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Risk of Proarrhythmic Events in the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) Study

A Multivariate Analysis

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OBJECTIVES This study examined the risk of proarrhythmic events in patients receiving antiarrhythmic drugs for treatment of atrial fibrillation (AF) according to present-day safety guidelines.

BACKGROUND Advances in understanding the proarrhythmic risk of antiarrhythmic drugs has led to development of safety guidelines for these agents. Such guidelines were used in the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study.

METHODS This study was an analysis of the risk of arrhythmic events (arrhythmic death, resuscitated cardiac arrest, sustained ventricular tachycardia (VT), and torsade de pointes VT) in the antiarrhythmic drug arm of the AFFIRM study. Each time an antiarrhythmic drug was begun, it was counted as an exposure to that drug and the risk of an arrhythmic event was calculated.

RESULTS A total of 2,033 patients received 3,030 exposures to antiarrhythmic drugs. Ninety-six arrhythmic events occurred by six years. Patients with a left ventricular ejection fraction <40% had more arrhythmic events. Twelve documented cases of torsade de pointes VT were noted. The incidence of torsade de pointes was 0.6% at five years (95% confidence interval 0.32 to 1.07).

CONCLUSIONS The overall risk of adverse arrhythmic events upon exposure to antiarrhythmic drugs in the AFFIRM study was reasonably low. Strict criteria for the safe use of antiarrhythmic drugs were successful in minimizing proarrhythmic events. (J Am Coll Cardiol 2004;44: 1276–82) © 2004 by the American College of Cardiology Foundation

Antiarrhythmic drugs can cause a substantial risk of proarrhythmia, a potentially lethal drug-induced provocation or worsening of cardiac arrhythmias (1–3). Previous studies, especially in the past two decades, have led to heightened awareness of this risk and to guidelines for safer use of antiarrhythmic agents (4–6). The present-day risk of proarrhythmia, when safety guidelines are followed, is not known. Because atrial fibrillation (AF) is treated with a variety of antiarrhythmic drugs, we evaluated the risk of proarrhythmia and arrhythmic death in patients treated with drugs administered to maintain sinus rhythm in the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study, a clinical trial that imposed formal restrictions on the use of these drugs (7–9).

Certain populations are at increased risk of proarrhythmia from specific antiarrhythmic agents. Women are more susceptible than men to torsade de pointes ventricular tachycardia (VT) (10–14), a morphologically distinct form of VT distinguished by its polymorphic appearance and association with a prolonged QT interval, caused by antiarrhythmic drugs (Vaughan Williams class IA and III), which prolong cardiac repolarization (15,16). Serious structural heart disease confers an increased risk of ventricular proarrhythmia (and, in particular, proarrhythmic death) from antiarrhythmic medication (5,17,18). We used multivariate analysis to determine the effects of clinical characteristics on the risk of proarrhythmia in the rhythm-control arm of the AFFIRM study.

METHODS

Patients. The methods and enrollment criteria for the AFFIRM study have been described in detail elsewhere (7–9). Briefly, eligible patients had AF requiring long-term treatment either with drugs intended to control the ventricular response during AF (rate-control group) or antiarrhythmic drugs (rhythm-control group). Eligible patients were either ≥65 years of age or had another risk factor for stroke or death and had no contraindication to anticoagulation. The institutional review boards of the University of Washington and of all enrolling sites approved the protocol. Each patient gave written informed consent for the study.

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Abbreviations and Acronyms

AF = atrial fibrillation
AFFIRM = Atrial Fibrillation Follow-up Investigation of Rhythm Management
CI = confidence interval
LV = left ventricular
VT = ventricular tachycardia

Antiarrhythmic drug therapy. Once assigned to the rhythm-control group, patients received antiarrhythmic drug treatment as chosen by their physicians. Possible therapy included quinidine, procainamide, disopyramide, flecainide, propafenone, moricizine, sotalol, and amiodarone. Dofetilide became available during the latter part of the study and was also an acceptable treatment. The protocol specified guidelines for the use of specific antiarrhythmic drugs in accordance with standard safe practice (e.g., flecainide was not to be prescribed for patients with coronary artery disease or left ventricular [LV] dysfunction) (Table 1). Drug doses were adjusted based on renal and hepatic function, and patients were monitored for electrocardiographic changes (7). Patients whose therapy with the initial drug choice failed could have a different drug administered.

