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Mortality risk of sotalol and amiodarone for post-CABG atrial fibrillation

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ABSTRACT

Background: Sotalol and amiodarone are commonly prescribed antiarrhythmics for the treatment of post-operative atrial fibrillation (POAF). Though they are effective in maintaining sinus rhythm in this population, little is known about their association with mortality.
Objectives: To examine the association between sotalol and amiodarone exposure and total mortality in individuals with new-onset POAF following CABG.
Methods: The computerised health databases of Quebec, Canada were used to identify all patients over 65 who had undergone CABG and were newly diagnosed with POAF (January 1993 to June 2003). A time-matched nested-case–control approach was used to compare current users of sotalol and amiodarone with those not exposed to either medication during the same period. Rate ratios of mortality were estimated using conditional logistic regression.
Results: 4770 eligible patients were identified (930 cases, 4648 matched controls). Sotalol users had fewer comorbidities and used fewer concomitant medications than amiodarone users at baseline. Current users of sotalol were at decreased risk of mortality compared to individuals not exposed to either study drug during the same period ($RR_{adj.}$ 0.56 (0.39, 0.80)) while current users of amiodarone were at increased risk of mortality ($RR_{adj.}$ 1.50 (1.15, 1.94)). However this association was not consistently observed across all sensitivity and subgroup analyses.
Conclusions: Current use of sotalol was associated with a decreased risk of mortality. Current use of amiodarone was associated with an increased risk of mortality but not for all subgroups. Additional research is required to better understand the safety of sotalol and amiodarone in individuals with POAF.

1. Introduction

Post-operative atrial fibrillation (POAF) is the most common complication of coronary artery bypass graft (CABG) surgery affecting approximately 30% of patients [1,2]. Many drugs are available to treat POAF, the most common being sotalol and amiodarone. These class III antiarrhythmics have been shown to be effective in restoring and maintaining sinus rhythm, however there is uncertainty regarding their association with mortality. Most safety data for sotalol and amiodarone are derived from randomised controlled trials (RCTs) which often do not reflect routine clinical practice and are not powered to look at mortality as an outcome [3,4]. Even results from meta-analyses of these RCTs remain unclear [5] although some studies do indicate a trend towards increased mortality for both sotalol and amiodarone [6,7]. Additionally most safety data for sotalol and amiodarone comes from studies of chronic atrial fibrillation or prevention of POAF and little is known about the risks and benefits of these medications in the post-operative setting. The objective of this study was to examine the association between sotalol and amiodarone exposure and total mortality in individuals with new-onset POAF following CABG.

2. Methods

2.1. Study sample and data source

Using the universal health insurance databases of Quebec, Canada, we identified a cohort of individuals aged 66 and older who had undergone CABG surgery between January 1, 1993 and June 30, 2003 and were diagnosed with new-onset POAF within 30 days of surgery. Although the Quebec administrative databases were developed in the context of the universal health insurance program for Quebec residents they are now extensively used for research purposes [8–12]. These databases include: 1) the beneficiary database which provides information on individual sociodemographic characteristics; 2) the prescription drug database which provides data on all outpatient prescriptions for those 65 years of age and older and includes the drug name, dosage,

Abbreviations: CABG, coronary artery bypass graft; POAF, post-operative atrial fibrillation.

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date of dispensation and duration of treatment; 3) the medical services database which contains information on all physician claims for medical services provided including the principal diagnosis and date and location of service; 4) the hospitalisation database which provides information on all hospitalisations including admission and discharge dates as well as a principal diagnosis and up to 15 secondary diagnoses; and 5) the vital statistics database which contains information on all deaths including date and cause. Each resident is given a unique encrypted identifier which is used to link the five databases at the level of the individual. The ethics board of the Research Institute of the McGill University Hospital Centre (RIMUHC) approved this study.

2.2. Study design and outcome

We conducted a population-based retrospective cohort study that was analyzed using a time-matched nested case–control approach. The study population consisted of all Quebec residents aged >65 years who had undergone CABG surgery between January 1, 1993 and June 30, 2003 and were subsequently diagnosed with POAF within 30 days of surgery. The date of cohort entry (t0) was taken as the date of discharge for the hospitalisation during which they were diagnosed. We excluded patients who had a diagnosis of atrial fibrillation in the year before admission for surgery as well as those who had been dispensed either of the anti-arrhythmic drugs of interest in the year before cohort entry. We also excluded patients without any prescriptions in the prescription drug database as they were likely privately insured, those who died before t0, those who were hospitalised or diagnosed with POAF more than 30 days post-surgery, and those who were not residents of Quebec. All patients were followed until death by any cause or the end of the study period (December 31, 2003), whichever occurred first. Death by any cause was the outcome of interest and was considered the case-defining event. Date of death was taken as the index date for both the case and their matched controls.

