Relationships Between Sinus Rhythm, Treatment, and Survival in the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) Study

The AFFIRM Investigators*

Background—The AFFIRM Study showed that treatment of patients with atrial fibrillation and a high risk for stroke or death with a rhythm-control strategy offered no survival advantage over a rate-control strategy in an intention-to-treat analysis. This article reports an "on-treatment" analysis of the relationship of survival to cardiac rhythm and treatment as they changed over time.

Methods and Results—Modeling techniques were used to determine the relationships among survival, baseline clinical variables, and time-dependent variables. The following baseline variables were significantly associated with an increased risk of death: increasing age, coronary artery disease, congestive heart failure, diabetes, stroke or transient ischemic attack, smoking, left ventricular dysfunction, and mitral regurgitation. Among the time-dependent variables, the presence of sinus rhythm (SR) was associated with a lower risk of death, as was warfarin use. Antiarrhythmic drugs (AADs) were associated with increased mortality only after adjustment for the presence of SR. Consistent with the original intention-to-treat analysis, AADs were no longer associated with mortality when SR was removed from the model.

Conclusions—Warfarin use improves survival. SR is either an important determinant of survival or a marker for other factors associated with survival that were not recorded, determined, or included in the survival model. Currently available AADs are not associated with improved survival, which suggests that any beneficial antiarrhythmic effects of AADs are offset by their adverse effects. If an effective method for maintaining SR with fewer adverse effects were available, it might be beneficial. **(*Circulation*. 2004;109:1509-1513.)**

Key Words: antiarrhythmia agents ■ anticoagulants ■ arrhythmia ■ fibrillation

The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Study compared 2 long-term treatment strategies for atrial fibrillation (AF) in patients who had a high risk of stroke or death.[1–3] Patients were randomized to either a rhythm-control strategy of cardioversion and treatment with antiarrhythmic drugs (AADs) to maintain sinus rhythm (SR) or a rate-control strategy that allowed AF to persist while the ventricular response to AF was controlled. Anticoagulation was used in both arms of the study and was encouraged even if SR was thought to have been maintained, although warfarin could have been discontinued in the rhythm-control group after a minimum of 4 (and preferably 12) weeks of apparently constant SR. In the primary intention-to-treat analysis, the AFFIRM Study showed that management of AF with the rhythm-control strategy offered no survival advantage over the rate-control strategy and that there were potential advantages, such as lower risk of adverse drug effects, with the rate-control approach. Crossovers between strategies and subsequent return to the original strategy were common.[3]

In a series of trials assessing the efficacy and safety of dofetilide to treat AF, the Danish Investigations of Arrhythmia and Mortality on Dofetilide (DIAMOND) studies showed that patients who had SR either with or without AAD therapy had a superior prognosis compared with patients with continued AF.[4] Thus, the possibility arose that the presence or absence of SR itself, rather than treatment strategy, is responsible for outcome.

The purpose of the present analysis was to assess further the relationship of survival to cardiac rhythm and treatment in the AFFIRM Study. Whereas the primary analyses in the AFFIRM Study were performed according to the randomized treatment strategy assignment by the intention-to-treat principle, the present study evaluated patients according to the actual treatment they received. Because a patient's treatment strategy could change over the course of the study, this

Received July 15, 2003; de novo received September 26, 2003; revision received December 17, 2003; accepted December 23, 2003.

From the University of Alabama at Birmingham.

*The Writing Group is listed in the Appendix. The AFFIRM Investigators and Coordinators and their affiliations are listed in Reference 2.

Dr Epstein has served on the advisory boards of Berlex Laboratories and Pfizer and on the speakers' bureaus of Berlex Laboratories, Pfizer, and Wyeth Pharmaceuticals.

Correspondence to Andrew E. Epstein, MD, Division of Cardiovascular Disease, Department of Medicine, The University of Alabama at Birmingham, Tinsley Harrison Tower 321L, 1530 3rd Ave South, Birmingham, AL 35294-0006. E-mail aepstein@uab.edu

Circulation **is available at http://www.circulationaha.org** **DOI: 10.1161/01.CIR.0000121736.16643.11**

analysis used time-dependent covariates to evaluate the impact of variables that changed over time. Time-dependent treatment variables included rhythm-control drugs, rate-control drugs, and anticoagulation with warfarin. The presence of SR was also included as a time-dependent covariate.