Exposure to the various antiarrhythmic drugs was tabulated at each follow-up visit. Any administration of an antiarrhythmic drug was considered to be an exposure to that drug. The precise duration of time that a person was

Table 1. Antiarrhythmic Drug Use (7–9)

Drug	Starting Dose	Minimum Maintenance Dose (mg/day)	Precautions†	Contraindications‡
Class I			Left ventricular dysfunction CHF Low LVEF Ischemic heart disease	
Quinidine		600		
Procainamide		1,500	Blood counts weekly for 12 weeks and as needed thereafter Blood tests for lupus syndrome every 3–6 months	
Disopyramide		300		LVEF <0.30
Moricizine		400		
Class I-C			Required for use of class I-C agents: Normal LV Normal stress test	CHF Structural heart disease Myocardial disease LVH CAD Abnormal LV function/ wall motion LVEF <0.50
Propafenone		450		
Flecainide		100		
Class III				
Dofetilide		Not specified	In-hospital administration for a minimum of 3 days Measurement of renal function ECG monitoring	
Ibutilide		Not applicable	In-hospital administration ECG monitoring	
Sotalol	160 mg/day	240		Asthma Renal dysfunction requiring dialysis Current CHF class ≥ II History of CHF and LVEF ≤ 0.30 or LVEF ≤ 0.25
Amiodarone	10 g over 1 or more weeks	200		

*100 mg/day could be used if adverse effects required a lower dose, and higher doses (up to 400 mg/day) could be used, as necessary. †General precautions to be observed: careful monitoring for proarrhythmia, bradycardia, and hypokalemia; caution for the negative inotropic effects of drugs; QTc must not exceed 0.52 s after drug titration; particular caution in patients with LVH or organic heart disease; atrioventricular nodal blocking drugs to be given as appropriate; monitoring for renal and hepatic dysfunction in the elderly. ‡Any drug associated with prior inefficacy, intolerable adverse effects, or torsades could not be used again.

CAD = coronary artery disease; CHF = congestive heart failure; ECG = electrocardiogram; LV = left ventricular; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; Stress test = evaluation for stress-induced ischemia (exercise test, stress thallium or sestamibi, stress echocardiogram, pharmacologic stress radionuclide scan, or pharmacologic stress echocardiogram), alternatively, a normal coronary angiogram could substitute for the stress test.

Table 2. Baseline Characteristics

	Total	Women	Men	p Value
n	2,033	771	1,262	
Age	69.7 ± 9.0	71.8 ± 8.6	68.4 ± 9.0	<0.0001
History of CAD	794 (39)	236 (31)	558 (44)	<0.0001
History of MI	373 (18)	102 (13)	271 (21)	<0.0001
History of CHF	464 (23)	177 (23)	287 (23)	0.91
History of hypertension	1,442 (71)	562 (73)	880 (70)	0.13
History of valvular heart disease	240 (12)	122 (16)	118 (9)	<0.0001
History of diabetes	389 (19)	139 (18)	250 (20)	0.32
History of hepatic or renal disease	102 (5)	28 (4)	74 (6)	0.025
History of smoking	255 (13)	71 (9)	184 (15)	0.0004
Rhythm at randomization				
Atrial fibrillation or flutter	894 (46)	315 (43)	579 (48)	0.03
Sinus rhythm	1,040 (54)	416 (57)	624 (52)	
Left ventricular ejection fraction				
Normal (≥50%)	1,113 (73)	475 (82)	638 (68)	<0.0001
Mild dysfunction (40%–49%)	200 (13)	55 (10)	145 (15)	
Moderate dysfunction (30%–39%)	134 (9)	32 (6)	102 (11)	
Severe dysfunction (<30%)	74 (5)	17 (3)	57 (6)	

Data are presented as n (%) or mean ± SD.
CAD = coronary artery disease; CHF = congestive heart failure; MI = myocardial infarction.

exposed to a drug was not reported. Drug levels were not reported, though they may have been performed locally and used to monitor drug dosing. Doses likewise were not reported to the AFFIRM study coordinating center.

