorbid symptoms before death; witness accounts; activities before death; and the setting of the terminal event. Every effort was made to obtain any ECG recording surrounding the terminal event. If an ECG was performed, the time relative to collapse was noted, and the rhythm at the onset of recording of the event was characterized (ventricular fibrillation [VF], ventricular tachycardia [VT], torsades de pointes VT, VF diagnosed by automated external defibrillator, severe bradycardia, third-degree heart block, asystole, or others). The primary cause of death was declared to be arrhythmic if there was sudden collapse; unexplained death during sleep; spontaneous and rapid loss of circulation, respiration, and consciousness, with no antecedent proximate and active serious medical condition capable of precipitating a fatal arrhythmia (eg, congestive heart failure [CHF], cardiogenic shock, cardiac surgery or procedure); and the death was witnessed but unwitnessed. A specific time-based component was not required, although timing from the onset of symptoms to collapse was recorded. Death occurring during a hospitalization that was the result of complications from a nonfatal cardiac arrest was judged to be arrhythmic. Nonarrhythmic cardiac deaths, a presumed cause was specified, including CHF or cardiogenic shock (with or without antecedent myocardial infarction) or as a complication of cardiac surgery or percutaneous coronary intervention.

Vascular deaths were subclassified as non–central nervous system (CNS) hemorrhage, vascular catastrope, systemic embolism, pulmonary embolism, or CNS event. If a CNS event was judged to be the cause of death, the type of event was specified (ischemic stroke, primary intraparenchymal hemorrhage, subdural/subarachnoid hemorrhage, or other). The CNS events were classified further by the CNS Events Committee, composed of neurologists, cardiologists, and others.

Noncardiovascular death was further subclassified as cancer, sepsis, trauma, pulmonary disease, noncardiac surgery, suicide, or other. Cancer death was selected if the patient succumbed to a fatal neoplastic condition or complications of the condition or therapy. If pulmonary disease was selected, the degree of consistency with amiodarone pulmonary toxicity was entered (very consistent, moderately consistent, or inconsistent), although the Committee was blinded to the treatment and the treatment group.

**Statistical Analyses**

Survival rates derived from Kaplan-Meier probabilities were calculated. For unadjusted survival analyses, log rank tests were used to compare the 2 treatment arms. The relative hazard of events was calculated by use of Cox proportional hazards models. Full models including all covariates were run. These covariates were treatment arm, age, gender, coronary artery disease (CAD), history of CHF, left ventricular ejection fraction, history of hypertension, history of smoking, history of diabetes, history of stroke, history that the qualifying episode was the first episode of AF, in AF at the time of randomization, and the duration of the qualifying episode being ≥48 hours. Models in which left ventricular ejection fraction was not significant were modified to exclude this variable because of the large number of subjects who did not have this value available. Models forcing in treatment arm were run in a stepwise fashion. The variables selected in these models as well as treatment arm were included in a final, reduced model.

For patients having cardiac deaths, the numbers and proportions of patients having specific cardiac death characteristics were calculated and the treatment arms compared by χ² tests for homogeneity.

**Results**

In the AFFIRM study, 2033 patients were randomized to a rhythm-control strategy and 2027 patients to a rate-control strategy. The patients’ baseline characteristics in the randomized groups were well balanced. During a mean follow-up of 3.5 years, there were 356 deaths in the rhythm-control patients and 310 deaths in the rate-control patients (24% versus 21%, Kaplan-Meier estimates at 5 years, P=0.07). A cause of 53 deaths was not assigned because of unavailability of pertinent information at the local site.

**Cardiac Deaths**

In the rhythm-control group, 129 patients (9%) died of a cardiac cause, and in the rate-control group, 130 patients (10%) died of a cardiac cause (Table 1, Figure 1, P=0.95). There was no difference in the rates of arrhythmic and nonarrhythmic cardiac death between groups. Furthermore, there were no differences in the specific nonarrhythmic causes, including CHF or shock, with or without myocardial infarction, and death after a cardiac procedure or surgery. Table 2 lists characteristics of cardiac deaths in both treatment arms. Cardiac deaths were infrequently accompanied by ischemic symptoms or findings. However, new cardiac symptoms were not uncommon before the death, with the majority of the symptomatic patients describing symptoms lasting >24 hours. More than 50% of the deaths were witnessed, and the majority occurred outside the hospital.
More patients in the rate-control arm died in their sleep. Approximately 50% of the patients who died never had ECG recordings at the time of death; of those who did, most were monitored only after the event had started. The most common arrhythmias recorded in those who had ECG monitoring were VF and asystole, at similar proportions in both treatment arms, accounting for approximately 60% of monitored deaths. Severe bradycardia and VT were recorded less frequently, and torsades de pointes VT was never recorded as a cause of death.

