Risk of mortality associated with sotalol and amiodarone for new-onset post-operative atrial fibrillation following CABG

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Abstract

Background: Sotalol and amiodarone are commonly prescribed antiarrhythmics for the treatment of post-operative atrial fibrillation (POAF), a common occurrence following coronary artery bypass graft (CABG) surgery. Though they have been shown to be 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 linked computerised health databases of Quebec, Canada were used to identify all patients over 65 who had undergone CABG surgery and were newly diagnosed with POAF between January 1, 1993 and June 30, 2003. A nested-case-control approach was used with controls matched by cohort entry month and year. Current users of sotalol and amiodarone were compared to those who were not exposed to either medication during the same period. Rate ratios of mortality were estimated using conditional logistic regression. Due to the non-randomized study design, results were adjusted for potential confounders.

Results: 4,770 patients meeting our entrance criteria were identified consisting of 930 cases and 4648 matched controls. Mean follow up time for cases and controls was 3.9 years. Sotalol users were healthier than amiodarone users at baseline, having fewer comorbidities and using fewer concomitant medications. Current users of sotalol were at decreased risk of mortality compared to individuals not exposed to either study drug during the same period (RRadj. 0.56 (0.39, 0.80)). Compared to individuals not currently exposed to either study drug, current users of amiodarone were at increased risk of mortality (RRadj. 1.50 (1.15, 1.94)). However this mortality association was not consistently observed across all sensitivity and subgroup analyses. In one sensitivity

analysis, future cardiovascular hospitalizations were not associated with current sotalol exposure (RRadj. 1.07 (0.91, 1.27)) but were increased with amiodarone (RRadj. 1.31 (1.09, 1.57)).

Conclusions: Current use of sotalol was associated with a decreased risk of mortality but was not associated with a reduced risk of cardiovascular hospitalisation. Amiodarone was associated with an increased risk of mortality but not for all subgroups and an increased risk of cardiovascular hospitalisation. Additional research is required to more completely and reliably assess the safety of sotalol and amiodarone in individuals with POAF.

Résumé

Historique: Le sotalol et l'amiodarone sont des antiarythmiques couramment prescrits pour le traitement de la fibrillation auriculaire postopératoires (FAPO), une situation courante suite à un pontage aortocoronarien (PAC). Bien qu'il fût démontré qu'ils sont efficaces pour maintenir le rythme sinusal dans cette population, on connaît bien peu leur association avec la mortalité.

Objectifs: Examiner l'association entre l'exposition aux sotalol et amiodarone et la mortalité totale chez les personnes qui développent la FAPO suite à un PAC.

Méthodes: Les bases de données administratives jumelées sur la santé du Québec (Canada) furent utilisées pour identifier tous les patients de 65 ans et plus qui ont été opérés pour un PAC et qui ont été nouvellement diagnostiqués avec la FAPO entre le premier Janvier 1993 et le 30 juin 2003. Une étude cas-témoins a été utilisée où les contrôles sont appariés par le mois et l'année d'entrée dans la cohorte. Les utilisateurs courants de sotalol et amiodarone furent comparés à ceux qui n'étaient exposés à aucun de ces médicaments durant la même période. Les rapports de taux de la mortalité furent estimés en utilisant une régression logistique conditionnelle. À cause du design non randomisé de l'étude, les résultats furent ajustés pour les facteurs potentiels de confusion.

Résultats: 4 770 patients qui étaient conformes aux critères d'entrée furent identifiés. Ils représentent 930 cas et 4648 contrôles appariés. Le temps de suivi moyen pour les cas et contrôles était de 3.9 années. Au départ les utilisateurs de sotalol étaient plus en santé que les utilisateurs d'amiodarone; ils avaient moins de comorbidités et utilisaient moins de médicaments concomitants. Les utilisateurs courants de sotalol avaient un moins grand risque de mortalité comparé aux personnes qui ne prenaient aucun des médicaments étudiés durant la même période

RRadj.0,56 (0,39 ; 0,80)). Comparé aux personnes qui n'étaient pas couramment exposées à aucun des deux médicaments étudiés, les utilisateurs courants de l'amiodarone avaient un risque plus accru de mortalité (RRadj.1,50 (1,15 ; 1,94)). Cependant cette association avec la mortalité n'était pas systématiquement observée à travers toute les analyses de sensibilité et autres groupes d'analyses. Dans une analyse de sensibilité, les hospitalisations futures de cause cardiovasculaire n'étaient pas associées avec l'exposition courante au sotalol (RRadj. 1,07 (0,91; 1,27)) mais augmentaient avec l'amiodarone (RRadj. 1,31 (1,09 ; 1,57)).

Conclusion: L'utilisation courante du sotalol était associée avec une réduction du risque de mortalité mais n'était pas associée à une réduction des hospitalisations de cause cardiovasculaire. L'utilisation de l'amiodarone était associée à une augmentation du risque de mortalité mais pas pour les sous-groupes et était aussi associée à une augmentation du risque des hospitalisations de cause cardiovasculaire. Des recherches supplémentaires sont nécessaires afin d'évaluer de façon complète et fiable la sécurité du sotalol et de l'amiodarone chez les personnes ayant la FAPO.

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Contribution of Authors

Sarasa Johnson and Dr. James Brophy collaboratively designed the study, defined variables, developed an analysis plan and interpreted results. Sarasa Johnson, as MSc candidate, was responsible for carrying out the literature review as well as managing and analysing the data using SAS programming. She was also responsible writing the thesis. Dr. James Brophy, as thesis supervisor, was responsible for the study as a whole. He developed the research question, obtained the data, and critically reviewed drafts of the thesis.