Drugs considered to pose the most serious risk for QT prolongation and proarrhythmia were quinidine, procainamide, disopyramide, sotalol, ibutilide, and dofetilide. Amiodarone was thought to have a lesser risk of QT prolongation and proarrhythmia.

Data acquisition. Data collected prospectively included baseline clinical characteristics, drugs taken, electrocardiographic parameters, and the reporting of significant arrhythmic events: resuscitated cardiac arrest, torsade de pointes VT, sustained VT, and arrhythmic death. These arrhythmic events were adjudicated by an Events Committee blind to treatment arm and drug assignment (19). This substudy was designed after initiation of the AFFIRM study protocol, but before results were available. Analysis was performed by intention-to-treat.

Statistical analysis. Student *t* test was used to compare continuous variables. Chi-square analyses were used to compare categorical values; when one or more expected cell frequencies were <5, Fisher exact tests were used instead of the chi-square approximation. Kaplan-Meier methods were used to determine event-free survival, and groups were compared using log-rank tests. A Cox proportional hazards model was used to adjust for significant covariates. Some analyses were restricted to subjects who were exposed to drugs more likely to prolong the QT interval (quinidine, procainamide, disopyramide, sotalol, ibutilide, and dofetilide).

RESULTS

Characteristics of study population. Of 4,060 patients enrolled in the AFFIRM study, 2,033 were randomized to the rhythm-control arm of the study to receive antiarrhythmic drugs for treatment of AF and form the basis for this analysis (8,9). Patients were followed for an average of 3.5 years.

Table 2 displays the baseline patient characteristics, highlighting a comparison between women and men. Women were older ($p < 0.0001$) and more had valvular heart disease ($p < 0.0001$). Men were more likely to have coronary artery disease ($p < 0.0001$), past myocardial infarction ($p < 0.0001$), hepatic or renal disease ($p = 0.025$), history of smoking ($p = 0.0004$), AF at the time of randomization ($p = 0.03$), and abnormal LV function ($p < 0.0001$). The ejection fraction was not available in 25% of women and 25% of men.

Drugs used. Initial antiarrhythmic drug therapy and overall exposure to antiarrhythmic agents are shown in Table 3. More men were prescribed amiodarone, and more women used disopyramide, flecainide, and propafenone. In follow-up, more women used diuretics.

Arrhythmic events. The cumulative incidence of all arrhythmic events at six years was 7%, 6% in women (34 events in 771 patients), compared with 7% in men (62 events in 1,262 patients). Figure 1 shows that the Kaplan-Meier estimates of the cumulative incidence of a first ventricular proarrhythmic event by five years among the 1,047 patients exposed to drugs known to have a high risk of QT prolongation (quinidine, procainamide, disopyramide, sotalol, ibutilide, and dofetilide) was 5% in women (n = 14 events) and 5% in men (n = 23 events). Congestive heart failure increased the risk of proarrhythmia to 9.7% at five years, compared to 4.0% in those without congestive heart failure ($p = 0.001$). After adjusting for gender, the predictors of ventricular proarrhythmic events in all patients were age ≥65 (hazard ratio = 1.96, $p = 0.03$), history of congestive heart failure (hazard ratio = 2.68, $p < 0.0001$),

