Published in final edited form as:
Arch Intern Med. 2007 August 13; 167(15): 1648–1653.

Sex Differences in the Relationship Between Amiodarone Use and the Need for Permanent Pacing in Patients With Atrial Fibrillation

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Abstract

Background—Amiodarone use was associated with an increased need for pacemaker insertion in a retrospective study of patients with atrial fibrillation (AF) and prior myocardial infarction. The aims of this study were to determine prospectively whether amiodarone increases the need for pacemakers in a general population of patients with AF and whether this effect is modified by sex.

Methods—The study included 1005 patients with new-onset AF who were enrolled in the Fibrillation Registry Assessing Costs, Therapies, Adverse events, and Lifestyle (FRACTAL). Multivariable Cox regression models, including time-dependent covariates accounting for medication exposure, were used to evaluate the risk of pacemaker insertion associated with amiodarone use.

Results—Amiodarone use was associated with an increased risk of pacemaker insertion (hazard ratio [HR], 2.01; 95% confidence interval [CI], 1.08–3.76) after adjustment for age, sex, atrial flutter, coronary artery disease, heart failure, and hypertension. The effect of amiodarone use was modified

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Financial Disclosure: None reported.

Previous Presentation: This study was presented in part at the American Heart Association Scientific Sessions; November 13–16, 2005; Dallas, Texas.

Additional Information: The following list is of the participating centers (local investigators) in the Fibrillation Registry Assessing Costs, Therapies, Adverse Events, and Lifestyle (FRACTAL): Beth Israel Deaconess Medical Center (Drs Josephson and Zimetbaum); Rhode Island Hospital (Drs Lemery and Buxton); Mayo Clinic, Rochester, Minnesota (Paul A. Friedman, MD, and Marshall S. Stanton, MD); Montreal General Hospital, Montreal, Quebec, Canada (Dr Hadjis); Sentara Virginia Beach General Hospital, Virginia Beach, Virginia (John J. Griffin, MD); Victoria Heart Institute, Victoria, British Columbia, Canada (Richard A. Leather, MD); University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania (David Schwartzman, MD); Good Samaritan Hospital, Los Angeles, California (David Cannom, MD); Loyola University Medical Center, Chicago, Illinois (Dr Olshansky); Kaiser Permanente Medical Center, Los Angeles (Adam Kotlewski, MD, PhD); Duke University Medical Center, Durham, North Carolina (Tristram D. Bahnson, MD); Framingham/MetroWest Medical Center, Framingham, Massachusetts (Donald Love, MD); St Paul Heart Clinic, St Paul, Minnesota (David N. Dunbar, MD); University of Maryland Medical Center, Baltimore (Michael R. Gold, MD, PhD); Mount Auburn Hospital, Cambridge, Massachusetts (Panagiatos Voukydis, MD); University of Rochester Medical Center, Rochester, New York (David T. Huang, MD); Hospital of the University of Pennsylvania, Philadelphia (David Callans, MD).

Author Contributions: Dr Essebag had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Essebag, Reynolds, Hadjis, Josephson, and Zimetbaum. *Acquisition of data:* Essebag, Hadjis, Lemery, Buxton, Josephson, and Zimetbaum. *Analysis and interpretation of data:* Essebag, Reynolds, Hadjis, Olshansky, and Zimetbaum. *Drafting of the manuscript:* Essebag, Hadjis, and Lemery. *Critical revision of the manuscript for important intellectual content:* Essebag, Reynolds, Hadjis, Olshansky, Buxton, Josephson, and Zimetbaum. *Statistical analysis:* Essebag and Reynolds. *Obtained funding:* Essebag, Hadjis, and Zimetbaum. *Administrative, technical, and material support:* Essebag, Hadjis, Lemery, and Josephson. *Study supervision:* Hadjis, Buxton, Josephson, and Zimetbaum.

by sex, with a significant risk in women but not in men (HR, 4.69; 95% CI, 1.99–11.05 vs HR, 1.05; 95% CI, 0.42–2.58 [*P* = .02]). This interaction remained significant after adjustment for weight, body mass index, weight-adjusted amiodarone dose, and use of other antiarrhythmic or rate control drugs.

Conclusion—The risk of bradyarrhythmia requiring pacemaker insertion associated with amiodarone use for AF is significantly greater in women than in men, independent of weight or body mass index.

