JACC Vol. 20, No. 3
September 1992:527–32

Antiarrhythmic Drug Therapy and Cardiac Mortality in Atrial Fibrillation

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Background and Objectives. **The relation between cardiac mortality and antiarrhythmic drug administration has not been fully determined. This relation was analyzed in 1,330 patients enrolled in the Stroke Prevention in Atrial Fibrillation Study, a randomized clinical trial comparing warfarin, aspirin and placebo for the prevention of ischemic stroke or systemic embolism in patients with nonvalvular atrial fibrillation.**

Methods. **Patients who received antiarrhythmic drug therapy for atrial fibrillation in this study were compared with patients not receiving antiarrhythmic agents. The relative risk of cardiac mortality, including arrhythmic death, in patients receiving antiarrhythmic drug therapy was determined and adjusted for other cardiac risk factors.**

Results. **In patients receiving antiarrhythmic drug therapy, cardiac mortality was increased 2.5-fold ($p = 0.006$, 95% confidence interval [CI] 1.3 to 4.9) and arrhythmic death was increased 2.6-fold ($p = 0.02$, 95% CI 1.2 to 5.6). Among patients with a history of congestive heart failure, those given antiarrhythmic medications had a relative risk of cardiac death of 4.7 ($p < 0.001$, 95% CI 1.9 to 11.6) compared with that of patients not so treated; the relative risk of arrhythmic death in the treated group was 3.7 ($p = 0.01$, 95% CI 1.3 to 10.4). Patients without a history of congestive heart failure had no increased risk of cardiac mortality (relative risk 0.70, 95% CI 0.2 to 3.1) during antiarrhythmic drug therapy.**

After exclusion of 23 patients with documented ventricular arrhythmias and adjustment for other variables predictive of cardiac death, patients receiving antiarrhythmic drugs were not at increased risk of cardiac death or arrhythmic death. However, in patients with a history of heart failure who received antiarrhythmic drug therapy, the relative risk of cardiac death was 3.3 ($p = 0.05$, 95% CI 0.99 to 11.1) and that of arrhythmic death was 5.8 ($p = 0.009$, 95% CI 1.5 to 21.7) compared with the risk in patients not taking antiarrhythmic medications.

Conclusions. **Although antiarrhythmic drug therapy was not randomly determined in this trial, the data suggest that in patients with atrial fibrillation and a history of congestive heart failure, the risk of such therapy may outweigh the potential benefit of maintaining sinus rhythm.**

(J Am Coll Cardiol 1992;20:527–32)

Antiarrhythmic medications are commonly given to patients with atrial fibrillation to restore or maintain sinus rhythm, but the balance between risk and benefit of such therapy is undergoing reassessment. A meta-analysis of six randomized, controlled trials incorporating 808 patients with chronic atrial fibrillation (1) evaluated quinidine for maintenance of sinus rhythm after cardioversion. Although quinidine was more effective than no antiarrhythmic therapy in preventing the recurrence of atrial fibrillation, the risk of death was approximately threefold greater among drug-treated patients ($p < 0.05$), a conclusion based on only 15 deaths. Data from a randomized trial of patients with ventricular ectopic activity after myocardial infarction also suggest an increased mortality rate in patients treated with antiarrhythmic agents (2,3). The mechanism of death among participants in these studies is speculative, but a proarrhythmic drug effect is one consideration (4).

Prompted by these reports of increased mortality attributed to antiarrhythmic drug therapy, we examined the relation between cardiac mortality and antiarrhythmic drug therapy in the Stroke Prevention in Atrial Fibrillation Study. In this trial we observed excess cardiac mortality in patients treated with antiarrhythmic drugs. This report describes the use of antiarrhythmic drugs in patients with nonvalvular atrial fibrillation, the magnitude of increased mortality associated with antiarrhythmic drug therapy, and the clinical features of patients treated with antiarrhythmic drugs at risk for cardiac mortality.

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Manuscript received November 12, 1991; revised manuscript received February 25, 1992, accepted March 30, 1992.

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0735-1097/92/$5.00

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September 1992:527–32

Methods

Design of the Stroke Prevention in Atrial Fibrillation Study. The main objective of the Stroke Prevention in Atrial Fibrillation Study was to define the efficacy and toxicity of warfarin and aspirin, administered separately, for prevention of ischemic stroke and systemic embolism in patients with constant or intermittent nonvalvular atrial fibrillation. The design, subjects and definition of clinical variables of this randomized clinical trial have been previously described in detail (5,6). Between June 1987 and November 1989, 1,330 patients were enrolled at 15 clinical centers in the United States. On entry into the study, historical features including cardiovascular risk factors and previous cardiac events were recorded. A physical examination with an evaluation of functional status was performed. Medications administered for cardiovascular disorders were noted. Blood chemistry and hematologic profiles, 12-lead electrocardiograms and M-mode and two-dimensional echocardiograms were performed. Atrial fibrillation was characterized by its duration, intermittency and presumed etiology. Patients were followed up at 3-month intervals to record concurrent medications, detect ischemic stroke and systemic emboli and identify complications of drug therapy.