Table 3. Drug Therapy

	Total	Women (n = 771)	Men (n = 1,262)	p Value
Initial antiarrhythmic drug therapy after randomization				
Quinidine	92 (5)	32 (5)	60 (5)	0.53
Disopyramide	42 (2)	28 (4)	14 (1)	0.0001
Procainamide	103 (5)	29 (4)	74 (6)	0.04
Moricizine	14 (1)	7 (1)	7 (1)	0.35
Flecainide	88 (5)	48 (7)	40 (3)	0.001
Propafenone	183 (10)	94 (13)	89 (8)	< 0.0001
Dofetilide	0	0	0	
Ibutilide	0	0	0	
Sotalol	612 (33)	228 (32)	384 (33)	0.69
Amiodarone	735 (39)	240 (34)	495 (42)	0.0002
Antiarrhythmic drugs taken at any time after randomization				
Quinidine	139 (7)	41 (5)	98 (8)	0.04
Disopyramide	83 (4)	55 (7)	28 (2)	< 0.0001
Procainamide	159 (8)	52 (7)	107 (9)	0.17
Moricizine	35 (2)	14 (2)	21 (2)	0.79
Flecainide	166 (8)	87 (12)	79 (6)	< 0.0001
Propafenone	283 (14)	140 (19)	143 (12)	< 0.0001
Dofetilide*	12 (0.60)	3 (0.40)	9 (0.73)	0.55
Ibutilide*	4 (0.20)	2 (0.26)	2 (0.16)	0.64
Sotalol	817 (41)	313 (41)	504 (41)	0.71
Amiodarone	1,257 (63)	444 (59)	813 (66)	0.003
Other drugs taken at any time after randomization				
Digoxin	1,052 (53)	409 (54)	643 (52)	0.31
Diuretic	1,332 (67)	553 (73)	779 (63)	< 0.0001

*Fisher exact test used due to expected cell frequencies <5. Data are presented as n (%).

and mitral regurgitation ≥2+/4+ (hazard ratio = 2.04, p = 0.003). After adjustment for significant covariates, gender did not confer any additional risk for ventricular proarrhythmic events.

The incidence of torsade de pointes VT was low and similar in women and men, 7 versus 5 (1.0% and 0.4%) (Tables 4 to 6). The QTc was dramatically prolonged in most patients with torsade de pointes at the time of the event, and QTc was frequently accompanied by bradycardia, hypokalemia, or hypomagnesemia (Table 5).

Mortality. Overall mortality in the rhythm control arm was 22% in women and 25% in men at five years (p = 0.3024).

DISCUSSION

Low number of arrhythmic events related to selection of antiarrhythmic agents. In this substudy of a large group of patients with AF treated with antiarrhythmic agents using strict guidelines, the risk of proarrhythmia was low. The cumulative incidence of all arrhythmic events in patients exposed to QT-prolonging drugs was 5% at five years. With the overall mortality in the rhythm control group at 27%, arrhythmic events were a small portion of the adverse outcomes. Furthermore, the incidence of strokes and noncardiac events was much higher than the incidence of arrhythmic events.

Torsade de pointes VT is the major type of proarrhythmia that can be definitively ascribed to an antiarrhythmic drug. Other types of proarrhythmia (arrhythmic death, sustained VT, resuscitated cardiac arrest) could be secondary to the progression of intrinsic disease. Overall incidence of torsade de pointes VT was 1% for women and 0.4% for men. This incidence of torsade de pointes VT in the AFFIRM study was far below the rate of 2% to 10% suggested in older literature (20–27). More recently, Hohnloser et al. (28) reported torsade de pointes in 13/947 (1.4%, 95% confidence interval [CI] 0.77 to 2.4) patients treated with sotalol, compared with 77/3,944 (2.0%, 95% CI 1.6 to 2.5) patients reported by Lehmann et al (29) and 4/839 (0.48%, 95% CI 0.15 to 1.3) patients given sotalol in the AFFIRM study. For dofetilide (30), torsade de pointes was documented in 11/1,346 (0.82%, 95% CI 0.43 to 1.5) patients and 4/249 (1.6%, 95% CI 0.52 to 4.3) patients in AF, compared with 1/12 (8.3%, 95% CI 0.44 to 40.3) in the AFFIRM study. The overall risk of torsade de pointes in the AFFIRM study for all subjects was 12 of 2,006 (0.6%, 95% CI 0.32 to 1.07); limiting the analysis to sotalol or dofetilide, torsade de pointes was seen in 5 of 851 (0.6%, 95% CI 0.22 to 1.45). This overall risk of torsade de pointes in the AFFIRM study reflects the restrictions on drug use imposed in the AFFIRM study, as well as the drug dose adjustments based on drug metabolism, renal and hepatic function, and the monitoring of electrocardiographic changes (7).