Methods

The AFFIRM Study compared survival in patients with AF at high risk for stroke or death treated with a rate-control versus a rhythm-control strategy. At enrollment, patients had to have been either ≥65 years of age or <65 years with at least one of the following risk factors for stroke or death: hypertension, diabetes, congestive heart failure (CHF), previous stroke, previous transient ischemic attack (TIA), systemic embolism, left atrial (LA) size ≥50 mm by echocardiography, left ventricular (LV) ejection fraction <0.40, or LV fractional shortening <25%, determined by any technique. All patients gave informed consent to participate in the AFFIRM Study; all procedures followed institutional guidelines, and all participating institutions received approval from their respective Institutional Review Boards. In all, 4060 patients were randomized over a 4-year period that ended on October 31, 1999. Follow-up ended October 31, 2001. The mean duration of follow-up was 3.5 years, with a maximum of 6 years. The primary study results were reported in 2002.[3]

Statistics

The most valid assessment of a randomized study is performed by "intention-to-treat analysis," as was used in the main AFFIRM Study report.[3] In that approach, patients are analyzed according to their assigned treatment, regardless of the treatment actually administered. Important advantages of that approach are that it maintains the baseline comparability between treatment groups achieved by randomization and prevents biases that can occur when patients stop or change their treatment strategy for reasons related to the end point of interest.

An alternative statistical approach is "on-treatment analysis." In this approach, patients are analyzed according to the actual therapy they received. The advantage of this method is that adverse events or outcomes are attributed to the treatment actually used. A disadvantage is that this method is inherently biased. For example, if sicker patients are prescribed one therapy more than another, adverse outcomes may mistakenly be attributed to the more frequently prescribed therapy rather than the underlying clinical condition of the patient. In the context of a parallel-design drug-treatment trial, on-treatment analysis may involve censoring of subjects at the moment therapy is changed. For AFFIRM, such an approach is inappropriate because there were often multiple changes of therapy during the long follow-up.

For this study, an on-treatment analysis was done using Cox proportional hazards regression with the evaluation of time-dependent covariates. This method allows for drug therapies and heart rhythm to be evaluated as they change over time and for multiple covariates to be included in a statistical model to assess each variable's relationship to the primary end point (survival), after adjustment or control for the influence of the other covariates included in the analysis.[5]

Six time-dependent covariates were entered in a Cox proportional hazards survival model: SR (ie, absence of AF) and the use of warfarin, digoxin, a β-blocker, calcium channel blocker, or rhythm-control drug. Calcium channel blockers included diltiazem and verapamil. Rhythm-control drugs included amiodarone, sotalol, and 6 class I AADs: disopyramide, flecainide, moricizine, procainamide, propafenone, and quinidine.

Individual rate-control drugs (digoxin, β-blockers, and calcium channel blockers) were included as separate covariates in the analysis. Rhythm-control drugs, however, were grouped together rather than included as separate covariates because of bias associated with protocol-recommended differences in how the specific drugs were prescribed. For example, the study protocol advised against prescribing class I AADs for patients with CHF or coronary artery disease and recommended that another AAD (eg, amiodarone) be used for patients with these conditions.

TABLE 1. Covariates Analyzed in the Cox Proportional Hazards Regression

Covariate	Type
Age at enrollment	Baseline
Sex	Baseline
History of coronary artery disease	Baseline
History of congestive heart failure	Baseline
History of hypertension	Baseline
History of diabetes	Baseline
History of stroke or transient ischemic attack	Baseline
Recent history of smoking	Baseline
Qualifying episode is first episode of atrial fibrillation	Baseline
Left atrial enlargement (>4.0 cm)*	Baseline
Left ventricular dysfunction (ejection fraction <50%)*	Baseline
Mitral valve regurgitation*	Baseline
Presence of sinus rhythm	Time-dependent
Warfarin use	Time-dependent
Rate-control drug use	
Digoxin	Time-dependent
β-Blocker	Time-dependent
Calcium channel blocker	Time-dependent
Rhythm-control drug use	Time-dependent

*Echocardiographic variables.

Each patient's heart rhythm and treatment (ie, the time-dependent covariates) were determined at baseline and at various time points over the course of follow-up. Follow-up forms were completed at 2 and 4 months after randomization and every 4 months thereafter until the patient died, was lost to follow-up, or completed the study. Specific start and stop dates for the presence of SR and for use of the various drugs were not recorded. Instead, responses on the follow-up form indicated whether the patient had been in AF or had used a particular drug since the previous follow-up. A patient was considered to have maintained SR or to have used a drug if it was recorded as such on the most recent available form before the time point of interest.