The decision to administer antiarrhythmic drug therapy was made by the patient's personal physician and was not randomly assigned. Patients receiving antiarrhythmic drug therapy were identified at entry into the study or during routine follow-up and form the basis of this report. Patients receiving antiarrhythmic drug therapy at the time of death but not recorded as receiving these drugs at the time of last follow-up visit (n = 5) are not included in our analysis to avoid potential bias.

Classification of cause of death. Medical records pertaining to all deaths were initially reviewed by members of an Events Verification Committee who had no knowledge of antithrombotic treatment assignment and who classified all deaths as vascular or nonvascular. A second group of investigators (cardiologists), who had no knowledge of antiarrhythmic therapy status, made a subsequent review to classify the cause of death as cardiac or noncardiac. Cardiac deaths were subclassified as arrhythmic or nonarrhythmic by using standards similar to those set forth by the Cardiac Arrhythmia Suppression Trial (CAST) investigators (3). Death was considered to be due to an arrhythmia in the following circumstances: 1) witnessed and instantaneous, without new accelerating symptoms; 2) witnessed and preceded by chest pain, overt myocardial infarction, or arrhythmic symptoms (syncope or near syncope); or 3) unwitnessed but without evidence of another cause. Deaths preceded by shock or severe heart failure were considered cardiac related but not due to an arrhythmia even if the terminal event was an arrhytamia.

Statistical methodology. The analysis proceeded in a stepwise fashion to determine the independent contribution of antiarrhythmic drug therapy to cardiac death in the entire Stroke Prevention in Atrial Fibrillation Study cohort and in patient subgroups at increased risk when exposed to antiarrhythmic drug therapy. Cardiac mortality in patients during antiarrhythmic drug therapy was analyzed. This survival analysis considered all exposure to antiarrhythmic drugs whether present at entry or initiated during follow-up to estimate the risk associated with antiarrhythmic drug therapy. Second, 16 variables considered potential independent risk factors for cardiac death were prospectively selected. These variables were characterized at study entry and included age; gender; current smoking; history of hypertension; history of diabetes; definite history of angina; history of myocardial infarction; definite history of congestive heart failure (defined as orthopnea, dyspnea or edema responding to diuretic therapy; third sound gallop and rales; X-ray evidence of cardiomegaly or vascular distribution; and left ventricular filling pressure >18 mm Hg); New York Heart Association functional class II or III (patients in class IV were excluded from the study); recent heart failure (within 100 days); moderate to severe left ventricular wall motion abnormality by echocardiography; assignment to aspirin or warfarin, and the use of digitalis, diuretics, beta-adrenergic blocking agents or calcium channel blockers. A multivariate analysis was performed by using the proportional hazards failure time model of Cox. The adjusted risk (instantaneous hazard ratio) of cardiac death independently associated with antiarrhythmic drug therapy was estimated by using covariables significantly associated with cardiac death. Third, we examined the interaction between antiarrhythmic drug therapy and the other predictors of cardiac death to identify subgroups of patients in whom the risk of antiarrhythmic drugs was especially great. Finally, we assessed the independent contribution of antiarrhythmic drug therapy to cardiac mortality in these high risk subgroups after adjusting for the 16 variables described.

Patients receiving antiarrhythmic drugs for ventricular arrhythmias. Specific antiarrhythmic drugs included quinidine (n = 127), procainamide (n = 57), disopyramide (n = 15), flecainide (n = 34), encainide (n = 20) and amiodarone (n = 7). Patients may have been taking more than one agent during follow-up. The presence of ventricular arrhythmias was not assessed at entry into the study. However, medical records of all patients receiving antiarrhythmic drugs were reviewed to identify additional indications for therapy. These indications included symptomatic ventricular premature complexes and nonsustained and sustained ventricular tachycardia. Twenty-three patients were identified who received antiarrhythmic drugs for chronic ventricular arrhythmias and atrial fibrillation. An analysis similar to that described for the entire population was then repeated after exclusion of patients receiving antiarrhythmic drugs for ventricular arrhythmias.