The overall number of proarrhythmic events may have been small because of the mix of antiarrhythmic agents

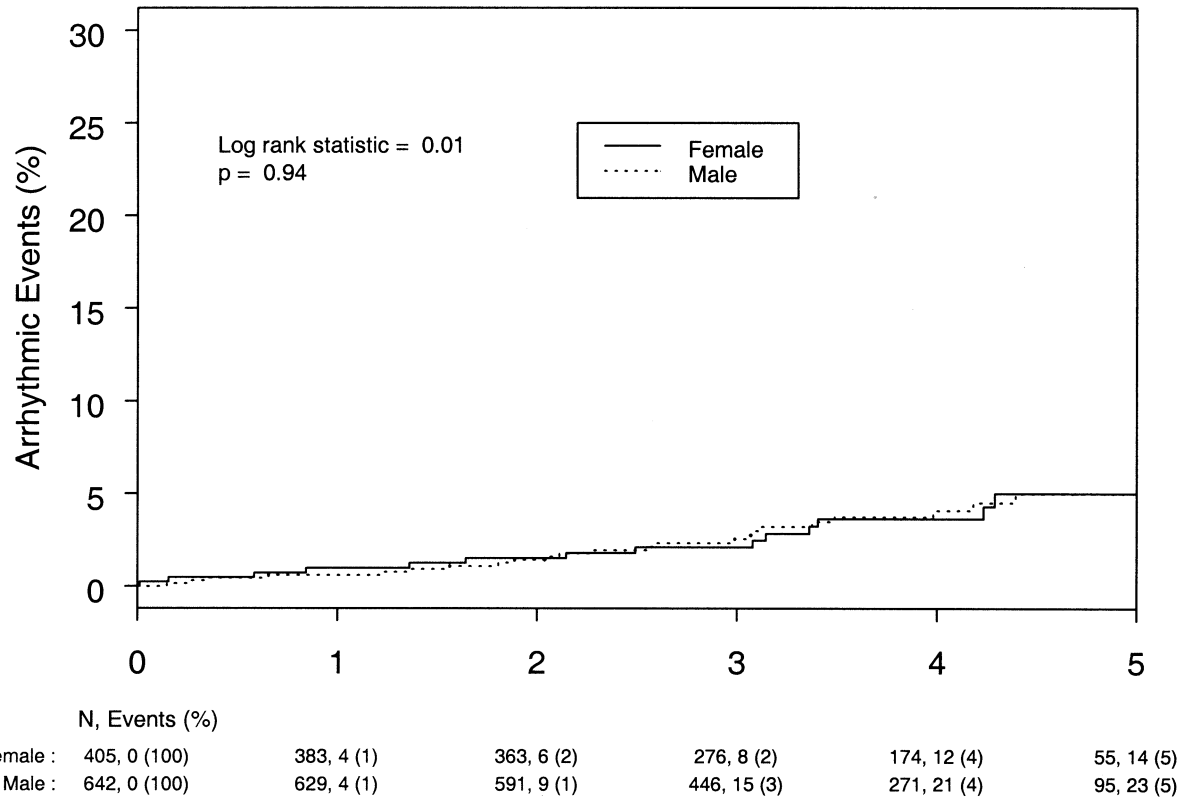

Figure 1. Time to significant ventricular arrhythmias (defined as resuscitated cardiac arrest, torsades de pointes ventricular tachycardia, sustained ventricular tachycardia, or arrhythmic death) in the antiarrhythmic drug arm of the AFFIRM study exposed to quinidine, disopyramide, procainamide, sotalol, ibutilide, or dofetilide at any time.