List of Acronyms

Acronym	Definition
ACE Inhibitor	Angiotensin-converting-enzyme inhibitor
ARB	Angiotensin II receptor blocker
CABG	Coronary artery bypass graft
CHF	Congestive heart failure
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
GFR	Glomerular filtration rate
HR	Hazard ratio
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
OR	Odds ratio
PCI	Percutaneous coronary intervention
POAF	Post-operative atrial fibrillation
RAMQ	Régie de l'Assurance-Maladie du Québec
RCT	Randomised controlled trial
RR	Rate ratio
RR_{adj}	Adjusted rate ratio

List of Tables, Figures and Appendices

1. Introduction

Heart disease is a major public health concern in North America. In Quebec alone, approximately 6,000 individuals undergo coronary artery bypass surgery (CABG) each year. This surgery aims to improve blood flow to the heart; however around 30% of CABG patients experience a complication known as atrial fibrillation. Individuals with this condition have an irregular heart beat due to the muscles of the upper chambers of the heart not contracting in a coordinated manner. This post-operative condition is associated with increased risk of death, stroke and decreased quality of life. It is also associated with lengthened hospital stays which increases healthcare costs. There are many drugs available to treat atrial fibrillation, however there is uncertainty regarding the risks and benefits of these medications. The objective of this project is to compare the risk of mortality of two such medications, sotalol and amiodarone, in Quebec patients who have undergone CABG surgery. A better understanding of the risk and benefits of these medications could have a meaningful impact on patient outcomes, and reduce the burden of post-operative atrial fibrillation (POAF) on the healthcare system.

2. Background

2.1 CABG

Coronary artery bypass graft or CABG is a surgery performed on individuals with severe coronary heart disease in order to alleviate symptoms and in some specific cases improve survival. Coronary heart disease involves the build up of plaque in the arteries supplying blood to the heart and can lead to angina, myocardial infarction (MI), heart failure and rhythm abnormalities and sudden cardiac death. The surgery involves the grafting of a healthy artery or vein from elsewhere in the body, proximally to the ascending aorta and distally beyond the blocked coronary artery, in order to bypass the blockage and re-establish blood flow to that area of the heart. It is the most common type of open-heart surgery in North America with approximately 6,000 surgeries being preformed yearly in Quebec alone.

2.2 Post-operative atrial fibrillation

POAF is the most common complication of cardiac surgery occurring in approximately 30% of patients undergoing CABG and 40% of those undergoing valve surgery[1,2]. POAF is an arrhythmia wherein the atria of the heart contract rapidly and irregularly resulting in the pooling of blood and possible formation of blood clots. As such, individuals with POAF are at higher risk of stroke[2]. Other consequences of POAF include patient discomfort and anxiety, hemodynamic deterioration including heart failure, cognitive impairment, longer hospital stays and increased health care costs[2]. POAF can be associated with significant morbidity, particularly in the elderly and individuals with left ventricular dysfunction[1].

POAF often occurs early in the post-operative period[1,2]. Of those who develop POAF, 70% get it by post-operative day 4 and 94% do so by post-operative day 6[1,2]. The mechanism through which POAF is developed is multifactorial. Occurrence of POAF is facilitated by atrial

trauma, atrial stretch, atrial ischemia, epicardial inflammation, hypoxia, acidosis, electrolyte disturbances, ischemia, and changes in refractoriness associated with sympathetic nervous system discharge; factors which commonly occur during or immediately after cardiac surgeries[2]. Independent patient characteristics associated with the development of POAF include previous history of atrial fibrillation, male gender, decreased left-ventricular ejection fraction, left atrial enlargement, withdrawal of beta-blocker therapy, hypertension, COPD, chronic renal failure, diabetes, and rheumatic heart disease[1,2]. However advanced age is the most significant predictor of POAF[1,2]. Operative risk factors for POAF include the type of procedure e.g. CABG or valve surgery or both, the number of bypass grafts, duration of aortic cross-clamp time and duration of surgery[2].

2.3 Treatment of POAF

Treatment strategies for POAF are similar to those for atrial fibrillation. Generally one of two strategies is chosen: rate control or rhythm control. Anticoagulation therapy to prevent stroke is also provided with whichever treatment strategy is selected[1–3].

Rate control

Decreasing the ventricular response rate is the objective of the rate control approach. Though the optimal ventricular rate should be determined on a case-by-case basis, a ventricular rate of 110 or less is usually sufficient to improve cardiac performance[3]. Beta-blockers are most commonly used to this end but calcium channel blockers and digoxin have also been shown to be effective[1].

Rhythm control

The aim of the rhythm control strategy is restoring and maintaining normal sinus rhythm. This can be achieved either electrically or pharmacologically. Pharmacologic options for rhythm control are known as antiarrhythmics and include sotalol, amiodarone, procainamide, ibutilide as well as others[1–3]. Sotalol and amiodarone, as the most common drugs employed for this condition, are the focus of this study.

2.4 Amiodarone

Amiodarone is a Class III anti-arrhythmic as it acts by blocking potassium channels in atrial, nodal and ventricular tissue. This prolongs the action potential duration and refractory period and it is the increase in the refractory period of atrial cells that contributes to control of atrial arrhythmias[4]. Amiodarone also has alpha- and beta- adrenergic blocking capabilities[1] and has an unusually long half-life of 14-110 days[4].

The majority of data regarding the efficacy of amiodarone for POAF comes from trials for chronic atrial fibrillation and trials for the prevention of POAF. A mixed treatment comparison study of 39 trials conducted in 2011 by Freemantle et al. found that amiodarone had the largest effect in reducing recurrence of atrial fibrillation compared to placebo (OR 0.22 (0.16, 0.29)) out of all study drugs investigated (amiodarone, sotalol, flecainide, propafenone, and dronedarone) [5]. In comparison to sotalol, a trial comparing the efficacy of sotalol and amiodarone for atrial fibrillation (SAFE-T) found that the median time to recurrence of atrial fibrillation was much longer for the amiodarone group compared to the sotalol and placebo groups (487 days vs. 74 days vs. 6 days respectively)[6].

Amiodarone has also been shown to be effective in prevention of POAF. A 2006 meta-analysis demonstrated that compared to placebo, amiodarone reduced the odds of POAF occurring by half (OR 0.50 (0.43-0.59))[7]. Six other meta-analyses have also confirmed the protective effect of amiodarone compared to placebo or usual care[8] as has a Cochrane review on prevention of POAF[9]. In comparison to sotalol, a meta-analysis of 10 trials comparing amiodarone and sotalol for the prevention of POAF did not find a significant difference between either treatment[10].