Statistical tests. Comparisons of baseline characteristics were made by the chi-square statistic or *t* test for categorical and continuous variables respectively. Mortality rates were estimated using the Kaplan-Meier method (7). Confidence intervals were calculated at the 95% level. Multivariate

Table 1. Characteristics of Patients Taking Antiarrhythmic Agents at Baseline Versus Those of Patients Who Were Not Taking Antiarrhythmic Agents at Baseline

	Taking Antiarrhythmic Agents at Baseline (n = 189)	Not Taking Antiarrhythmic Agents at Baseline (n = 1,151)	p Value
Demographic characteristics			
Mean age (yr)	62	68	<0.001
Male (%)	72	70	NS
Current smoker (%)	18	15	NS
Clinical baseline characteristics			
History of hypertension (%)	45	53	0.03
History of diabetes (%)	16	16	NS
Definite history of angina (%)	11	9	NS
History of myocardial infarction (%)	12	7	0.02
Definite history of CHF (%)	21	19	NS
NYHA functional class (%)			
II or III	13	12	NS
No impairment	87	88	NS
Constant atrial fibrillation (%)	27	73	<0.001
Onset of AF <1 yr ago (%)	40	30	0.002
Cardioversion attempted <1 mo after entry (%)	20	2	<0.001
Concurrent medications at baseline			
Digitalis (%)	78	73	NS
Diuretics (%)	52	41	0.04
Calcium channel blockers (%)	21	22	NS
Beta-blockers (%)	15	17	NS
Aspirin or warfarin as SPAF therapy (%)	60	57	NS
Echocardiographic variables			
LV wall motion abnormality (%):			
None	72	77	NS
Mild	16	13	NS
Moderate to severe	12	9	NS
Left atrial dimension (cm)			
<4.0	18	16	NS
4.0–5.0	60	57	NS
>5.0	22	27	NS
LV internal systolic dimension (cm)	3.6	3.4	0.007
LV internal diastolic dimension (cm)	5.4	5.2	0.005

AF = atrial fibrillation; CHF = congestive heart failure; LV = left ventricular; NS = not significant ($p > 0.05$); NYHA = New York Heart Association (class IV excluded by protocol); SPAF = Stroke Prevention in Atrial Fibrillation.

analyses to estimate the association between covariates and outcome were performed using the proportional hazards failure time model of Cox (8). Antiarrhythmic drug therapy status was assessed at each scheduled follow-up visit and was analyzed as a covariate varying with time.

Results

Of the 1,330 randomized patients, 244 (18%) received antiarrhythmic medications either at the time of enrollment (n = 189) or after enrollment (n = 55). In most cases (91%), antiarrhythmic drugs were prescribed for the prevention of symptomatic atrial fibrillation. Twenty-three patients (9%) also received these agents for ventricular arrhythmias including premature ventricular beats (n = 10), nonsustained ventricular tachycardia (n = 5), and sustained ventricular tachycardia or ventricular fibrillation (n = 8). Total exposure to antiarrhythmic drug therapy was 201 patient-years. Patients treated with antiarrhythmic agents were younger, had a lesser prevalence of hypertension and a greater prevalence of a history of myocardial infarction and of intermittent atrial fibrillation and recent cardioversion and used diuretics more frequently than did patients not given antiarrhythmic agents (Table 1).

During a mean follow-up interval of 1.3 years, 89 deaths occurred in the study cohort. Forty five deaths were classified as noncardiac and 44 as cardiac in origin. Thirty-two cardiac deaths were considered to be due to an arrhythmia, including 19 unwitnessed deaths, 7 witnessed deaths without preceding symptoms and 6 deaths preceded by chest pain or arrhythmic symptoms; 12 cardiac deaths were not related to an arrhythmia.

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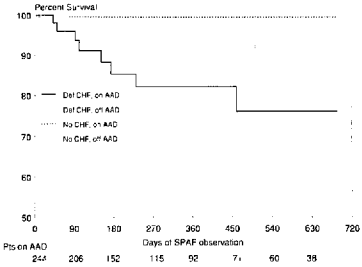

Figure 1. Survival to cardiac-related death in patients with and without heart failure (CHF) at entry. AAD = antiarrhythmic drug therapy; Def = definite history of; Pts = patients; SPAF = Stroke Prevention in Atrial Fibrillation.

