Amiodarone and the Risk of Bradyarrhythmia Requiring Permanent Pacemaker in Elderly Patients With Atrial Fibrillation and Prior Myocardial Infarction

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OBJECTIVES
The aim of this study was to determine whether the use of amiodarone in patients with atrial fibrillation (AF) increases the risk of bradyarrhythmia requiring a permanent pacemaker.

BACKGROUND
Reports of severe bradyarrhythmia during amiodarone therapy are infrequent and limited to studies assessing the therapy's use in the management of patients with ventricular arrhythmias.

METHODS
A study cohort of 8,770 patients age ≥65 years with a new diagnosis of AF was identified from a provinewise database of Quebec residents with a myocardial infarction (MI) between 1991 and 1999. Using a nested case-control design, 477 cases of bradyarrhythmia requiring a permanent pacemaker were matched (1:4) to 1,908 controls. Multivariable logistic regression was used to estimate the odds ratio (OR) of pacemaker insertion associated with amiodarone use, controlling for baseline risk factors and exposure to sotalol, Class I antiarrhythmic agents, beta-blockers, calcium channel blockers, and digoxin.

RESULTS
Amiodarone use was associated with an increased risk of pacemaker insertion (OR: 2.14, 95% confidence interval [CI]: 1.30 to 3.54). This effect was modified by gender, with a greater risk in women versus men (OR: 3.86, 95% CI: 1.70 to 8.75 vs. OR: 1.52, 95% CI: 0.80 to 2.89). Digoxin was the only other medication associated with an increased risk of pacemaker insertion (OR: 1.78, 95% CI: 1.37 to 2.31).

CONCLUSIONS
This study suggests that the use of amiodarone in elderly patients with AF and a previous MI increases the risk of bradyarrhythmia requiring a permanent pacemaker. The finding of an augmented risk of pacemaker insertion in elderly women receiving amiodarone requires further investigation. (J Am Coll Cardiol 2003;41:249–54) © 2003 by the American College of Cardiology Foundation

As the elderly population continues to expand, atrial fibrillation (AF) is becoming an increasingly common medical condition. Approximately 85% of patients with AF are older than 65 years (1), and the prevalence of AF can increase from 2% in people age 60 to 69 years to 9% in people age 80 to 89 years (2,3). Atrial fibrillation has been shown to quadruple the risk of stroke and double the risk of mortality (2,4). Coronary artery disease is also a risk factor for AF. The first Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries trial (GUSTO-1) reported AF in 10% of 21,722 post-myocardial infarction (MI) patients whose median age was 61 years (5).

One strategy for treating AF involves the use of antiarrhythmic medications to maintain sinus rhythm after spontaneous, pharmacologic, or electrical cardioversion. Alternative strategies focus on heart rate control and anticoagulation (6). The goal of maintaining sinus rhythm is to decrease the risks associated with AF (7). Other presumed benefits of rhythm control include improved exercise tolerance, decreased symptoms, and improved quality of life. A number of trials are investigating whether maintaining sinus rhythm with antiarrhythmic medications decreases mortality or improves quality of life (8–11). The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study (11) found no survival benefit of rhythm control over rate control strategies in patients with AF and at least one other risk factor for stroke or death.

Despite the potential benefits of antiarrhythmic therapy, these agents can be associated with dangerous cardiovascular side effects. Data on the use of sotalol for AF describe the occurrence of heart rate slowing requiring permanent pacemaker implantation (12,13). Using multivariate analysis, previous MI and older age were associated with the greatest risk of cardiac adverse events, most commonly bradyarrhythmias (13). Recent studies suggest that amiodarone may be more effective than sotalol in maintaining sinus rhythm in patients with AF, with an increase in noncardiac side effects but no increased risk of significant bradyarrhythmias (14,15). Reports of amiodarone-induced severe bradycardia requiring permanent pacemaker are infrequent and have been limited to studies assessing amiodarone's efficacy in the treatment of ventricular arrhythmias (16).

The objective of this study was to evaluate the risk of...
bradyarrhythmia requiring permanent pacemaker insertion associated with the use of amiodarone to treat AF in patients at high risk of severe bradycardia. The study was therefore limited to elderly (≥65 years old) patients with previous MI.

METHODS

Study population. A provincewide database of residents having an acute myocardial infarction (AMI) between 1991 and 1999 in Quebec, Canada, was constructed by linking the Quebec hospital discharge summary database (Med-Echo) with the provincial physician and drug claims database (Regie de l’Assurance Maladie du Quebec [RAMQ]), using methods described previously (17). Patients were included in the database if they were admitted to hospital with a diagnosis of AMI (International Classification of Disease 9 [ICD9] code 410) between 1991 and 1999 and had no previous admission for an AMI (since 1985). Follow-up information was available until the end of 1999. This database included 113,012 patients.