2.3. Exposure

Prescriptions for sotalol and amiodarone were obtained from the prescriptions drugs database which has been shown to be both accurate and complete [13]. The exposure period of interest was current use. Individuals were considered 'current users' if a dispensed prescription indicated they were taking a study drug on or just prior to their index date. Patients who discontinued use of sotalol within 7 days of index, or amiodarone within 30 days of index were still considered current users as adverse effects during this period could still be reasonably linked to medication use. This post-discontinuation time window was longer for amiodarone than sotalol due to amiodarone's longer half-life (10–15 h for sotalol and 14–142 days for amiodarone). The reference group was individuals with POAF who did not have a dispensed prescription for sotalol or amiodarone during the same time window.

2.4. Statistical methods

To study exposure to sotalol and amiodarone in relation to the index date as well as simultaneously controlling for the potentially confounding effects of calendar time a time-matched nested case–control analysis was used. For each case-patient, up to 5 controls were randomly selected from the base cohort using incidence density sampling. Controls were matched to cases based on cohort entry month and year and were chosen from the risk set of each case, meaning they were still alive on the case's index date. This ensured identical follow-up time for cases and controls and as both groups were selected from the same cohort, comparability of cases and controls was maximised.

To measure the association between sotalol and amiodarone exposure and total mortality we compared the risk of current sotalol and amiodarone users with those who were not exposed to either drug during the same time window. We estimated rate ratios (RR) along with 95% confidence intervals (CI) using conditional logistic regression to account for individual-level matching. The rate ratios obtained are equivalent to the hazard ratios that would be estimated from the corresponding Cox proportional hazards regressions [14]. Two regression models were run: a crude model evaluating death as a function of exposure, and an adjusted model where confounders with statistically significant differences in their distributions amongst cases and controls were added. Conventional covariates that were considered potential confounders included age, sex, Charlson Comorbidity Score, duration of post-surgical hospital stay, diabetes, hypertension, previous MI, congestive heart failure, previous stroke, COPD, renal disease, cerebrovascular disease, thyroid disease, peripheral vascular disease and ventricular arrhythmias (premature ventricular contractions, non-sustained ventricular tachycardia). Use of concomitant medications including anti-arrhythmics (other than sotalol or amiodarone), calcium channel blockers, digoxin, ACE inhibitors, ARBs, diuretics, lipid modifying agents, diabetes medications, anti-platelets, beta-blockers, and anti-coagulants were also evaluated as a source of potential confounding. Information on risk factors, comorbid conditions and drug utilisation was taken from the various databases. Only potential confounders that occurred at or in the year before cohort entry were included in order to avoid controlling for factors along the causal pathway.

To assess the strength and validity of the results several sensitivity analyses were conducted. To test the robustness of the exposure definition we made the lag period equivalent for current use of both sotalol and amiodarone (i.e. both 7 days and 30 days). We also redefined current exposure as having a prescription for sotalol or amiodarone dispensed within 30 days of the index date. As one of the limitations of the provincial databases is uncertainty of exposure during hospitalisations we restricted an analysis to those who were not hospitalised at all during the 30 days before index. In order to limit potential differential follow-up between sotalol and amiodarone users we also investigated a more proximal outcome: any cardiovascular hospitalisation defined as a hospitalisation with a diagnosis of MI, stroke, CHF, arrhythmia (other than atrial fibrillation), or unstable angina. Effect measure modification by renal disease and by sex was also explored. All analyses were conducted with SAS version 9.3 (SAS Institute, Cary, NC).

3. Results

A total of 57,822 patients were identified who had undergone CABG surgery during the study period. Of these, 11,508 were diagnosed with atrial fibrillation following surgery. After applying the exclusion criteria, the study cohort consisted of 4770 subjects (Fig. 1). During follow-up 931 death cases and 29,585 potential controls were identified. Though the majority were matched to successfully 5 controls, 1 case had no controls and was excluded and 2 cases had only 4 possible controls thus the final cohort consisted of 930 cases and 4648 controls. Mean follow-up time (SD) for cases and controls was 1421 (969) days and 1422 (968) days respectively.

Table 1 describes the characteristics of cases and controls at baseline. The mean age (SD) at cohort entry was 73.3 (4.7) and 72.4 (4.5) for case and controls respectively. Case-patients seemed generally sicker than controls having a higher Charlson Score, and significantly higher rates of vascular diseases, CHF, diabetes, COPD, renal disease and cancer. Cases were also more likely to have been prescribed digoxin, ACE inhibitors, anticoagulants and diabetes medications. Overall the distribution of pre-CABG diagnoses and number of bypasses did not differ in a meaningful manner between cases and controls. All significant differences were controlled for in the analysis to ensure the comparability of cases and controls.

During the study period 395 (7.1%) study participants were classified as current sotalol users and 375 (6.7%) were classified as current users of amiodarone (Table 2). The median duration of use was 2.2 years (interquartile range 0.5–4.5 years) for sotalol and 1.4 years (interquartile range 0.4–3.3 years) for amiodarone. Current sotalol users tended to be younger and healthier as compared to current amiodarone users and