**Vascular Deaths**

The numbers of vascular deaths were similar between the 2 groups: 35 (3%) in the rhythm-control group and 37 (3%) in the rate-control group ($P=0.82$). Specifically, there was no difference in the rates of total CNS events. The numbers of ischemic strokes and CNS hemorrhages were similar (Table 1). The numbers of other vascular deaths, such as vascular catastrophes and embolic events, were also similar.

**Noncardiovascular Deaths**

The trend toward a difference in total mortality between the 2 groups was entirely explained by differences in the number of noncardiovascular deaths (Table 1, Figures 2 through 4). In the rhythm-control arm, there were 169 noncardiovascular deaths (47.5% of the total number of deaths), whereas in the rate-control arm, there were 113 noncardiovascular deaths (36.5% of the total number of deaths, $P=0.0008$). At 5 years of follow-up, the rate of noncardiovascular death was 12% in the rhythm-control arm and 8% in the rate-control arm (Figure 2).

As shown in Table 1, the difference in noncardiovascular death rates between the rhythm-control and rate-control treatment arms was a result of significant differences in pulmonary causes (39 [4%] versus 23 [3%], Figure 3, $P=0.04$) and cancer-related death (81 [6%] versus 52 [4%], Figure 4, $P=0.01$). Lung cancer was the most common type of malignancy responsible for death and demonstrated a sizable disparity between groups: 30 in the rhythm-control group and 12 in the rate-control group. Only 3 deaths were caused by amiodarone pulmonary toxicity. Most pulmonary deaths were caused by pneumonia. Similar death rates were observed between treatment arms for other noncardiovascular causes.

Figure 5 is a comparison of cause-specific mortality events between the rate-control and rhythm-control patient groups.

**Multivariate Analyses**

The Cox model was used to identify independent predictors of cause-specific mortality and to adjust for baseline variables. In this manner, the independent predictive value of the
treatment assignment on the hazard of cause-specific death could be assessed. Table 3 displays these results, including hazard ratios. Significant predictors for noncardiovascular death included the assignment to the rhythm-control arm, age, male gender, qualifying episode of AF representing the patient’s first AF episode, and previous history of smoking, CHF, or CAD. The highest hazards were associated with age and a history of smoking, followed by being in the rhythm-control arm of the study. Adjustment for these baseline variables resulted in increased significance for assignment to the rhythm-control arm. Pulmonary death was predicted by age and rhythm-control arm. Cancer-related death was predicted by age, male gender, history of smoking, and rhythm-control arm. Adjustment for baseline variables resulted in a stronger association with the rhythm-control arm for both cancer and pulmonary death outcomes than was seen for unadjusted analyses.

**Discussion**

AFFIRM prospectively monitored more than 4000 patients for a mean of 3.5 years, using treatment strategies commonly used to control AF. The primary end point of the trial was total mortality, and treatment aiming to achieve rate control was equivalent to treatment to achieve rhythm control. There was, however, a trend toward increased mortality in the rhythm-control group (P=0.08, unadjusted for baseline variables but adjusted for multiple interim analyses) and a higher mortality in 2 important and large subgroups (those without

![Figure 2. Cumulative noncardiovascular mortality in the rhythm-control and rate-control groups.](image)
CHF and those with CAD). This report describes the cause-specific mortality rates in the AFFIRM study and shows differences only in the noncardiovascular death rates.

Cardiac Mortality Large population-based studies have shown AF to be associated with an increased risk of cardiovascular mortality. The most recent Framingham data calculated a 1.5-fold increase in mortality for men and a 1.9-fold increase for women after adjustment for potential covariates. AF has several deleterious cardiac and hemodynamic consequences that may explain this higher mortality. These include the loss of atrioventricular synchrony and rapid and irregular ventricular rates, which affect cardiac performance and decrease cardiac output, increase the risk of cardiomyopathy and heart failure, and increase myocardial oxygen demand but decrease myocardial perfusion to precipitate coronary ischemia. These issues could explain a higher risk of developing fatal ventricular tachyarrhythmias. If sinus rhythm were to be achieved permanently, these negative physiological effects may resolve. Antiarrhythmic drug therapy, however, rarely abolishes AF and thus, a risk may remain. Furthermore, AF itself may not be the direct cause of increased mortality. Fatal cardiac outcomes were the same in the rate- and rhythm-control groups of AFFIRM. Rhythm control did not reduce nonarrhythmic (including CHF) or arrhythmic deaths. For unclear reasons, there was a higher proportion of death during sleep in the rate-control arm, although the overall cardiac and arrhythmic death rates were similar. Interestingly, a specific proarrhythmic rhythm, torsade de pointes VT, was not observed as a fatal arrhythmia, even though it might be expected to occur in these patients and even though it was a reported nonfatal adverse event in the rhythm-control group. It is possible that by the time an ECG recording was made, VF might have replaced the more specific recognizable rhythm of torsades de pointes VT.