Cardiac and arrhythmic mortality in the entire cohort. Cardiac mortality among patients receiving antiarrhythmic drug therapy was 5%/patient-year; among patients not taking antiarrhythmic drugs, cardiac mortality was 2.2%/patient-year. The relative risk of cardiac death for patients receiving antiarrhythmic drug therapy was 2.5 ($p = 0.006$, 95% confidence interval [CI] 1.3 to 4.9) compared with the risk of patients not treated with these agents. Considering only arrhythmic deaths, the relative risk during antiarrhythmic drug use was 2.6 ($p = 0.02$, 95% CI 1.2 to 5.6). After adjustment for the prospectively selected predictors of cardiac death, the relative risk of cardiac death for patients receiving antiarrhythmic agents was 2.7 ($p = 0.007$, 95% CI 1.3 to 5.5) and the relative risk of arrhythmic death was 2.3 ($p = 0.04$, 95% CI 1.0 to 5.1) compared with that of patients not receiving antiarrhythmic agents.

Mortality in patients with a history of heart failure. The increased relative risk of cardiac and arrhythmic death during antiarrhythmic drug therapy was especially noted in patients with a history of heart failure. In these patients, the relative risk of cardiac death during antiarrhythmic therapy was 4.7 ($p < 0.001$, 95% CI 1.9 to 11.6). Restricting the analysis to arrhythmic deaths, the relative risk was 3.7 ($p = 0.01$, 95% CI 1.3 to 10.4). The increased relative risk of death in patients with a history of congestive heart failure who received antiarrhythmic drug therapy was constant throughout the 1st year of observation (Fig. 1). There was no increased risk of cardiac death during antiarrhythmic therapy in patients without a definite history of heart failure (relative risk 0.70, 95% CI = 0.2 to 3.1).

Mortality in patients without ventricular arrhythmias. After exclusion of the 23 patients with ventricular arrhythmias, the relative risk of cardiac death in patients receiving antiarrhythmic drug therapy was only 1.6 ($p = 0.24$) compared with the risk of those not taking these drugs. For arrhythmic deaths the relative risk in patients receiving antiarrhythmic drug therapy compared with the risk in patients not taking these drugs was only 2.0 ($p = 0.13$). Even after adjustment for other predictors of cardiac death, patients receiving antiarrhythmic drugs had a relative risk of 1.8 for cardiac death ($p = 0.20$) and a relative risk of arrhythmic death of 2.1 ($p = 0.11$) compared with the risk in those not receiving antiarrhythmic drug therapy. However, among patients with a history of heart failure who received antiarrhythmic drugs, the relative risk of cardiac death was 2.9 ($p = 0.04$, 95% CI 1.1 to 8.2) and the relative risk of arrhythmic death was 4.1 ($p = 0.02$, 95% CI 1.2 to 13.5) compared with the risk of patients not receiving these drugs. After adjustment for the prospectively selected predictors of cardiac death, these patients had a relative risk of cardiac death of 3.3 ($p = 0.05$, 95% CI 0.99 to 11.1) and a relative risk of arrhythmic death of 5.8 ($p = 0.009$, 95% CI 1.5 to 21.7) compared with the risk of patients not taking antiarrhythmic drugs (Table 2).

A comparison of the baseline clinical and echocardiographic features of the 239 patients without ventricular arrhythmias and with a history of heart failure showed that

Table 2. Increased Risk From the Use of Antiarrhythmic Drugs in the Stroke Prevention in Atrial Fibrillation Study*

	Patients	Cardiac Deaths	Unadjusted Risk			Adjusted Risk		
			Hazard	p Value	95% CI	Hazard	p Value	95% CI
All patients	1,307	39	1.6	0.24	0.7–3.7	1.8	0.20	
Patients with definite CHF	239	19	2.9	0.04	1.1–8.2	3.3	0.05	0.99–11.1
Patients without definite CHF	1,068	20	0.81	0.78	0.2–3.5	0.77	0.72	0.17–3.4
	Patients	Arrhythmic Deaths	Unadjusted Risk			Adjusted Risk		
			Hazard	p Value	95% CI	Hazard	p Value	95% CI
All patients	1,307	28	2.0	0.13	0.8–5.0	2.1	0.11	0.8–5.3
Patients with definite CHF	239	12	4.1	0.02	1.2–13.5	5.8	0.009	1.5–21.7
Patients without definite CHF	1,068	16	1.0	0.97	0.2–4.5	0.83	0.82	0.18–4.0

*This analysis was restricted to patients for whom antiarrhythmic agents were prescribed for atrial fibrillation only; 23 patients were excluded because antiarrhythmic agents were prescribed for ventricular arrhythmias. CHF = congestive heart failure; CI = confidence interval.