From the database, 14,187 patients (12.6%) were identified as having been diagnosed with AF (ICD9 code 427.3, 427.31, or 427.32) during their initial admission for an AMI, during any subsequent admission, or during any subsequent inpatient or outpatient physician visit. After patients with a previous diagnosis of AF (within one year before the date of their index AMI) were excluded, there remained 12,559 patients.

The time of entry into the study cohort (T = 0) was defined by the date of the first diagnosis of AF following (or concurrent with) the date of index AMI. Inclusion in the study cohort was limited to persons ≥65 years of age at the time of diagnosis of AF (9,323 patients) in order to have complete medication data for all patients (the RAMQ drug claims database contains information for all individuals ≥65 years of age).

Other exclusion criteria included previous pacemaker or defibrillator insertion (231 patients), or ventricular arrhythmia (356 patients) within one year before cohort entry. Persons with previous pacemaker were excluded because they would not be able to develop the outcome of interest (i.e., heart block requiring pacemaker insertion). Persons with previous ventricular arrhythmia or defibrillator were excluded because they were likely to have already been treated with antiarrhythmic medications before their diagnosis of AF. Persons who were diagnosed with a ventricular arrhythmia only after their diagnosis of AF were not excluded, but this information was recorded and adjusted for in the analysis.

The final study cohort included 8,770 patients. All subjects were followed until time of death, pacemaker implantation, or December 31, 1999. The study was approved by the McGill University Faculty of Medicine Institutional Review Board.

Cases. Cases consisted of patients who received a permanent pacemaker during the follow-up period. Of a total of 485 subjects who received a pacemaker, eight subjects were censored because they had undergone ablation of their atrioventricular (AV) node within two weeks of their permanent pacemaker insertion. The remaining 477 subjects were retained as cases. The index date for each case was defined as the date of permanent pacemaker implantation.

Controls. In a nested case-control design, four controls were randomly selected from the risk set of each case, defined by the cohort time axis (i.e., the number of days from entry into the cohort to the index date of each case). Controls were also matched according to the date (within a six-month period) that each case had a permanent pacemaker inserted in order to control for variations in medication use over time.

The index date for controls was defined according to the time from cohort entry to the date of pacemaker insertion of the respective case. Thus, the index date minus the AF diagnosis date is the same for all five members of each set, containing a case and its four controls.

Exposure assessment. Baseline information recorded for all cohort patients included age, gender, and presence of sinoatrial (SA) node dysfunction (ICD9 code 427.81) or conduction disorder (ICD9 code 426.1 to 426.6) within two years before cohort entry.

Any subsequent diagnosis of a ventricular arrhythmia (ICD9 code 427.1, 427.4, or 427.5) during the study period was recorded. Cases and controls were classified as having a ventricular arrhythmia if this diagnosis was made before their index date.

Details about exposure of cases and controls to various cardiac medications were also recorded during the study period. For each dispensed medication, information included the date and duration of the prescription. Antiarrhythmic agents included amiodarone, sotalol, and class I agents (disopyramide, flecainide, mexilitene, procainamide, propafenone, and quinidine). Beta-blockers, calcium channel blocking agents (diltiazem and verapamil), and digoxin were also included in the analysis.

The definition of exposure to a drug for both cases and controls was the use of a medication immediately before the index date of pacemaker insertion. It was assumed that subjects took their medication from the date that it was dispensed until the end of the duration of the prescription.
Because there may have been a lapse between the time a case was admitted for pacemaker implantation and the actual date of the procedure (index date), all study subjects were defined as having been exposed to a medication if the date of the last prescription (before index date) plus the duration of the prescription plus seven days exceeded the index date. Another factor taken into consideration was the half-life of the medication, with amiodarone being the one with the longest (>30 days compared to ≤48 h for all other medications). Thus it was decided a priori that subjects would be defined as having been exposed to amiodarone if the date of their last prescription plus the duration of the prescription plus 30 days (instead of 7 days) exceeded the index date.

A binary variable was created for each of the six medications (amiodarone, sotalol, class I agents, beta-blockers, calcium channel blockers, and digoxin) to indicate exposure or nonexposure. An additional ordinal variable was created to account for the simultaneous use of beta-blockers, calcium channel blockers, and digoxin.

**Statistical analysis.** Within the study cohort, a nested case-control analysis was performed. For each binary independent variable, chi-square tests, crude odds ratios (OR), and 95% confidence intervals (CI) were estimated. A p value ≤0.05 was considered statistically significant. All statistical analyses were performed using SAS Version 8 statistical software package.