The reason for the failure of a rhythm-control strategy to improve cardiac fatality rates is uncertain. Sinus rhythm was achieved moderately well in this arm in the AFFIRM study, with 62.6% of patients in the rhythm-control arm still in sinus rhythm at the 5-year visit (compared with 34.6% in the rate-control arm). Many patients continued to have AF, and probably many more had AF that was episodic and...
not recorded at the clinic follow-up (ambulatory recordings were not made routinely during AFFIRM). These observations raise the possibility that incomplete suppression of AF by the drugs used in AFFIRM left patients vulnerable to the consequences of AF (or that AF has nothing to do with mortality). The majority of patients were treated with amiodarone or sotalol, which were shown to be superior to class I agents for maintaining sinus rhythm. Whether there was a counterbalancing effect whereby some benefit was experienced only to be offset by a proarrhythmic fatal result cannot be definitively addressed.

The greater use of β-blockers in the rate-control arm (68% of patients versus 50% in the rhythm-control arm) could have provided additional cardiovascular “protection” not available to the rhythm-control patients, perhaps offsetting the negative effects of a greater burden of AF. β-Blockers are known to reduce cardiac mortality in patients with CAD and hypertension, common comorbidities in the AFFIRM population and in patients with AF. Use of amiodarone and sotalol may have confounded the beneficial effect of the more conventional β-blockers, because both of these drugs have some β-blocking properties, rendering the analysis of the use of β-blockers an insignificant factor in outcome.

Vascular Mortality
AF is an undisputed risk factor for stroke and is the most common cardiac cause of stroke. The incremental risk of stroke attributed to AF will vary relative to the patient population studied but is generally in the range of 5-fold. Chronic anticoagulation with warfarin markedly reduces this risk, and was required in all AFFIRM patients at study entry, and was recommended for all patients throughout the study, although it could be stopped for rhythm-control patients at the discretion of the investigator.

If sinus rhythm can be maintained consistently in the patient with a history of AF, the risk of stroke should fall. The overall nonfatal stroke rates in patients treated in AFFIRM were low, and the fatal stroke rates reported here were also low. There was no difference in these outcome events relative to the randomized treatment strategy in AFFIRM. Thus, a rhythm-control strategy failed to achieve one of its desired effects. This may have been in part because of a low event rate already achieved by the use of chronic anticoagulation, making it difficult to demonstrate additional benefit. Most patients who experienced strokes in AFFIRM were not treated with warfarin or had a subtherapeutic international normalized ratio at the time of stroke, and more patients in the rhythm-control arm had warfarin discontinued.

### TABLE 3. Relative Hazards of Death

<table>
<thead>
<tr>
<th>Source of information</th>
<th>Hazard Ratio</th>
<th>95% CIs</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhythm arm of study</td>
<td>1.53</td>
<td>1.20–1.95</td>
<td>0.0007</td>
</tr>
<tr>
<td>Age (per year)</td>
<td>1.08</td>
<td>1.06–1.10</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.43</td>
<td>1.10–1.86</td>
<td>0.007</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1.31</td>
<td>1.02–1.69</td>
<td>0.03</td>
</tr>
<tr>
<td>CHF</td>
<td>1.45</td>
<td>1.11–1.89</td>
<td>0.006</td>
</tr>
<tr>
<td>Smoking</td>
<td>2.10</td>
<td>1.51–2.92</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>First AF episode</td>
<td>1.28</td>
<td>1.00–1.63</td>
<td>0.05</td>
</tr>
<tr>
<td>Rhythm arm of study</td>
<td>1.77</td>
<td>1.05–2.96</td>
<td>0.03</td>
</tr>
<tr>
<td>Age</td>
<td>1.11</td>
<td>1.08–1.15</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Rhythm arm of study</td>
<td>1.58</td>
<td>1.12–2.24</td>
<td>0.01</td>
</tr>
<tr>
<td>Age</td>
<td>1.06</td>
<td>1.03–1.08</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.60</td>
<td>1.10–2.34</td>
<td>0.01</td>
</tr>
<tr>
<td>Smoking</td>
<td>2.83</td>
<td>1.86–4.31</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

CI indicates confidence interval.
Noncardiovascular Mortality
The most striking observation from the mode-of-death analysis of the AFFIRM study is that there was a significant increase in fatal noncardiovascular events in the rhythm-control arm. At the end of 5 years of follow-up, there was a 50% increase in noncardiovascular deaths in the rhythm-control patients. The survival curves began to diverge at 1 year and gradually separated during the remainder of the study. After adjustment for other significant covariates, the risk of noncardiovascular death was increased 1.5-fold ($P=0.0007$) if the assignment in AFFIRM was to the rhythm-control arm.