2.5 Sotalol

Like amiodarone, sotalol is a Class III anti-arrhythmic that acts by blocking potassium channels and it also acts as a beta-blocker[1]. Its class III property prolongs action potential duration and lengthens the effective refractory period in the atria, atrioventricular node, ventricles and accessory pathways enabling it's control of the heart's rythm[11]. As a beta-blocker it slows the heart rate. Sotalol also prolongs the QT interval which is linked to some of its potential proarrhythmic effects. Sotalol is primarily excreted renally, as such it is contraindicated in people with renal insufficiency as the half life of the medication is extended in this population[11]. The mean half-life of sotalol is 12.7 hours[11].

As with amiodarone, little data exists about sotalol's efficacy for the treatment of POAF; rather guidelines are based off of results from trials of non-surgically related atrial fibrillation, or prevention of POAF[2]. With respect to treatment of atrial fibrillation the mixed treatment comparison study by Freemantle et al. found sotalol to be equally efficacious in preventing recurrence of atrial fibrillation to all other study drugs compared except amiodarone, which was the best medication in this regard[5]. In regards to prophylaxis, sotalol is also an effective treatment. A meta-analysis including 14 trials of sotalol found that sotalol greatly reduced

incidence of POAF (OR 0.37 (0.29, 0.48)) compared to placebo or other beta-blocker therapy[12]. This result was also supported by a 2011 meta-analysis of 15 trials of sotalol for prevention of POAF[13] and the Cochrane review on POAF prevention[9]. In comparison to amiodarone, sotalol was found to be equally efficacious in preventing POAF following surgery[10]. However a study by Moos et. al that directly compared sotalol and amiodarone for the prevention of POAF found that the duration of atrial fibrillation was longer for those in the sotalol group[14]. This study also found that the incidence of POAF was higher in the sotalol group than the amiodarone group when specifically looking at people who had aortic valve replacement surgery, or combined CABG and aortic valve replacement surgery[14].

2.6 Adverse effects of amiodarone and sotalol

2.6.1 Morbidity

Though amiodarone and sotalol are generally considered to be well tolerated they are associated with several adverse effects. Amiodarone is associated with bradycardia requiring pacing and hypotension as demonstrated by a meta-analysis of safety outcomes of amiodarone in the context of POAF prevention[15]. Amiodarone use is also associated with thyroid dysfunction and pulmonary toxicity[16] In the mixed treatment comparison study, subjects on amiodarone had the highest likelihood to withdraw from treatment due to adverse effects compared to all other study drugs tested[5]. Cardiac toxicity in the form of bradycardia, hypotension, torsades de pointes and new or worsened heart failure are the main concerns with sotalol therapy[10,12,13,17]. In the Freemantle et al. study, subjects on sotalol were significantly more likely than those on placebo to experience a proarrhythmic event[5].

Rate of hospitalisation for cardiovascular causes is also an important indicator of cardiac morbidity. In a post hoc pooled analysis of the AFFIRM and AF-CHF studies of atrial fibrillation amiodarone use was compared to rate control treatment strategies[18]. However in this analysis no association was demonstrated between amiodarone and cardiovascular hospitalisation though the confidence interval does not rule out the possibility of meaningful increases or decreases in risk (HR (1.19 (0.76, 1.88))[18]. In comparison to amiodarone, an observational study looking at hospitalisation rates for people with atrial fibrillation found that sotalol increased risk of cardiovascular hospitalisation[19]. This study also showed that amiodarone reduced risk of cardiovascular hospitalisation compared with Class Ic antiarrhythmics.

2.6.2 Mortality

As the majority of mortality data for sotalol and amiodarone comes from RCTs which are not powered to look at mortality as an outcome, the association between these antiarrhythmics and mortality is unclear. For example, in the Moos et al. study directly comparing sotalol and amiodarone for the prevention of POAF there were 2 deaths in the sotalol group and none in the amiodarone group[14]. In an RCT of sotalol and amiodarone for atrial fibrillation there were 13 deaths in the amiodarone group, 15 in the sotalol group and 3 in the placebo group though none of these differences were statistically significant[6].

There have been some meta-analyses that have aggregated RCT data and investigated mortality as an outcome however the results from these studies are still unclear. The Cochrane review on the prevention of POAF meta-analysed 25 RCTs of amiodarone and found an OR of 1.08 (0.74, 1.56). In this study only 8 sotalol trials included mortality data and the resulting OR was even more inconclusive (0.65 (0.08, 5.37))[9]. The mixed treatment comparison study by

Freemantle et al. included 18 trials with mortality data. They found an increased risk of mortality with sotalol as compared to placebo (OR 3.44 (1.02, 11.59)) but the association between amiodarone and mortality while not significant was very under powered (OR 2.17 (0.63, 7.51))[5]. However when the analysis was restricted to studies with at least 100 people in each treatment arm, amiodarone increased the risk of mortality compared to placebo (OR 2.73 (1.00, 7.41))[5].

An observational study by Piccini et al. has also investigated the association between sotalol and amiodarone and mortality in individuals with atrial fibrillation and coronary artery disease[20]. Using the Duke Databank for Cardiovascular disease the authors compared the risk of mortality of sotalol users, amiodarone users, and users of no antiarrhythmics in this population. At almost all time points, risk of mortality was highest in the amiodarone group, followed by the no antiarrhythmics group and risk was lowest amongst sotalol users. However when time on therapy was taken into consideration sotalol was shown to be protective against mortality compared to amiodarone (HR 0.72 (0.55, 0.93)) but harmful compared to no anti-arrhythmic (HR 1.53 (1.19, 1.96))[20].

Given the lack of power and conflicting results of published studies regarding the association between sotalol and amiodarone and mortality the safety profile of these medications remains unclear.