Amiodarone is more effective than other antiarrhythmic agents at maintaining sinus rhythm in patients with atrial fibrillation (AF)[1–4]; however, its use is associated with a number of extracardiac and cardiac adverse effects.[5,6] An association between amiodarone use for AF and bradyarrhythmia requiring permanent pacemaker insertion has been demonstrated in a large retrospective cohort of elderly patients with prior myocardial infarction.[7] The study also found a statistically nonsignificant interaction with sex, suggesting that this effect may be greater in women.[7] The objectives of the current study were to determine prospectively whether amiodarone increases the need for pacemaker in a general population of patients with new-onset AF and whether this effect is modified by sex.

METHODS

STUDY POPULATION

The Fibrillation Registry Assessing Costs, Therapies, Adverse events and Lifestyle (FRACTAL) is a prospective cohort study of patients with AF. Details of the study organization and additional clinical, quality-of-life, and economic outcomes have been published previously.[8,9] Briefly, beginning in 1997, patients were enrolled at 17 centers in the United States and Canada after their first electrocardiographically confirmed episode of AF. Patients with AF occurring immediately after cardiac surgery and patients who had received prior therapy with antiarrhythmic drugs were excluded. Local investigators publicized the registry, and cases were identified through surveillance of emergency department and inpatient visits or by referral from out-patient practices. Patient treatment remained at the discretion of local practitioners. A total of 1005 patients were enrolled in the cohort and included in this study.

FOLLOW-UP

At each enrolling center, trained research assistants collected baseline data at study entry through chart review and interview of study subjects. Baseline data included demographic variables, in-depth cardiovascular and health history questions, and aspects of the initial treatment plan. Routine follow-up visits were conducted at 3, 6, 12, 18, 24, and 30 months after enrollment. At each visit, changes in treatment, current medication use, adverse events, cardiac procedures, AF recurrence, and health care resource use were ascertained. Initiation of new or continuation of therapy with previously prescribed antiarrhythmic agents was recorded, as was any attempt at cardioversion back to sinus rhythm or insertion of a permanent cardiac pacemaker.

OUTCOME

The outcome variable for this analysis was insertion of a new permanent pacemaker for bradyarrhythmia. The date and details of pacemaker implantation were recorded during follow-up visits. The analysis excluded 32 patients with pacemaker or pacemaker-defibrillator implantation before cohort entry and censored patients when a pacemaker was implanted in the context of atrioventricular (AV) node ablation (17 patients) or when a pacemaker-defibrillator was implanted (8 patients).

VARIABLES

Time-dependent variables were created to account for changes in exposure over time to antiarrythmic and rate control medications (β-blockers, diltiazem or verapamil, and digoxin). Variables for rate control medications recorded the use of these medications over time, regardless of the specific indication for the use of the medication (ie, whether used primarily for rate control, hypertension, or heart failure). Separate time-dependent variables were created for amiodarone, sotalol, class 1 antiarrythmic agents, β-blockers, calcium channel blockers (diltiazem and verapamil), and digoxin. Other variables studied included sex, age, weight, body mass index (BMI), coronary artery disease, congestive heart failure, hypertension, and atrial flutter.

STATISTICAL ANALYSIS

The incidence of pacemaker insertion was calculated by dividing the number of subjects with pacemaker insertion by the sum of observation times of all subjects in the study cohort and was expressed as percentage per person-year. The risk of pacemaker implantation associated with amiodarone exposure was estimated with multivariable Cox regression using a time-dependent covariate to account for variation in amiodarone exposure.[10,11] The risk of pacemaker insertion associated with other antiarrhythmic agents (sotalol or class 1 drugs) was similarly evaluated in separate regression models. It was decided on clinical grounds to adjust all regression models for variables likely associated with pacemaker insertion and/or amiodarone use, ie, age, coronary artery disease, congestive heart failure, hypertension, and atrial flutter. The effect of amiodarone dose was also evaluated (using time-dependent covariates to compare doses >200 mg with doses ≤200 mg) because doses greater than 200 mg have been associated with an increased risk of pacemaker insertion.[12] The significance of the modification of the effect of amiodarone use by amiodarone dose was evaluated by including an interaction term in the model. Because a previous study raised the possibility of an interaction between female sex and the risk of pacemaker insertion associated with amiodarone use, the decision was made a priori to assess modification of the effect of amiodarone use by sex.[7] Modification of the effect of amiodarone use by sex was further evaluated in different regression models after adjustment for weight, BMI, amiodarone dose, weight-adjusted amiodarone dose (ie, amiodarone dose divided by body weight), and use of other antiarrhythmic or rate control drugs (digoxin, β-blockers, and calcium channel blockers such as diltiazem or verapamil). Weight, BMI, and weight-adjusted amiodarone dose were each separately adjusted for in different models as continuous variables, as binary variables dichotomized at median values, and as categorical variables divided into 4 quartiles. Results of multivariable Cox regression models are reported using hazard ratios (HRs), 95% confidence intervals (CIs), and *P* values ($P \leq .05$ was considered statistically significant). All statistical analyses were performed using a commercially available statistical software package (SAS Release 8.2; SAS Institute Inc, Cary, North Carolina).