In addition to the 6 time-dependent covariates, 12 baseline variables were included in the analysis to adjust for these factors and to assess their relationships to survival. Baseline variables included age at enrollment in the study; sex; a history of coronary artery disease, CHF, hypertension, diabetes, and stroke or TIA; a recent history of smoking; qualifying for inclusion in the study with a first (versus recurrent) episode of AF; LA enlargement (>4.0 cm); LV dysfunction (ejection fraction <50%); and mitral valve regurgitation (Table 1).

Following a backward stepwise approach, covariates were removed from the model until the probability value of all remaining covariates was <0.01. The significance level of 0.01 was chosen over the less restrictive 0.05 level because of the relatively large number of covariates entered into the model.

Because echocardiograms were performed for only ≈75% of patients, a second analysis was done that excluded the echocardiographic variables (ie, LA enlargement, LV dysfunction, and mitral valve regurgitation). Excluding the echocardiographic data increased the sample size and thus the statistical power and removed any potential bias introduced by selection for echocardiography.

TABLE 2. Covariates Significantly Associated With Survival Results With Echocardiographic Data Included

Covariate	*P*	HR	HR: 99% Confidence Limits Lower	Upper
Age at enrollment*	<0.0001	1.06	1.05	1.08
Coronary artery disease	<0.0001	1.56	1.20	2.04
Congestive heart failure	<0.0001	1.57	1.18	2.09
Diabetes	<0.0001	1.56	1.17	2.07
Stroke or transient ischemic attack	<0.0001	1.70	1.24	2.33
Smoking	<0.0001	1.78	1.25	2.53
Left ventricular dysfunction	0.0065	1.36	1.02	1.81
Mitral regurgitation	0.0043	1.36	1.03	1.80
Sinus rhythm	<0.0001	0.53	0.39	0.72
Warfarin use	<0.0001	0.50	0.37	0.69
Digoxin use	0.0007	1.42	1.09	1.86
Rhythm-control drug use	0.0005	1.49	1.11	2.01

*Per year of age.

A time-dependent analysis does not lend itself to standard Kaplan-Meier survival plots. The relationship of time-dependent covariates with the survival end point can be estimated only in relative terms (ie, hazard ratios [HRs]). Absolute survival estimates for time-dependent covariates cannot be computed because the patients associated with each category (eg, use of warfarin) change over time, making it impossible to compute baseline hazard functions.

Results

Data for 2796 patients were available for the analysis when the echocardiographic data were included. After stepwise elimination, 12 covariates remained. Probability values, HRs, and their 99% confidence limits for these 12 covariates are shown in Table 2. The average (±SD) follow-up was 3.31 (±1.28) years. The average percent time in follow-up across all patients for each of the significant time-dependent variables was: on warfarin 84%, off warfarin 16%; on digoxin 43%, off digoxin 57%; on AAD 45%, off AAD 55%; and in AF 44%, in SR 56%.

The following baseline variables were significantly associated with an increased risk of death: increasing age (HR=1.06), history of coronary artery disease (HR=1.56), history of CHF (HR=1.57), history of diabetes (HR=1.56), history of stroke or TIA (HR=1.70), recent history of smoking (HR=1.78), LV dysfunction (HR=1.36), and mitral regurgitation (HR=1.36).

Among the time-dependent factors, SR, warfarin use, digoxin use, and rhythm-control drug use were significantly related to survival after adjustment for the other covariates retained in the model. The presence of SR was associated with a decreased risk of death (HR=0.53). Warfarin use was also associated with a decreased risk of death (HR=0.50). Digoxin was the sole rate-control drug retained in the model and was associated with an increased risk of death (HR=1.42). Neither the use of β-blockers nor the use of calcium channel blockers was significantly associated with survival. Use of rhythm-control drugs was associated with increased mortality after adjustment for the other covariates (HR=1.49).

TABLE 3. Covariates Significantly Associated With Survival Results With Echocardiographic Data Excluded

Covariate	*P*	HR	HR: 99% Confidence Limits Lower	Upper
Age at enrollment*	<0.0001	1.06	1.04	1.08
Coronary artery disease	<0.0001	1.65	1.31	2.07
Congestive heart failure	<0.0001	1.83	1.45	2.32
Diabetes	<0.0001	1.56	1.22	2.00
Stroke or transient ischemic attack	<0.0001	1.54	1.17	2.05
Smoking	<0.0001	1.75	1.29	2.39
First episode of atrial fibrillation	0.0067	1.27	1.01	1.58
Sinus rhythm	<0.0001	0.54	0.42	0.70
Warfarin use	<0.0001	0.47	0.36	0.61
Digoxin use	<0.0001	1.50	1.18	1.89
Rhythm-control drug use	0.0005	1.41	1.10	1.83

*Per year of age.