In order to identify possible confounders or modifiers of the effect of the main exposure (amiodarone) on the outcome, a series of analyses were performed with stratification by every other binary variable in turn. Possible effect modifiers, identified using Breslow-Day tests for homogeneity (18), and possible confounders, identified by comparing Mantel-Haenzel and crude ORs, were subsequently analyzed in regression models.

After satisfaction of the linearity assumption for continuous and ordinal variables was confirmed, multivariable conditional logistic regression was used to estimate ORs (and 95% CIs) for pacemaker implantation. It was decided a priori to adjust for the effects of age and gender regardless of statistical significance. Starting from a model including all variables (age, gender, baseline SA node dysfunction or conduction disorder, ventricular arrhythmia, and exposure to amiodarone, sotalol, class I antiarrhythmics, beta-blockers, calcium channel blockers, and digoxin), nonsignificant variables (other than age and gender) were sequentially removed if the resultant model had improved Akaike Information Criteria with a minimal decrease in likelihood ratio, and without a significant change in ORs for remaining variables. A separate but similar analysis was also performed using an ordinal variable indicating the number of SA/AV nodal suppressing medications (the sum of the three binary variables for beta-blockers, calcium channel blockers, and digoxin).

The multivariable regression analysis was repeated with several modifications in definition of exposure to medications to determine whether there were any changes in the effects observed. In particular, the definition of exposure to amiodarone was modified to “date of last prescription plus duration of prescription plus seven days (or 60 days, instead of 30 days) exceeds index date.” Likewise, the definition of exposure to other medications (such as digoxin) was modified to “date of last prescription plus duration of prescription plus 14 days (or 60 days, instead of 7 days) exceeds index date.”

**RESULTS**

**Patient population.** The study cohort included 8,770 patients, 477 (5.4%) of whom met criteria for definition as cases. The 477 cases were matched (1:4) to 1,908 controls.

The mean age of cases and controls was 76.6 years, and 58.3% were men. Table 1 provides summary statistics. In bivariate analysis, a history of SA node dysfunction or conduction disorder, new ventricular arrhythmia, exposure to amiodarone, and exposure to digoxin significantly increased the odds of pacemaker implantation (Table 1). Only one patient was exposed to both amiodarone and a class I
agent, one patient was exposed to both sotalol and a class I agent, and no one was exposed to both sotalol and amiodarone.

Risk of pacemaker insertion associated with use of amiodarone. After adjusting for age, gender, SA node dysfunction or conduction disorder, ventricular arrhythmia, and digoxin exposure (as both a negative chronotrope and a marker of left ventricular [LV] dysfunction), amiodarone use was associated with an increased risk of pacemaker implantation (OR: 2.14, 95% CI: 1.30 to 3.54) (Table 2).

The final model adjusted for the effects of age and gender despite lack of statistical significance, as was decided a priori. The variables ventricular arrhythmia and digoxin were adjusted because they were identified as confounders of the effect of amiodarone. The variable baseline SA node dysfunction or conduction disorder, although not a confounder, was included in the final model because it was a significant independent predictor of pacemaker insertion. All other nonsignificant variables (sotalol, class I antiarrhythmics, beta-blockers, and calcium channel blockers) were sequentially removed from the model without significant change in ORs for remaining variables.

The number of SA/AV nodal suppressing medications was not found to be an independent predictor of pacemaker insertion after adjustment for digoxin use (OR: 0.93, 95% CI: 0.69 to 1.25).

Results were not significantly changed when the multivariable regression analysis was repeated using several modifications in the definition of exposure to amiodarone and other medications.

Modification of the effect of amiodarone by gender. Gender was the only variable identified as a possible effect modifier of the relationship between amiodarone use and the subsequent need for a permanent pacemaker. Inclusion of an interaction term for amiodarone and gender in the final model suggests that pacemaker insertion is more frequent in women receiving amiodarone (OR: 3.86, 95% CI: 1.70 to 8.75 vs. OR: 1.52, 95% CI: 0.80 to 2.89). Although the interaction term for amiodarone and gender (OR: 0.39, 95% CI: 0.14 to 1.11) was not statistically significant, the magnitude of the effect suggests the possibility of modification of the effect of amiodarone by gender. For this reason, a second final model with this interaction term is presented in Table 2.

Risk of pacemaker insertion associated with use of sotalol. Although there was a trend toward an association between sotalol and pacemaker implantation, the magnitude of the effect was small and was not statistically significant (OR: 1.30, 95% CI: 0.79 to 2.14, p = 0.29).