2.7 Limitations of the current evidence base

The bulk of the literature on the safety of sotalol and amiodarone comes from RCTs and meta-analyses of RCTs which, despite providing invaluable evidence, have some limitations which are worth noting. Firstly, the populations and environment of RCTs are highly selected and controlled and as such are not reflective of real world clinical practice. Therefore

generalising results from RCTs for the purpose of clinical decision-making can be difficult. Along the same lines, many RCTs do not provide direct comparisons of treatment regimens but rather compare treatments of interest to placebo[16]. This poses challenges for clinical decision-making as treatments of interest should be compared to standard of care in order to better inform healthcare practitioners. Though reporting of adverse effects in clinical trials is now standard practice there is a lack of reporting of rare adverse effects, and a lack of standardisation of what effects are reported which limits the pool of available information. Furthermore due to the high cost of conducting clinical trials, sample sizes are often limited meaning that studies are not powered to detect rare but potentially important safety signals. Cost also restricts potential follow-up time with studies of sotalol and amiodarone often following subjects for a few months or less[14]. This means that adverse effects that occurred beyond this point would not be detected. This is of particular relevance considering the half-life of amiodarone ranges up to four months. Though techniques such as meta-analysis are a possible solution for the lack of statistical power resulting from small sample sizes, meta-analyses can still be underpowered to investigate safety outcomes as is the case with the Cochrane review on the prevention of POAF[9].

A particular limitation of the literature on the safety of sotalol and amiodarone for the management of POAF is that there are very few studies that specifically address treatment during the post-operative period. Studies predominantly focus on either treatment of chronic atrial fibrillation or the prevention of POAF following cardiac surgery. Generalising safety information from studies of different populations and for different purposes other than the treatment of POAF is clearly not ideal. Guidelines for the management of POAF also recognise this as a substantial limitation[2].

2.8 Rationale and study objectives

POAF is the most common complication of cardiac surgery however little evidence exists to guide clinicians in the treatment of this condition. Rather guidelines are based on studies on the prevention of POAF or for the treatment of chronic atrial fibrillation[2]. The majority of studies that make up this evidence base are RCTs and meta-analyses of RCTs which are afflicted by several limitations as outlined above. Though evidence from these studies is inconclusive in regards to the safety profile of sotalol and amiodarone, the most common treatments for POAF, we cannot ignore the possibility of increased risk of mortality with these medications.

For these reasons we conducted an observational study which reflects real world practice and specifically addresses treatment of atrial fibrillation during the post-operative period. Our primary objective was to assess the risk of mortality of sotalol and amiodarone for the treatment of new-onset POAF following CABG surgery. By using administrative data we had increased power to detect rare safety signals and were able to follow subjects over a long period of time to identify non-proximal adverse events. Furthermore we assessed the safety of both sotalol and amiodarone meaning that a direct comparison of the risk with these medications was possible. We believe that our study contributes valuable complimentary evidence to the current knowledge base on the treatment of this condition.

3. Methods

3.1 Study design overview

A retrospective population-based cohort of individuals diagnosed with new-onset POAF following CABG was created using the universal health insurance databases of Québec. In light of the time-varying nature of drug exposure, and the potential effect of calendar time, a time-matched nested case-control analysis was conducted[21,22] to assess the risk of mortality associated with sotalol and amiodarone in this population.

3.2 Sources of data

In order to compare the risk of mortality with amiodarone and sotalol amongst those with new-onset POAF, the computerised health insurance databases of the province of Québec were used. Provincial health insurance is available to all residents of Québec, and prescription medications are covered for individuals 65 years old and older, meaning that comprehensive healthcare information is available for all elderly residents of the province. The Québec health insurance databases include medical and drug services databases from the Régie de l'Assurance-Maladie du Québec (RAMQ), a vital status database administered by the Institut de la Statistique du Québec and an extensive hospitalisations database (Med-Écho). Each resident of the province is assigned a unique encrypted identification number, the Numero d'Assurance Maladie (NAM), which enables record linkage between the databases at the level of the individual. These datasets have been previously validated [23–25] and have been used extensively for research purposes [26–30].

For the purposes of this study, data from the RAMQ on all patients in Québec who had undergone CABG surgery from 1993 to 2003 was utilised. This set of databases served to form the cohort, determine follow up time, and identify exposures, outcomes and covariates.

Beneficiary database:

The beneficiary database contains basic socio-demographic information about residents receiving the provincial health insurance plan. This includes the patient's encrypted ID (NAM), geographic information, as well as sex, and year of birth.

Vital statistics database (1992-2005):

The vital statistics database is a listing of individuals who died between 1992 and 2005 inclusive and contains their NAM, date of death, and underlying cause of death (ICD-9 coding).

Prescription drugs database (1992-2003):

The prescription drugs database contains data on all dispensed outpatient prescriptions for those covered by the provincial plan. Aside from the beneficiary's NAM, information on the type of medication dispensed (drug identification number (DIN) and drug common denomination codes), the date of dispensation, form of the medication, dosage, quantity and duration of treatment are provided.

Medical services database (1992-2003):

The medical services database contains information on all physician claims for medical services provided. The services are coded according to RAMQ conventions. Patient NAM, principal diagnosis for the specific medical encounter (ICD-9 coding), as well as the date of and location of service, are included.

Hospitalisation database (Med-Écho) (1992-2004):

Med-Écho is a database containing records on all patient hospitalisations, including admission and discharge dates, discharge type, procedure codes, type of establishment, and type

of admission (day surgery vs. inpatient stay). A primary diagnoses is provided for each hospitalisation and up to 15 different secondary diagnoses, thus capturing detailed clinical information for each patient. Key hospital procedures, including CABG operations are also recorded and permit a validation with the medical services database.

3.3 Creation of cohort and follow-up

The cohort was defined as all 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. Though most instances of POAF occur within one week of surgery [1] a larger time window was chosen to allow for delays in diagnosis. Patients with POAF were identified using the ICD-9 diagnoses codes 427.31 (atrial fibrillation) and 427.32 (atrial flutter) which have been shown to have high specificity and positive predictive value[30] (Appendix 1) . Hospitalisations with an atrial fibrillation diagnosis were selected if the admission date was within 30 days of surgery because an exact date of diagnosis was not available. Date of cohort entry (t0) was taken as the date of discharge for those diagnosed while hospitalised for surgery. For individuals who received a POAF diagnosis during a subsequent hospitalisation, the corresponding date of discharge was considered their cohort entry date.