Results were similar when the analysis was redone without the echocardiographic data, except that qualifying for inclusion in the study with a first episode of AF was associated with increased mortality (HR=1.27, Table 3). Data for 3677 patients were available for the analysis when the echocardiographic data were excluded.

Discussion

Since the publication of the intention-to-treat analysis of the AFFIRM Study,[3] inquiries have frequently been made regarding an "on-treatment" analysis. This report addresses those inquiries by presenting the results for the AFFIRM Study of a Cox proportional hazards regression for an on-treatment analysis of important drug therapies and the presence or absence of SR, all of which changed frequently over the course of the study.

In this analysis, the presence of SR was associated with a considerable reduction in the risk of death. These findings are consistent with those of the DIAMOND Study, in which the presence of SR throughout that trial was associated with improved survival.[4] Because of the retrospective, nonrandomized nature of the analyses, however, neither the DIAMOND Study nor ours can distinguish whether SR is an important determinant of survival or a marker for other factors associated with survival that were not recorded, determined, or included in the survival model.

In this analysis, AAD use was associated with increased mortality. This association is not new. The proarrhythmic effects of encainide, flecainide, and moricizine were shown in the Cardiac Arrhythmia Suppression Trial (CAST).[6–8] In the SWORD Trial, *d*-sotalol also increased mortality when given prophylactically after myocardial infarction.[9] Similarly, in the Stroke Prevention in Atrial Fibrillation (SPAF) Study, AADs prescribed for AF were associated with increased mortality.[10]

Thus, the finding of decreased survival in the setting of AAD therapy is consistent with previous data.

Despite the association of AADs with increased mortality, the present analysis does not necessarily indicate an overall deleterious effect of rhythm-control drugs on survival because it treats the presence of SR and AAD use as separate variables. In other words, AAD use had a deleterious effect on survival only after adjustment for the presence of SR. When the models were run without adjustment for SR, AADs were no longer associated with adverse outcomes. One hypothesis to explain these results is that the beneficial antiarrhythmic effect of these drugs (eg, maintenance of SR) on survival may be offset by the impact of their adverse effects (eg, toxicity, morbidity, and mortality, both cardiac and noncardiac). Analyzing the results by use of a statistical model that treats the presence or absence of SR as a separate factor may remove this beneficial part of the AAD profile, allowing the detrimental effects to be expressed. The finding in the AFFIRM Study that the risk of noncardiac death was higher in the rhythm-control arm[11] could be explained by noncardiac adverse effects of AADs. It is also possible that the observed outcome was a result of biases in the model that were not identified.

It might seem contradictory that, in the primary results of the AFFIRM Study, treatment strategy (rate-control versus rhythm-control) was not related to death, whereas in this analysis, the presence of SR was associated with a lower risk of death, and the use of AADs was associated with increased mortality. It is important to recognize, however, that this analysis includes the presence of SR and the use of AADs as separate variables, effectively separating the beneficial effects of SR and the detrimental nonantiarrhythmic properties of the rhythm-control drugs. When the SR variable is removed from the model, the beneficial antiarrhythmic effects are effectively restored to the rhythm-control drug variable, which then is no longer associated with increased mortality. This lack of association between AAD use and survival is comparable to the main results of the AFFIRM Study.[3] It should also be noted that, for some patients, SR was achieved in the absence of AADs.

The association of SR but not AADs with improved survival may reflect the fact that currently available AADs are neither highly efficacious nor completely safe. One could reasonably expect that a treatment that was highly effective in maintaining SR and had minimal adverse effects would have had a similar association with death as the time-dependent factor reflecting the presence of SR. In this regard, Pappone et al[12] recently reported that, unlike AAD therapy, circumferential pulmonary vein ablation provided symptomatic relief without increasing mortality in patients with symptomatic AF compared with an age- and sex-matched control cohort. Although their findings are seemingly consistent with those in our study, their patients were not randomized, and their demographics were different from those in the AFFIRM Study. Most importantly, a requirement for high risk for stroke or death was not an entry criterion. Like our findings, these data require confirmation by further randomized, controlled clinical trials.