used. Only one-third of patients took class I agents, and roughly one-third took sotalol. One-third took amiodarone, which is thought to cause ventricular proarrhythmia only rarely. Class I agents have been shown to have significant proarrhythmic effects with an associated mortality up to 6% (20–27). The risk of proarrhythmia from class I agents is higher in patients with underlying significant structural heart disease such as congestive heart failure (18). The relatively low use of class I agents in this study (and the AFFIRM study guidelines designating which patient groups could appropriately receive which specific drugs) probably contributed to the low number of proarrhythmic events. Specifically, class IC drugs were prohibited in patients with organic heart disease, and investigators were to use caution in the use of any class I agents in patients with LV dysfunction (7).

Effect of gender. There was no statistically significant gender difference in the risk of arrhythmic events, including torsade de pointes VT. However, prior studies observed an increased risk for women when QT-prolonging drugs were given, even after correction for baseline clinical inequalities between men and women (12–14,31,32). There are several plausible explanations for our results. First, the low number of adverse events may have precluded finding a statistically significant gender difference (i.e., a possible type II statistical error). Second, the selection of antiarrhythmic drugs may have influenced the outcome. The use of antiarrhythmic drugs was neither randomized nor blinded, and women received a different mix of drugs throughout the study. Women may have had their drug administration followed more closely and drugs discontinued more quickly if adverse effects or electrocardiographic changes appeared, in recog-

Table 4. Arrhythmic Events

	Total (n = 2,033)	Women (n = 771)	Men (n = 1,262)	p Value
Total subjects with event	96 (5)	34 (4)	62 (5)	0.60
Cardiac arrest*	16 (0.79)	4 (0.52)	12 (1)	0.44
Torsades de pointes VT*	12 (0.59)	7 (1)	5 (0.4)	0.23
Sustained VT*	5 (0.25)	0 (0)	5 (0.4)	0.16
Arrhythmic death	77 (4)	27 (4)	50 (4)	0.60

*Fisher exact test used due to expected cell frequencies <5. Data are presented as n (%).
VT = ventricular tachycardia.

Table 5. Torsade de Pointes Ventricular Tachycardia

Patient #	Age; Gender; Diagnosis	LVEF	Antiarrhythmic Drug	Time on Drug	*Time From ECG to Torsade Event; Heart Rate; QTc	*Time From Torsade Event to ECG; Heart Rate; QTc	Other
1	76; F; CAD, RHD, CHF	40%–49%	amiodarone	9 days	1 min; 53; 590	NA	K^+ = 3.2, LBBB
2	78; M; CAD, DM, COPD, HTN, CHF, CRF	≥50%	quinidine	1.5 yrs	NA/paced	NA/paced	K^+ = 3.4, Mg^{++} = 1.5
3	81; F; HTN	≥50%	amiodarone, ibutilide	17 min	3.75 h; 74; 418	5 min; 74; 600	K^+ = 4.0, Mg^{++} = 1.6 On amio before ibutilide
4	68; F; HTN, DM	≥50%	disopyramide	4 days	4 days; 50; 429	20 min; 43; 576	"low K," "low Mg^{++}"
5	74; M; HTN	≥50%	amiodarone, dofetilide	2 days	9 h; 52; 521	13 days; 63; 422	On amio before dofetilide
6	75; M; CAD, HTN, CRF	≥50%	sotalol	2.5 yrs	2 days; 61; 535	9 h; 54; 605	K^+ = 4.8, Mg^{++} = 1.4
7	79; F; CAD, CHF, sepsis	40%–49%	amiodarone	2 months	NA	NA	K^+ = 3.7, pH = 7.28
8	69; M; HTN, CAD	≥50%	sotalol	2 days	1 min; 48; 718	1 min; 52; 669	On amio before sotalol; RBBB, LAFB
9	55; M; HTN	≥50%	amiodarone	1 yr	3 days; 56; 560	1 min; 55; 632	K^+ = 3.4, Mg^{++} "low"
10	76; F; CHF, CVA, old MI, CAD, DM, HTN, new MI	NA	sotalol	1 yr	NA	NA	K^+ = 3.3, Mg^{++} = 1.7
11	75; F; HTN, CAD, CHF	55%	sotalol	1 month	1 month; 56; 494	1 h; 50; 548	LBBB
12	52; F; DM, HTN, new MI, sepsis	≥50%	amiodarone	11 months	2 h; 98; 588	1.5 h; 91; 603	K^+ = 3.3, Mg^{++} = 1.6