**DISCUSSION**

The results of this study support the initial hypothesis that elderly patients post-AMI treated with amiodarone for AF are at increased risk of bradyarrhythmia requiring a permanent pacemaker. These patients were more than twice as likely to require a permanent pacemaker, even after adjusting for time since AF, calendar time, age, gender, SA node dysfunction or conduction disorder, ventricular arrhythmia, and exposure to antiarrhythmic and rate control agents. Of note, there was no significant association between the use of sotalol and permanent pacemaker insertion (adjusted OR: 1.30, 95% CI: 0.79 to 2.14, p = 0.29). Digoxin was the only other medication that was associated with a significant increase in odds of requiring a permanent pacemaker (OR: 1.78, 95% CI: 1.37 to 2.31). This study also demonstrated a strong association between prior SA node dysfunction or conduction disorder and the need for a permanent pacemaker (Table 2).

Exposure to amiodarone was associated with a greater risk of pacemaker implantation in women. This finding may be related to the tendency to treat women with the same doses of amiodarone as men, despite a relatively smaller body size, weight, and volume of distribution.

The absence of previous reports describing bradyarrhythmia requiring permanent pacemaker insertion during amiodarone therapy for AF may be due to the study populations and their risk of bradyarrhythmias. The Canadian Trial of Atrial Fibrillation, for example, reported a relatively low incidence of serious bradyarrhythmias (3%), with no difference between groups randomized to amiodarone versus sotalol or propafenone. The study patients had a low
incidence of coronary disease (19%) and a mean age of 65 years (14). Given that elderly patients with prior MI are at greatest risk for bradyarrhythmias during antiarrhythmic drug therapy for AF (13), the current study was designed to include only elderly patients (≥65 years old) with AF post-MI. In this higher risk population, amiodarone was found to increase the risk of bradyarrhythmia requiring permanent pacemaker insertion.

We found no significant effect of sotalol on the risk of pacemaker insertion despite results of previous studies on the risk of in-hospital initiation of antiarrhythmic drugs for patients with AF. In one study (12), initiation of sotalol was associated with significant bradycardia in 20 of 120 patients (16.7%), requiring permanent pacemaker in three patients (2.5%) and dose reduction in most of the other patients. The episodes of bradyarrhythmia occurred soon after initiation of sotalol; 50% by day 1 and 90% by day 3 after initiation. In another study (13), bradyarrhythmias occurred in eight of 72 patients (11.1%) started on sotalol and one of 25 patients (4%) started on amiodarone. It is possible that the number of patients on sotalol in our study was not large enough to detect a statistically significant increased risk of pacemaker insertion. Our study may have also underestimated the use of sotalol in cases of pacemaker insertion if patients started sotalol in hospital and had a pacemaker placed before filling their prescription. An important difference between amiodarone and sotalol is the much longer half-life of amiodarone (>30 days vs. <24 h). When bradyarrhythmias complicate sotalol therapy, permanent pacemaker insertion is often avoided by reducing the dosage. When severe bradyarrhythmias complicate amiodarone therapy, they may be less likely to resolve soon after cessation of amiodarone.

The strong association between a previous diagnosis of SA node dysfunction or conduction disorder and the risk of pacemaker insertion is not surprising. Use of amiodarone in patients with SA node dysfunction or conduction disorder carries a high risk of severe bradyarrhythmia. The finding that a diagnosis of ventricular arrhythmia was strongly associated with pacemaker insertion, even after adjustment for other variables, including amiodarone, may in part be related to a tendency for these patients to be treated with higher doses of amiodarone.

**Study limitations.** This is a retrospective analysis of data derived from administrative databases. Although such databases allow for access to a wide variety of data on very large numbers of patients, certain clinical information is not available. We were unable to directly adjust for LV dysfunction in our study. However, by adjusting for digoxin use, we at least partially adjusted for LV dysfunction.

Identification of patients with AF may have been incomplete because some patients may have had AF without ever having a diagnosis recorded. However, we found a diagnosis of AF in 12.6% of the 113,012 post-AMI patients in our database, which is in keeping with results of previous studies (5). Furthermore, even if the identification of patients with AF was incomplete, this is unlikely to have introduced selection bias because identification of AF was independent of future pacemaker insertion.

Although drug claims data have been found to be reliable (19), medication exposure data are limited by the assumption that dispensed medication is consumed until the end of the duration of the prescription. Given that the data represent filled prescriptions as opposed to written prescriptions, patients are more likely to be compliant. However, the effect of noncompliance with supplied medications would be nondifferential misclassification of exposure in our study that would make our result a conservative estimate (biased towards the null) of the true effect of amiodarone.

**Conclusions.** This study suggests that the use of amiodarone in elderly patients with AF and a previous MI increases the risk of bradyarrhythmia requiring a permanent pacemaker. The finding that the risk of bradyarrhythmia associated with amiodarone use is greater in women than in men requires further investigation.

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