Cohort members were required to be at least 66 years old at cohort entry in order to ensure that one-year of baseline pharmacologic data was available for everyone. Patients who had a diagnosis for atrial fibrillation in the year before admission for surgery were excluded, as were those who had been dispensed either of the anti-arrhythmic drugs of interest in this study, sotalol or amiodarone, in the year before cohort entry in order to minimise the potential for survivor bias. Cohort members without any prescriptions in the RAMQ dataset were excluded as they are likely privately insured and no exposure data would be available for them. Individuals

who would have entered the cohort after June 30th, 2003 were excluded so that at least 6 months of follow-up was available for each cohort member, as were those who died at or before cohort entry. Postal codes were used to determine individuals residing outside the province of Québec and these people were excluded due to potential loss to follow-up. Patients with a diagnosis of atrial fibrillation made more than 30 days after their CABG surgery were excluded. This group also included patients who were hospitalised for more than 30 days post-surgery as they are likely very ill and represent a different population from the one of interest to this study. Additionally, as prescription data is not available for subjects while they are hospitalised, having a cut-off minimises the time when drug exposure is unknown. All patients were followed until death by any cause or the end of the study period (December 31, 2003), whichever occurred first.

3.4 Case and control selection

The primary outcome of interest was total mortality and was selected because it is clinically important, and can be reliably measured using the Québec databases[24,25,30]. As such, death was considered the case-defining event. Cases were identified using the vital status database, and date of death was taken as the index date.

Up to 5 controls were randomly selected for each case 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 type of sampling is especially efficient in the context of large cohorts, and does not result in a lack of precision despite only a portion of the cohort's data contributing to the analysis[21,29] . Matching on cohort entry month and year ensured similar follow-up time for both cases and controls and eliminated potential confounding due to calendar-time. Though age and sex are common potential confounders, they were not used as matching criteria to avoid the need to exclude cases

due to lack of eligible controls. Additionally, by not matching on age and sex, we were able to evaluate the importance of these variables.

3.5 Exposure assessment

Prescriptions for sotalol and amiodarone during the study period were obtained from the prescription drugs database. The exposure time window of interest was current use. Individuals were considered currently exposed if the duration of a dispensed prescription, plus a lag period of 7 days for sotalol or 30 days for amiodarone, overlapped with the index date. This lag period was included to take into account the pharmacologically pertinent period of exposure[31] as amiodarone has a much longer half-life than sotalol (>14 days vs. ~12 hours)[4,11,32].The reference group was individuals with POAF who did not have a dispensed prescription for sotalol or amiodarone during the relevant time window. Subjects who had prescriptions making them eligible to be classified as both a current user of sotalol and of amiodarone would have been excluded as these medications are rarely prescribed concurrently, however this situation did not arise. As current use was the exposure period of interest, it is however possible that subjects were previously exposed to either study drug during the study period.

It should also be noted that drug dispensation was used as a proxy for consumption, which is a limitation of most pharmacoepidemiological studies. However as most drug prescriptions were only for 30 days, the extent of misclassification should be minimal and previous studies have still been able to identify real drug safety issues despite this limitation[26,28,29].

3.6 Covariates and potential confounders

As treatment selection is not random, a number of well-established conventional covariates were considered potential confounders and adjusted for in the analysis. Only potential confounders that occurred at or in the year before cohort entry (i.e. at baseline) were included in order to avoid controlling for factors along the causal pathway. Rate ratios were adjusted for age and sex as well as several comorbid conditions. The conditions considered potential confounders included diabetes, hypertension, previous MI, congestive heart failure, previous stroke, COPD, renal disease, cerebrovascular disease, and peripheral vascular disease. Hyperthyroidism was also added due to amiodarone's potential to induce thyroid dysfunction and the possibility of increased thyroid hormone levels with sotalol treatment[4,11]. These comorbidities were identified using both discharge diagnosis codes from the Med-Écho database and the presence of drug treatments from the prescription drugs database that would only be prescribed for a specific condition. See Appendix 1 and Appendix 2 for a list of the ICD-9 codes and medications that were used to determine the presence of each condition. Utilising two sources of data increased sensitivity and the likelihood of identifying comorbidities. In addition, the Charlson Comorbidity Index[33] and the duration of post-surgical hospital stay were also included. Use of concomitant medications including antiarrhythmics (other than sotalol or amiodarone), calcium channel blockers, digoxin, ACE inhibitors, ARBs, diuretics, lipid modifying a gents, diabetes medications, anti-platelets, beta-blockers, and anti-coagulants was also evaluated as source of potential confounding (Appendix 3).

3.7 Statistical methods

3.7.1 Statistical analysis

Characteristics of cases and controls were summarised using descriptive statistics including t-tests and chi-square tests. Descriptive statistics were also done to compare characteristics of sotalol and amiodarone users. Conditional logistic regression was performed to estimate the rate ratio (RR) of each death associated with current sotalol or amiodarone use, along with 95% CI. The rate ratios obtained are equivalent to the hazard ratio that would be estimated from the corresponding Cox proportional hazards regression[21]. Three regression models were run: a *crude* model evaluating death as a function of exposure, a *reduced* model where confounders with statistically significant differences in their distributions amongst cases and controls were added, and a *full* model including all potential confounders listed above. In order to determine which confounders differed between cases and controls t-tests were performed for continuous variables and the chi-square test of homogeneity was performed for categorical variables. The variables included in the *reduced* model were age at cohort entry, hospital stay, Charlson Index, certain comorbidities present in the year before cohort entry (diabetes, CHF, COPD, renal failure, cerebrovascular disease, peripheral vascular disease, previous stroke, cancer), and use of certain medications in the year before cohort entry (digoxin, ACE inhibitors, lipid modifiers, diabetes medications, beta-blockers, anti-coagulants). Each regression model was conditioned on two matching factors: cohort entry month and year, and duration of follow-up thereby controlling for these variables in the analysis. All analyses were conducted with SAS version 9.3 (SAS Institute, Cary, NC).