amio = amiodarone; CAD = coronary artery disease; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; CRF = chronic renal failure; CVA = cerebrovascular accident; DM = diabetes mellitus; ECG = electrocardiogram; HTN = hypertension; LAFB = left anterior fascicular block; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NA = not available; RBBB = right bundle branch block; RHD = rheumatic heart disease; *ECG measurements immediately before and after torsade event. All QTc measurements are in milliseconds.

nition of the literature demonstrating that women have a higher risk for proarrhythmia (12,13,31,32). Last, the severity of heart disease in this study was higher in men than in women.

Severity of underlying heart disease. It is well-established that LV dysfunction in a population of patients with underlying ischemic heart disease predisposes to arrhythmic events and death (33). Thus, a tendency toward more proarrhythmia in women may have been offset by the more serious underlying heart disease in the men in this study. Only age ≥65 years, mitral regurgitation, and congestive heart failure were significant covariates in the multivariate analysis.

Table 6. Torsade de Pointes VT

Drug	N Exposed to Drug	N With Torsades	% Incidence
Quinidine	151	1	0.7
Procainamide	170	0	0
Disopyramide	86	1	1.2
Moricizine	35	0	0
Flecainide	168	0	0
Propafenone	292	0	0
Dofetilide	12	1	8.3
Ibutilide	4	1	25
Sotalol	839	4	0.5
Amiodarone	1,273	5	0.4

*One patient was taking both amiodarone and dofetilide at time of the event.
VT = ventricular tachycardia.

Time course of proarrhythmia. Importantly, torsade de pointes VT did not necessarily occur early upon exposure to a QT-prolonging drug. Six of the 12 patients had been receiving their medication for more than two months and three were taking amiodarone alone. Other authors have also reported late onset of proarrhythmia (4), and the concept that adverse effects of antiarrhythmic drugs always occur early is incorrect. The fact that many of the patients had coexistent bradycardia, hypokalemia, and/or hypomagnesemia emphasizes the need to avoid these conditions in patients treated with QT-prolonging agents.

Strengths and uniqueness of the study. The careful selection of antiarrhythmic drugs and monitoring of their use in the AFFIRM study was associated with a low risk of proarrhythmic events, despite a high-risk patient population. In contrast to many study designs, in AFFIRM study physicians were not blinded to patient treatment, nor mandated to administer specific drugs or doses to all patients. In fact, within the rhythm control strategy, specific

safety guidelines were imposed. This situation mirrors good clinical practice and illustrates that thoughtful, informed physicians following standard safety guidelines can use antiarrhythmic drugs with relatively low risk.

Study limitations. The present study was conducted in patients with AF who were age ≥65 years or had another risk factor for stroke or death. It does not necessarily apply to other patients with AF.

This substudy was analyzed by retrospective analysis of data. The arrhythmia event rates were too low to detect even major differences in proarrhythmic risk. Furthermore, proarrhythmic events may have been missed or misclassified. Doses of the various antiarrhythmic drugs were not routinely reported, nor were routine electrocardiographic measurements, so we are unable to demonstrate any effect of careful dose adjustments that might have occurred. The precise duration of time that a person was exposed to a drug was not reported, and drug levels were not measured.

Conclusions. If patients with AF are treated with antiarrhythmic agents selected appropriately and monitored carefully, overall proarrhythmia risk is relatively low. Drug selection is crucial, and dose adjustments are necessary, based on hepatic and renal function, along with monitoring of electrocardiographic changes. These measures will help to reduce adverse arrhythmia outcomes for patients needing these drugs.

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