Warfarin markedly reduced the risk of death. This finding is consistent with the unquestionable utility of warfarin in reducing strokes in high-risk patients, results found in multiple trials focused on anticoagulation.[13] Warfarin has also been shown repeatedly to reduce risk of death in coronary artery disease.[14] Thus, the salutary effect of warfarin may be multifactorial. Given that even patients on AAD therapy may have spontaneous and often undetected recurrences of AF, it is possible that all patients with AF would benefit from warfarin use regardless of the treatment strategy.

It was unexpected that the use of β-blocking agents did not appear to improve survival in this population because β-blockers have been shown to have a beneficial effect in other studies of coronary artery disease, myocardial infarction, hypertension, arrhythmias, and CHF. The lack of effect in AFFIRM could be explained by the confounding of outcomes by other factors, such as the frequent use in the rhythm-control arm of sotalol, propafenone, and amiodarone, all of which have some mild β-blocking properties, and the relatively low prevalence of coronary heart disease and CHF.

Digoxin was the sole rate-control drug that was significantly related to survival in this analysis. Like AADs, digoxin has been associated with increased death rates in other studies. In a retrospective analysis of data from the DIG Study, higher serum digoxin concentrations were found to be associated with increased mortality in patients with heart failure.[15] Rather than reflecting a deleterious effect of digoxin on survival, however, the present result may represent the prescription of digoxin for patients at greater risk of death, such as those with CHF. There may be other measured or unmeasured variables that influence physicians to choose digoxin.

Other factors traditionally considered to have a negative impact on survival also proved to be important in this analysis: age, coronary artery disease, CHF, diabetes, stroke or TIA, smoking, LV dysfunction, and mitral regurgitation.

In the model that excluded the echocardiographic parameters, qualifying for enrollment in the study with a first (versus recurrent) episode of AF was significantly associated with decreased survival. Risk factors for death were more prevalent among patients who qualified with their first episode of AF. These patients were more likely to have a history of myocardial infarction, CHF, and a lower LV ejection fraction.[2]

Limitations

This analysis was not planned at the outset of the AFFIRM Study and is therefore both retrospective and nonrandomized. Accordingly, it may suffer from hidden biases and other unidentified confounders. For example, differential prescription of drugs on the basis of patients' conditions may have biased the associations between treatment variables (eg, digoxin use) and mortality. Because the analyses did not involve randomized comparisons, they cannot demonstrate a cause-and-effect relationship of the various factors on the risk of death. Thus, the observations made in the present study must be considered to be hypothesis-generating.

Specific start and stop dates for the presence of SR and for use of the various drugs were not recorded. Instead, responses

on the follow-up forms indicated whether the patient had AF or had used a particular drug since the previous follow-up. A patient was considered to have maintained SR or to have used a drug if it was recorded as such on the most recent form before the time point of interest. Furthermore, for many patients AF is paroxysmal. Accordingly, with intermittent determination of the presence or absence of AF, it was not possible to identify accurately all patients who were in SR throughout each follow-up period. These limitations in data recording potentially introduced error because a patient's rhythm and drug use at the time of an event were not known with certainty. However, the added error would be expected to weaken the association between the time-dependent variables and the survival end point, making it more difficult to detect significant associations, rather than falsely strengthening the effect of one type of rhythm or drug over another. Because of these data collection limitations and potential biases, we concluded that analysis of interactions and subgroups involving the time-dependent covariates could not be reliably performed.

In these analyses, only SR and drug therapy for AF were considered to be time-related events. However, other clinical factors may also have changed during the study as disease processes worsened, such as the degree of mitral regurgitation, LV dysfunction, LA size, and CHF status. The aggressiveness and success of heart failure therapies, non–arrhythmia-related drug therapy, the adequacy of anticoagulation, and blood pressure all may have changed over the course of the study. AF is most likely to recur in patients with unstable, new-onset, or progressive cardiac disease or other serious intervening illnesses. In the face of these potentially unmeasured changes, AF may appear to be a determining factor in causing death or other adverse outcomes, when it was really just a marker for progression of disease.

Finally, because including echocardiographic data substantially reduced the number of patients available for the analysis, separate analyses were performed with and without the echocardiographic data. Despite the possible bias and difference in sample size, and thus statistical power, between the 2 analyses, the results were similar.

Implications

In patients with AF such as those enrolled in the AFFIRM Study, warfarin use improves survival. The presence of SR but not AAD use is associated with a lower risk of death. These results suggest that if an effective method for maintaining SR with fewer adverse effects were available, it might improve survival.