Table 3. Baseline Characteristics of Patients With a History of Heart Failure Who Were and Were Not Taking Antiarrhythmic Agents at Baseline*

	Taking Antiarrhythmic Agents at Baseline (n = 26)	Not Taking Antiarrhythmic Agents at Baseline (n = 213)	p Value
Demographic characteristics			
Mean age (yr)	66	70	0.02
Male (%)	73	68	NS
Current smoker (%)	31	16	NS
Clinical baseline characteristics			
History of hypertension (%)	65	62	NS
History of diabetes (%)	31	25	NS
Definite history of angina (%)	38	18	0.03
History of myocardial infarction (%)	27	15	NS
NYHA functional class (%)			
II	83	76	NS
III	17	24	NS
Constant atrial fibrillation (%)	35	80	<0.001
Onset of AF <1 yr ago (%)	38	28	NS
Cardioversion attempted <1 mo after entry (%)	18	6	NS
Concurrent medications at baseline			
Digitalis (%)	90	89	NS
Diuretics (%)	74	82	NS
Calcium channel blockers (%)	18	31	NS
Beta-blockers (%)	10	12	NS
Aspirin or warfarin as SPAF therapy (%)	56	56	NS
Echocardiographic variables			
LV wall motion abnormality (%)			
None	29	48	NS
Mild	38	24	NS
Moderate to severe	33	28	NS
Left atrial dimension (cm)			
<4.0	8	8	NS
4.0–5.0	67	50	NS
>5.0	25	42	NS
LV internal systolic dimension (cm)	4.3	4.0	NS
LV internal diastolic dimension (cm)	5.9	5.5	NS

*This analysis excludes patients with ventricular arrhythmias. Abbreviations as in Table 1.

patients taking antiarrhythmic drugs were younger, and had a greater prevalence of intermittent atrial fibrillation and angina than did patients not taking antiarrhythmic drugs (Table 3).

Discussion

This study demonstrates increased cardiac mortality in patients with atrial fibrillation treated with antiarrhythmic drugs who had a history of definite congestive heart failure. In patients without a history of definite congestive heart failure, cardiac mortality did not increase with antiarrhythmic drug therapy.

Causes of increased mortality. The mechanism of increased cardiac mortality with antiarrhythmic drug therapy in this study remains speculative. A drug-induced ventricular arrhythmia is a possible explanation for these events. More than 70% of the cardiac deaths were considered to be due to an arrhythmia but >50% were unwitnessed, raising uncertainties about the cause of death. The relatively small number of cardiac deaths prevents us from commenting on individual antiarrhythmic drugs and their association with cardiac mortality.

Antiarrhythmic agents may provoke ventricular arrhythmias in patients treated for atrial or ventricular arrhythmias (9–12) and have been implicated as a cause of out-of-hospital cardiac arrest (9). Quinidine, a class IA agent and the most commonly prescribed antiarrhythmic drug in the study cohort, has a reported proarrhythmic rate of 15% in patients treated for ventricular arrhythmias (13). This early proarrhythmic effect usually occurs within 3 to 4 days (14) and often occurs in patients with left ventricular dysfunction (12). In most of our patients, antiarrhythmic drugs were initiated before study entry. Consequently, an early proarrhythmic effect would not have been observed. Our data suggest that the risk of cardiac death in patients with a

history of heart failure who receive antiarrhythmic drug therapy continues throughout the period of drug use. This is consistent with a late proarrhythmic effect.

Our analysis was based on observations of a large cohort representative of a broad population of patients with nonvalvular atrial fibrillation. Treatment with antiarrhythmic agents was not randomly allocated. Hence other cardiovascular variables associated with the use of antiarrhythmic drugs may have accounted for the increased mortality rate. Ventricular arrhythmias may have been one such variable. Another plausible basis for excess deaths is that patients with more severe congestive heart failure may have been selected for antiarrhythmic drug treatment. The similarity of functional classification at the time of enrollment and comparable echocardiographic measurements of left ventricular size and function in patients who were and were not receiving antiarrhythmic drugs suggest that such a selection bias does not account entirely for the observed difference in mortality. The possibility that certain patients experienced hemodynamic deterioration during the study and received antiarrhythmic drug therapy which contributed to increased mortality cannot be excluded by our data.

Clarification of the relation of antiarrhythmic drug therapy was not a primary objective of the Stroke Prevention in Atrial Fibrillation Study. However, this analysis was performed specifically seeking an association between antiarrhythmic drug therapy and an increase in increased cardiac mortality, strengthening its validity. We recognize that this type of analysis cannot replace a prospective, randomized trial but at present this type of trial has not been organized.

Conclusions. Antiarrhythmic drugs are frequently prescribed in patients with congestive heart failure to preserve atrial transport and improve cardiac output. A cautious interpretation of the available data favors the addition of antiarrhythmic drugs in patients with atrial fibrillation who have a history of heart failure only in circumstances when symptoms are severe and not amenable to other forms of therapy.

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