The reason for this increased risk is uncertain. The randomization in AFFIRM was to a strategy, rather than a specific drug or treatment, further complicating the potential to understand why this pattern was seen. The specific noncardiovascular causes of death that were more frequently experienced by the rhythm-control patients were cancer- and pulmonary-related. Nonfatal pulmonary complications requiring drug discontinuation were also more common in the rhythm-control arm.$^3$

The fundamental treatment of the rhythm-control group was an antiarrhythmic drug; the most commonly used drug was amiodarone, ultimately prescribed in approximately 60% of patients.$^3$ Amiodarone has previously been associated with an increased noncardiac mortality rate (including cancer and pulmonary deaths). For example, in the post–myocardial infarction EMlAT trial (European Myocardial Infarct Amiodarone Trial), noncardiac mortality was 37% higher, although statistically insignificant, in the patients treated with amiodarone.$^{25}$ Although the numbers were small, cancer and pulmonary deaths were increased as well. In the Antiarrhythmics Versus Implantable Defibrillators (AVID) trial, noncardiac deaths were 78% greater ($P=0.053$) in patients treated for ventricular tachycardia with antiarrhythmic drugs (mostly amiodarone) than with the implanted defibrillator.$^{26}$ However, in other studies, this association was not observed.$^{27,28}$

AFFIRM is larger than most previous studies using amiodarone, and it involved an older cohort of patients who did not always have significant cardiac disease. The absence of severe cardiac disease may allow noncardiac causes of death to emerge in a longitudinal study, when not overwhelmed by cardiac deaths. Thus, the follow-up results in AFFIRM may be unique, in part because of the size and nature of the patient population. However, such an explanation does not account for the differences between the rate-control and rhythm-control groups. Given the age of the enrolled patients, for example, it is conceivable that noncardiovascular death may be hastened by adverse effects of antiarrhythmic drugs. Alternatively, complications of antiarrhythmic drug therapy may be more lethal in patients with serious medical diseases, such as cancer or pulmonary disease. It is also conceivable that adverse effects of potent and toxic medications may be more obscure in this setting.

It is intriguing that cancer deaths were more common in the rhythm-control arm. In AFFIRM, rhythm-control patients were treated less often with warfarin at the later stages of the trial.$^3$ In some studies, warfarin has shown a beneficial antineoplastic effect, particularly on the extent of metastatic spread of cancer but also on the known hypercoagulable state that accompanies many cancers.$^{29}$ If warfarin was used less frequently in the rhythm-control arm, it was less available to contribute to the treatment of cancers that developed in patients randomized to this arm. This scenario may have had adverse consequences on cancer-related outcomes in the elderly patients of AFFIRM.

Warfarin therapy may have played a role in the cancer deaths from another perspective. The patients in the rate-control arm were treated more frequently with warfarin and thus were more likely to experience bleeding complications. Because bleeding events during anticoagulant therapy not infrequently arise from a pathological source, it is conceivable that more cancers were exposed at an earlier stage in their progression. A diagnosis of cancer may have been facilitated because of earlier recognition, leading to intervention and treatment. In this way, some cancers may have been made less fatal in the rate-control arm relative to the rhythm-control arm.

The present analysis does not permit an examination of a relationship of any specific drug to the outcome events. This restriction was established a priori to avoid spurious associations, given that drug therapy was not randomized but was specified by protocol on the basis of the severity and type of underlying cardiac disease. Selection of a specific drug may have reflected serious bias. Sicker patients may have received amiodarone, for example, and healthier patients may have been prescribed flecainide and propafenone. The one such prespecified analysis (performed in a blinded manner) in AFFIRM evaluated the probability of a pulmonary death being attributable to amiodarone pulmonary toxicity; there were only 3 such deaths in the rhythm-control arm and none in the rate-control arm. This leaves open the question of whether other pulmonary deaths were caused by less recognizable forms of amiodarone pulmonary toxicity.

The differences in noncardiovascular mortality may also be caused by a combination of the explanations described above.

Limitations
The finding of increased noncardiovascular mortality risk in the rhythm-control arm must be interpreted cautiously. Cause-specific mortality analysis is a challenging exercise despite diligent efforts, and assignment of death is sensitive to guidelines and rules established by the adjudication committee (see Methods). Explanation is hampered by the very nature of the AFFIRM study’s treatment scheme: strategies rather than drugs. A chance association between the rhythm-control strategy and cancer or pulmonary deaths cannot be excluded, despite the apparent statistical associations.

Conclusions
Drug-based management of AF with a rhythm-control strategy conferred no advantage over a rate-control strategy in cardiac or vascular mortality and may be associated with an increased noncardiovascular death rate.

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