RESULTS

PATIENT CHARACTERISTICS

Thirty-two patients were excluded from the initial cohort of 1005 patients with new-onset AF because they had a pacing device (8 pacemaker-defibrillators and 24 pacemakers) implanted before the start of the study. The final study cohort comprised 973 patients who were followed up for a mean (SD) of 2.0 (0.9) years from AF diagnosis to the first pacemaker insertion, death, or end of follow-up. The mean (SD) age of the patients, 40% of whom were female, was 66 (14) years. The AF was symptomatic in 85% of patients. Baseline characteristics are listed in Table 1. Antiarrhythmic and rate control medication use at baseline and at anytime during follow-up is presented in Table 2.

PACEMAKER INSERTION

Of the 973 patients included in this study, 85 (46 men and 39 women) underwent implantation of a pacing device during follow-up. Eight of the 85 patients (4 men and 4 women) received pacemaker-defibrillators, which were implanted to treat tachyarrhythmias (monomorphic ventricular tachycardia in 7 patients and family history of sudden cardiac death in 1 patient). Seventeen of the 77 remaining pacemakers were implanted in the context of AV node ablation; the other 60 were implanted for bradyarrhythmias. The most common bradyarrhythmias requiring pacemaker insertion were sick sinus syndrome (47 patients) and AV block (9 patients) (Table 3). Of the patients with sick sinus syndrome, 55% had symptomatic bradycardia and 11% had syncope. Of the patients with pacemakers that were implanted for AV block, 22% had symptomatic bradycardia and 22% had syncope. The overall incidence of permanent pacemaker insertion for bradyarrhythmia was 3.1% per person-year.

RISK OF PACEMAKER INSERTION ASSOCIATED WITH AMIODARONE USE

Amiodarone use was associated with an increased risk of pacemaker insertion (HR, 2.01; 95% CI, 1.08–3.76) after adjustment for age, sex, atrial flutter, coronary artery disease, congestive heart failure, and hypertension. Age (HR, 1.44 per decade; 95% CI, 1.13–1.83) and atrial flutter (HR, 3.83; 95% CI, 1.53–9.58) were also independently associated with an increased risk of pacemaker insertion. There was no association between use of sotalol or class 1 antiarrhythmic agents and pacemaker insertion. There was a trend suggesting that the risk of pacemaker insertion was higher with amiodarone doses greater than 200 mg/d than with those less than or equal to 200 mg/d (HR, 2.27; 95% CI, 1.05–4.91 vs HR, 1.75; 95% CI, 0.73–4.20); however, this difference was not statistically significant.

SEX DIFFERENCES IN THE EFFECT OF AMIODARONE ON THE RISK OF PACEMAKER INSERTION

The effect of amiodarone use was modified by sex, with a significant risk of pacemaker insertion in women but not in men (HR, 4.69; 95% CI, 1.99–11.05 vs HR, 1.05; 95% CI, 0.42–2.58; *P* value for interaction, .02). As presented in Table 4, the interaction between sex and amiodarone use remained significant after adjustment for daily dose of amiodarone (*P* value for interaction, .02). The interaction between sex and amiodarone also remained significant in different regression models after adjustment for weight, BMI, weight-adjusted amiodarone dose (ie, amiodarone dose divided by body weight), and use of other antiarrhythmic or rate control drugs (β-blockers, diltiazem or verapamil, and digoxin).

COMMENT

This study found that amiodarone use in patients with new-onset AF was associated with an increased need for permanent pacemaker insertion. Furthermore, our findings suggest that the risk of pacemaker insertion associated with amiodarone use is significantly greater in women than in men. The association between amiodarone use in the treatment of AF and the need for permanent pacemaker has been previously reported in a large retrospective study of elderly (≥65 years) patients with prior myocardial infarction.[7] That study evaluated a particularly high-risk subset of patients, given that elderly patients with prior myocardial infarction are at greatest risk of bradyarrhythmias during antiarrhythmic therapy for AF.[13] The present study confirms prospectively that amiodarone use is associated with a greater need for permanent pacemaker insertion in a general population of patients with AF.