Appendix

Writing Group

Cofacilitators: Scott D. Corley, MS, Axio Research Corporation, Seattle, Wash; Andrew E. Epstein, MD, University of Alabama at Birmingham. Members (in alphabetical order): John P. DiMarco, MD, PhD, University of Virginia, Charlottesville; Michael J. Domanski, MD, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Md; Nancy Geller, PhD, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Md; H. Leon Greene, MD, Axio Research Corporation, Seattle, Wash; Richard A. Josephson, MD, Akron Cardiology Consultants, Akron, Ohio; Joyce C. Kellen, RN, MSc, University of Calgary, Calgary, Alberta, Canada; Richard C. Klein, MD, University of Utah Medical Center, Salt Lake City; Andrew D. Krahn, MD, London Health Sciences Centre, London, Ontario, Canada; Mary Mickel, MS, Axio Research Corporation, Seattle, Wash; L. Brent Mitchell, MD, University of Calgary, Calgary, Alberta, Canada; Joy Dalquist Nelson, RN, Axio Research Corporation, Seattle, Wash; Yves Rosenberg, MD, MPH, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Md; Eleanor Schron, RN, MS, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Md; Lynn Shemanski, PhD, Axio Research Corporation, Seattle, Wash; Albert L. Waldo, MD, University Hospitals of Cleveland, Cleveland, Ohio; D. George Wyse, MD, PhD, University of Calgary, Calgary, Alberta, Canada.

Acknowledgments

This study was supported by contract N01-HC-55139 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Md.

References

1. The Planning and Steering Committees of the AFFIRM Study for the NHLBI AFFIRM Investigators. Atrial Fibrillation Follow-up Investigation of Rhythm Management: The AFFIRM Study design. *Am J Cardiol*. 1997;79:1198–1202.
2. The AFFIRM Investigators. Baseline characteristics of patients with atrial fibrillation: the AFFIRM Study. *Am Heart J*. 2002;143:991–1001.
3. The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med*. 2002;347:1825–1833.
4. Pederson OD, Bagger H, Keller N, et al. Efficacy of dofetilide in the treatment of atrial fibrillation-flutter in patients with reduced left ventricular function. A Danish Investigations of Arrhythmia and Mortality ON Dofetilide (DIAMOND) Substudy. *Circulation*. 2001;104:292–296.
5. Kalbfleisch JD, Prentice RL. *The Statistical Analysis of Failure Time Data*. New York, NY: John Wiley & Sons Inc; 1980:122–127.
6. Echt DS, Liebson PR, Mitchell LB, et al. Mortality and morbidity in patients receiving encainide, flecainide, or placebo: the Cardiac Arrhythmia Suppression Trial. *N Engl J Med*. 1991;324:781–788.
7. The Cardiac Arrhythmia Suppression Trial II Investigators. Effect of the antiarrhythmic agent moricizine on survival after myocardial infarction. *N Engl J Med*. 1992;327:227–233.
8. Epstein AE, Bigger JT, Wyse DG, et al. Events in the Cardiac Arrhythmia Suppression Trial (CAST): mortality in the entire population enrolled. *J Am Coll Cardiol*. 1991;18:14–19.
9. Waldo AL, Camm AJ, deRuyter H, et al. Effect of *d*-sotalol on mortality in patients with left ventricular dysfunction after recent and remote myocardial infarction. *Lancet*. 1996;348:7–12.
10. Flaker GC, Blackshear JL, McBride R, et al. Antiarrhythmic drug therapy and cardiac mortality in atrial fibrillation. *J Am Coll Cardiol*. 1992;20:527–532.
11. Steinberg JS, Sadaniantz A, Kron J, et al. Analysis of cause-specific mortality in the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Study. *Circulation*. In press.
12. Pappone C, Rosanio S, Augello G, et al. Mortality, morbidity, and quality of life after circumferential pulmonary vein ablation for atrial fibrillation. *J Am Coll Cardiol*. 2003;42:185–197.
13. Atrial Fibrillation Investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. *Arch Intern Med*. 1994;154:1449–1457.
14. Hurlen M, Abdelnoor M, Smith P, et al. Warfarin, aspirin or both after myocardial infarction. *N Engl J Med*. 2002;347:969–974.
15. Rathore SS, Curtis JP, Wang Y, et al. Association of serum digoxin concentration and outcomes in patients with heart failure. *JAMA*. 2003;289:871–878.

Relationships Between Sinus Rhythm, Treatment, and Survival in the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) Study

The AFFIRM Investigators

Circulation. 2004;109:1509-1513; originally published online March 8, 2004;
doi: 10.1161/01.CIR.0000121736.16643.11
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539