3.7.2 Sensitivity and additional analyses

To assess the strength and validity of the results an extensive series of sensitivity analyses were conducted. Crude and fully adjusted rate ratios were estimated for all of the below-mentioned sensitivity analyses unless otherwise stated. The length of the time window set for identification of current amiodarone use was longer than that of sotalol due to amiodarone's long and variable half-life[4]. However, as a result of the longer time window, we were more likely to capture amiodarone users than sotalol users resulting in potential information bias. Therefore a sensitivity analysis was conducted where the lag period was made equivalent for current use of both sotalol and amiodarone (i.e. both 7 days, and 30 days). To further test the robustness of the exposure definition a sensitivity analysis was performed where exposure (i.e. current use) was redefined as having a prescription for sotalol or amiodarone dispensed within 30 days of the index date. Though the majority of prescriptions were for 30 days, some were for longer. In the main analysis we had defined exposure based on prescription duration, therefore it is possible that we were considering individuals exposed who had already stopped taking the medication, especially for those with long prescriptions.

One of the limitations of using the provincial drug databases is that it is only comprised of outpatient prescriptions. Thus hospitalisations that occur during the exposure window of interest are periods where exposure is uncertain. As such patients who are hospitalised are considered unexposed, unless they have other outpatient prescriptions during the same window of interest. As cases are sicker than controls they are more likely to be hospitalised and thus considered unexposed meaning the number of unexposed cases could be artificially high. To assess the extent of this potential immeasurable time bias[34] on the results, the cohort was restricted to only those who were not hospitalised at all in the 30 days before index. Analyses

were repeated with the aim of obtaining more internally valid results, though at the cost of generalizability. A subsequent sensitivity analysis was performed where the definition of the case's index date, and their matched controls, was changed to the hospital admission date for those who died in hospital. This allowed exposures to be captured that could be related to the reason for admission and ultimate death. Effect measure modification by sex was also explored, as sex is a conventional potential effect modifier. Effect measure modification by renal disease was also investigated due to the fact that sotalol is excreted by the kidneys and is contraindicated in people with renal disease[11].

The main outcome of interest was total mortality, however a more proximal outcome, any cardiovascular hospitalisation, was also examined in order to limit potential differential follow-up between sotalol and amiodarone users. This was of concern because if the hazard ratio increases with time, the drug with longer follow-up will artificially look more harmful. A cardiovascular hospitalisation was defined as a hospitalisation with a diagnosis of MI, stroke, CHF, arrhythmia (other than atrial fibrillation), or unstable angina and the date of admission was taken as the index date. Cases were identified, controls were matched, and exposure was measured in the same manner as for the main analysis.

Finally, the functionality of the nested case control was tested by looking at an exposure and outcome that should have absolutely no relationship in this population. The association between lorazepam and MI was explored to this end. Methods were conducted as for the main analysis with the exception of a reduced model.

3.8 Ethical considerations

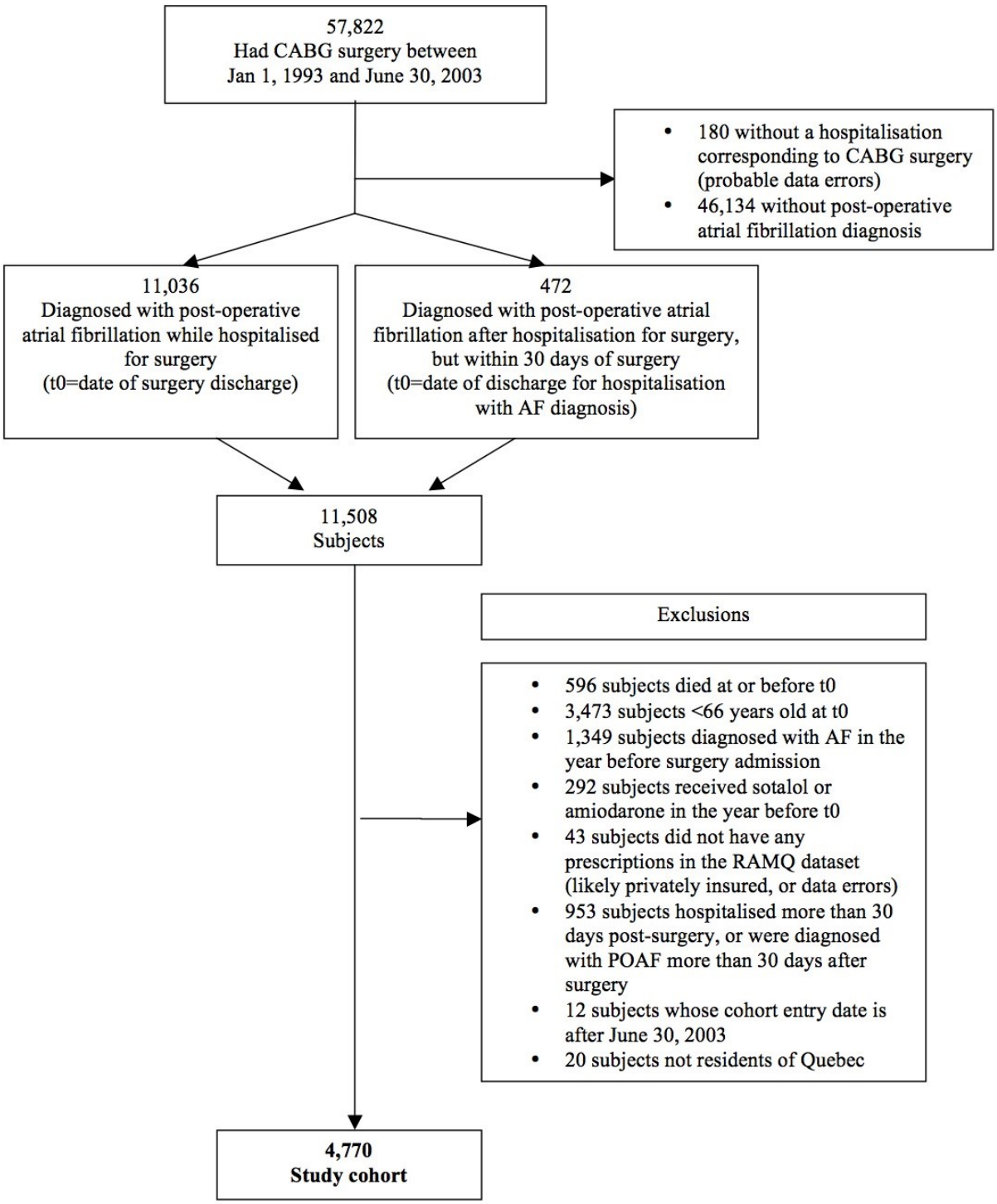
The ethics board of the Research Institute of the McGill University Hospital Centre (RIMUHC) approved this study.