While amiodarone use was associated with an increased risk of pacemaker insertion, the use of other antiarrhythmic medications (ie, sotalol or class 1 antiarrhythmic agents) or rate control medications (β-blockers, calcium channel blockers, or digoxin) was not. In addition to the likelihood that amiodarone is more potent at causing bradyarrhythmia, this observation may

also be related to the fact that amiodarone has a significantly longer half-life than other antiarrhythmic or rate control medications (>30 days vs <1 day). When medication-related bradycardia occurs, avoidance of pacemaker insertion by dose reduction or medication cessation may be less likely with amiodarone than with other medications.

The only variables other than amiodarone use that were independently associated with an increased risk of pacemaker insertion were increased age and the presence of concomitant atrial flutter. While an association with increased age is not surprising, the association with atrial flutter is unexpected and of unclear significance. Atrial flutter differs from AF in that it involves a macro-reentrant (often right atrial) circuit with a regular atrial rate. Rate control of atrial flutter tends to be more difficult than for AF. It is possible that doses required for rate or rhythm control of atrial flutter are more likely to result in bradycardia requiring pacemaker insertion. Our patients did not undergo ablation procedures other than AV junction ablation for rate control. The question of whether current ablative procedures for rhythm control of atrial flutter or AF will decrease the need for pacemaker insertion requires further investigation.

This study also found that the risk of pacemaker insertion associated with amiodarone use is significantly greater in women than in men (HR, 4.69 vs HR, 1.05; $P = .02$). This finding is consistent with a previous retrospective study demonstrating a difference of similar magnitude (odds ratio, 3.86 vs odds ratio, 1.52; $P = .08$).[7] Given that the effect of amiodarone is dose-dependent,[12] we adjusted for amiodarone dose and found that the effect of amiodarone use remained significantly greater in women. Furthermore, amiodarone use was significantly more likely to be associated with pacemaker insertion in women even after sex differences in weight, BMI, weight-adjusted amiodarone dose, and differences in use of other cardiac medications, age at presentation, and presence of cardiovascular disease were accounted for.

The reason for the greater risk of bradyarrhythmia requiring permanent pacemaker associated with amiodarone use in women is unclear and is likely multifactorial. It has been documented that the risk of tachyarrhythmia (specifically torsades des pointes) associated with amiodarone use is greater in women than in men.[14–16] Female sex has also been associated with a greater risk of adverse effects from the use of many other medications.[17–19] Potential factors include sex-specific differences in pharmacokinetics and pharmacodynamics.

Variability in drug bioavailability, distribution, metabolism, and elimination may result from sex-specific differences in drug absorption, protein binding, body composition, hepatic cytochrome P450 activity, drug transporter function, and drug elimination.[20–23] Sex-specific pharmacokinetic differences resulting in greater drug effect in women have been reported for other cardiac medications, including isosorbide-5-mononitrate, metoprolol, and verapamil.[24–26] Amiodarone's pharmacokinetic properties are complex and differ from those of other medications owing to its much greater half-life, lipophilicity, and volume of distribution.[27] It is possible that sex-specific differences in amiodarone's pharmacokinetic properties result in relatively higher amiodarone levels in women, which may increase the risk of adverse effects such as bradycardia.[28–30]

Sex differences in the pharmacodynamics of cardiac medications have been less well investigated than sex differences in the pharmacokinetics. One study concluded that the greater quinidine-induced increases in the corrected QT interval in women compared with men are attributed to sex-specific pharmacodynamic differences because no pharmacokinetic differences were found.[31] Sex-specific differences in heart rate, heart rate variability, and electrophysiological characteristics of the AV conduction system have been reported[32–34]; however, it is unclear whether there are sex-specific pharmacodynamic differences in the complex profile of amiodarone's electrophysiological effects[35] that may contribute to an

increased incidence of bradyarrhythmia. Further research is required to better elucidate clinically relevant sex differences in the effect of amiodarone use.

The findings of this study have important clinical implications in the treatment of patients with new-onset AF. Although recent trials have failed to demonstrate mortality benefit in patients treated with a rhythm control strategy,[1,36–40] amiodarone continues to be used, particularly in symptomatic patients, because it is more effective than other medications at maintaining sinus rhythm.[1–4,41,42] Because women are more susceptible than men to amiodarone-associated bradycardia requiring pacemaker insertion, additional caution should be taken when amiodarone is being prescribed to women. Also, because the bradycardic effect of amiodarone is dose related,[12] it would be prudent to consider using lower loading and maintenance doses, particularly in elderly women, because age is also associated with an increased need for pacemaker insertion.

We should mention that our study has certain limitations, eg, the use of amiodarone was not randomized. Also, other than adjusting separately for weight and BMI, it was not possible to quantitatively evaluate any sex-specific differences in amiodarone's pharmacokinetic properties, because serum and tissue concentrations were not measured.

In conclusion, amiodarone use in the treatment of patients with new-onset AF increases the risk of bradyarrhythmia requiring pacemaker insertion. The risk of this adverse effect of amiodarone use is significantly greater in women than in men, independent of weight or BMI.

Acknowledgements

Funding/Support: Dr Essebag is the recipient of a Clinician Scientist Award from the Canadian Institutes of Health Research. Dr Reynolds is the recipient of grant K23-HL077171 from the National Heart, Lung, and Blood Institute. This study was funded in part by grant 014100 from the Fonds de la Recherche en Santé du Québec, by Medtronic Inc, and by AstraZeneca Inc.

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Table 1

Patient Characteristics at Baseline

Characteristic	All Patients (n = 973)	Women (n = 390)	Men (n = 583)	*P* Value
Age, mean (SD), y	66.1 (14.4)	69.4 (12.9)	63.9 (14.8)	<.001
BMI, mean (SD)	28.9 (6.6)	28.9 (6.7)	28.9 (6.6)	.93
Coronary artery disease, No. (%)	233 (24)	64 (16)	169 (29)	<.001
Congestive heart failure, No. (%)	288 (30)	102 (26)	186 (32)	.05
Hypertension, No. (%)	478 (49)	217 (56)	261 (45)	.001
Arial flutter, No. (%)	112 (12)	29 (7)	83 (14)	.001

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

Table 2

Rhythm and Rate Control Medication Use at Baseline and at Any Time During Follow-up

	Women, %		Men, %		*P* Value	
Medication	**Baseline**	**Follow-up**	**Baseline**	**Follow-up**	**Baseline**	**Follow-up**
Amiodarone	5.1	19.5	6.5	26.2	.37	.02
Sotalol	5.6	14.4	6.0	14.8	.81	.86
Class 1 antiarrhythmics	8.0	26.2	6.7	22.5	.46	.19
β-Blockers	41.3	46.4	39.5	46.5	.57	.98
Calcium channel blockers	38.7	43.3	29.5	33.3	.003	.002
Digoxin	40.3	46.2	36.0	39.3	.18	.03

Table 3

Indications for Pacemaker Insertion

	No. (%)			
Variable	**All Patients (n = 973)**	**Women (n = 390)**	**Men (n = 583)**	***P* Value**
Total pacemakers implanted	77 (7.9)	35 (9.0)	42 (7.2)	.32
Pacemaker indication				
AV junction ablation	17 (1.8)	10 (2.6)	7 (1.2)	.11
Sick sinus syndrome	46 (4.7)	21 (5.4)	25 (4.3)	.43
AV block	9 (0.9)	2 (0.5)	7 (1.2)	.27
Bradycardia, unspecified	5 (0.5)	2 (0.5)	3 (0.5)	>.99

Abbreviation: AV, atrioventricular.

Table 4

Cox Multivariable Regression Models Examining Sex Differences in the Association Between Amiodarone Use and Risk of Permanent Pacemaker Insertion

Models[a]	HR (95% CI)[b]	*P* Value
Effect of amiodarone use[c]		
Women	4.69 (1.99–11.05)	<.001
Men	1.05 (0.42–2.58)	.92
Effect of amiodarone dose[d]		
Women (doses ≤200 mg)	3.89 (1.39–10.88)	<.01
Women (doses >200 mg)	5.73 (2.12–15.47)	<.001
Men (doses ≤200 mg)	0.83 (0.27–2.58)	.75
Men (doses >200 mg)	1.23 (0.46–3.27)	.68

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] Separate models were used to examine sex differences in the effects of amiodarone use and amiodarone dose (daily doses >200 mg vs ≤200 mg) on the risk of permanent pacemaker insertion.

[b] The HRs and the 95% CIs have been adjusted for age, atrial flutter, coronary artery disease, heart failure, and hypertension.

[c] The interaction between sex and amiodarone use was statistically significant ($P = .02$).

[d] The interaction between sex and amiodarone remained statistically significant after adjustment for amiodarone dose ($P = .02$). The interaction between amiodarone dose and amiodarone use (ie, the difference between daily doses >200 mg vs ≤200 mg) was not statistically significant ($P = .48$).