4. Results

4.1 Description of the cohort

A total of 57, 822 patients were identified who had undergone CABG surgery between January 1, 1993 and June 30, 2003. Of these patients, 11, 508 were diagnosed with atrial fibrillation following surgery. After applying the exclusion criteria, the final study cohort included 4,770 subjects (Figure 1).

Figure 1 Study flow chart



During the follow-up period, 931 death cases were identified and 29,585 corresponding potential controls. 1 case had no controls therefore was excluded and 2 cases had only 4 possible controls. The remainder of the cases were each matched to 5 controls. The final cohort consisted of 930 cases and 4648 matched controls. The mean (SD) duration of patient follow up 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 cases and control respectively. 73.7% of cases and 72.8% of controls were male. The mean (SD) hospital stay following CABG surgery was 12.9(6.3) days for cases where as it was 11.7(5.9) days for controls. Study subjects had many comorbid conditions at baseline the most prevalent being hypertension (70.5% of cases, 71.0% of controls) and previous MI (46.0% of cases, 43.9% of controls). As expected case-patients appeared to be more ill at baseline than control-patients (mean (SD) Charlson Index 2.4(1.9) vs. 1.8(1.5) $p<0.0001$) and had significantly higher rates of cerebrovascular disease, peripheralvascular disease, congestive heart failure, previous stroke, diabetes, COPD, renal disease and cancer ($p<0.001$). In the year before cohort entry more than half of subjects received a prescription for anti-platelet medications, and calcium channel blockers. Significantly more cases were prescribed digoxin (16.0% vs. 8.9%), ACE inhibitors (33.3% vs. 25.2%), anticoagulants (9.7% vs. 6.3%) and diabetes medications (25.4% vs. 18.2%) ($p<0.001$). Controls were significantly more likely to have received a prescription for beta-blockers (54.8% vs. 49.7%), or lipid modifying agents (34.8% vs. 29.1%) ($p<0.01$). 2.3% of cases and 1.9% of controls had received an anti-arrhythmic (other than sotalol or amiodarone) during this period.

Table 1 Characteristics of cases and controls at baseline

Characteristic	Cases (n=930)	Controls (n=4648)	p-value
Age (mean (SD))			
At cohort entry	73.3(4.7)	72.4(4.5)	<.001
At index date	77.2(5.3)	76.3(4.9)	<.001
Sex (%)			.58
Female	26.3	27.2	
Male	73.7	72.8	
Follow-up (mean(SD) days)	1421 (969)	1422(968)	.99
Comorbid conditions (%)*			
Hypertension	70.5	71.0	.80
Cerebrovascular disease	15.0	10.3	<.001
Peripheralvascular disease	13.9	9.8	<.001
Previous MI	46.0	43.9	.23
Congestive heart failure	37.4	25.0	<.001
Previous stroke	12.3	8.2	<.001
Diabetes	30.2	22.4	<.001
COPD	32.9	22.1	<.001
Acute or chronic renal disease	16.5	10.2	<.001
Hyperthyroidism	1.1	0.9	.62
Cancer	6.3	3.2	<.001
Charlson Comorbidity Index*			
Mean (SD) Charlson Index score	2.4(1.9)	1.8(1.5)	<.001
Charlson Index score (%)			<.001
0	12.8	19.8	
1	26.7	33.0	
2	21.4	21.9	
≥ 3	39.1	25.2	
Use of concomitant treatment (%)*			
Antiarrhythmics†	2.3	1.9	.49
Calcium channel blockers	64.1	61.8	.18
Beta blockers	49.7	54.8	.004
Digoxin	16.0	8.9	<.001
Lipid modifying agents	29.1	34.8	<.001
ACE inhibitors	33.3	25.2	<.001
ARBs	3.3	2.6	.20
Diuretics	18.4	18.2	.88
Anticoagulants	9.7	6.3	<.001
Anti-platelet agents	64.1	63.0	.51

Diabetes medications	25.4	18.2	<.001
Length of post-surgical hospital stay			
Mean (SD) hospital stay	12.9(6.3)	11.7(5.9)	<.001
Hospital stay (%)			<.001
≤ 10 days	45.6	56.7	
> 10 days	54.4	43.3	

*In the year before cohort entry
†Except amiodarone or sotalol

4.2 Analysis of risk

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). Temporal trends in the prescribing of sotalol and amiodarone are described in Appendix 4.Current sotalol users tended to be younger and healthier as compared to current amiodarone users, and those who were not exposed to either drug during the relevant time period (Charlson Index mean (SD) 1.6(1.4) sotalol, 2.2(1.8) amiodarone, 1.9(1.6) neither). However current sotalol users were more likely to have been diagnosed with a stroke or cerebrovascular disease in the year before cohort entry than those 'currently' unexposed to either drug ($p<.01$). Current amiodarone users were less healthy overall having a significantly higher prevalence of cerebrovascular disease, previous MI, congestive heart failure, previous stroke, COPD and renal disease in the year before cohort entry than those in the other exposure categories ($p<.01$). Current amiodarone users were also significantly more likely to have been prescribed another anti-arrhythmic, digoxin, ACE inhibitors, or ARBs in the same period ($p<.001$). Additionally, follow-up time for current amiodarone users was longer than that of current sotalol users (mean (SD) 1392(1114) days vs. 1112(950) days).

Table 2 Characteristics of current sotalol and amiodarone users

Characteristic	Sotalol (n=395)	Amiodarone (n=375)	Neither (n=4808)	p-value
Age (mean (SD))				
At cohort entry	71.7(4.4)	73.0(4.6)	72.4(4.5)	
At index date	74.7(5.0)	76.8(4.7)	76.5(5.0)	
Sex (%)				.21
Female	23.5	25.9	27.5	
Male	76.5	74.1	72.6	
Follow-up (mean(SD) days)	1112(950)	1392 (1114)	1450(953)	
Comorbid conditions (%)*				
Hypertension	73.4	71.5	70.6	.49
Cerebrovascular disease	12.2	17.6	10.5	<.001
Peripheralvascular disease	7.9	11.2	10.6	.20
Previous MI	41.8	51.7	43.8	.007
Congestive heart failure	23.0	41.6	26.2	<.001
Previous stroke	10.4	13.6	8.4	.002
Diabetes	21.0	23.2	24.0	.39
COPD	16.5	27.5	24.2	<.001
Acute or chronic renal disease	6.56	18.1	11.1	<.001
Hyperthyroidism	1.0	1.6	0.9	.36
Cancer	2.8	3.7	3.8	.67
Charlson Comorbidity Index*				
Mean (SD) Charlson Index score	1.6(1.4)	2.2(1.8)	1.9(1.6)	
Charlson Index score (%)				<.001
0	21.3	13.6	18.8	
1	37.0	27.2	31.9	
2	21.3	24.3	21.7	
≥ 3	20.5	34.9	27.6	
Use of concomitant treatment (%)*				
Antiarrhythmics†	1.8	5.6	1.7	<.001
Calcium channel blockers	61.8	65.1	61.9	.48
Beta blockers	67.3	48.5	53.3	<.001
Digoxin	10.38	18.40	9.42	<.001
Lipid modifying agents	32.9	38.7	33.5	.12
ACE inhibitors	24.6	34.9	26.1	<.001
ARBs	0.3	5.3	2.7	<.001
Diuretics	17.7	20.8	18.1	.40
Anticoagulants	5.6	9.6	6.7	.06

Anti-platelet agents	63.8	62.1	63.2	.89
Diabetes medications	17.5	20.8	19.5	.49
Length of post-surgical hospital stay				
Mean (SD) hospital stay	11.5(5.4)	13.4(6.3)	11.8(6.0)	
Hospital stay (%)				<.001
≤ 10 days	55.2	45.1	55.6	
> 10 days	44.8	54.9	44.4	

*In the year before cohort entry

† Except amiodarone or sotalol

Looking at exposure for cases and controls specifically, 4.0% of case-patients and 7.7% of control-patients were categorised as current users of sotalol and 10.2% of case-patients and 6.0% of control-patients were considered current users of amiodarone (Table 3). Crude estimates indicate a strong protective relationship between sotalol and death as compared to subjects who were not current users of either medication (RR_{crude} 0.51 (0.36, 0.72)). When adjusted for confounders with statistically significant differences in their distributions between cases and controls (*reduced* model: age at baseline, hospital stay, Charlson Index, diabetes, CHF, COPD, renal failure, cerebrovascular disease, peripheral vascular disease, previous stroke, cancer, digoxin, ACE inhibitors, lipid modifiers, diabetes medications, beta-blockers, and anti-coagulants), and for all potential confounders (*full* model: additionally including sex, hypertension, previous MI, hyperthyroidism, antiarrhythmics (excl. amiodarone and sotalol), calcium channel blockers, ARBs diuretics, and anti-platelet agents) estimates remained relatively unchanged ($RR_{reduced}$ 0.56 (0.39, 0.81), RR_{full} 0.56 (0.39,0.80)). Conversely, crude estimates for amiodarone indicate a strong harmful relationship between current use and death as compared to neither users (RR_{crude} 1.74 (1.36, 2.24)). When adjusted for potential confounders, the association was lessened but remained statistically significant (RR_{full} 1.50(1.15, 1.94)).

Table 3 Sotalol and amiodarone use amongst death cases and controls

Current use of sotalol or amiodarone	Cases (n=930)	Controls (n=4648)	Crude RR (95%CI)	Adjusted (reduced) RR (95%CI)*	Adjusted (full) RR (95% CI)†	P value (full)
Neither	798 (85.8)	4010(86.3)	1.00	1.00 (ref.)	1.00 (ref.)	Reference
Sotalol	37 (4.0)	358 (7.7)	0.51 (0.36, 0.72)	0.56 (0.39, 0.81)	0.56 (0.39, 0.80)	.002
Amiodarone	95 (10.2)	280 (6.0)	1.74 (1.36, 2.24)	1.48 (1.14, 1.91)	1.50 (1.15, 1.94)	.002

*__Adjusted for__: age at cohort entry, hospital stay, Charlson Index, diabetes, CHF, COPD, renal failure, cerebrovascular disease, peripheral vascular disease, previous stroke, cancer, use of digoxin, ACE inhibitors, lipid modifiers, diabetes medications, beta-blockers, and anti-coagulants in the year before cohort entry

†__Adjusted for__: age at cohort entry, sex, hospital stay, Charlson Index, diabetes, hypertension, previous MI, CHF, COPD, renal failure, cerebrovascular disease, peripheral vascular disease, previous stroke, hyperthyroidism, cancer, use of antiarrhythmics, calcium channel blockers, digoxin, ACE inhibitors, lipid modifiers, ARBs, diabetes medications, beta-blockers, anti-coagulants, and anti-platelet agents in the year before cohort entry

4.3 Sensitivity and additional analyses

When the exposure time window for current use of sotalol was changed to match that of amiodarone (i.e. date of dispensation, plus duration plus 30 days), the estimate was very similar to the adjusted main results (Appendix 5). However, the number of amiodarone cases dropped from 95 to 73 when the time window was changed to be equal to that of sotalol (i.e. date of dispensation, plus duration, plus 7 days) making the rate ratio non-statistically significant (RR 1.20 (0.90, 1.60)) (Appendix 6).

The association between current amiodarone use and mortality was also not statistically significant when the definition of current use was changed to mean that a prescription for the medication was dispensed within 30 days of the index date (Appendix 7) though this does not

preclude the possibility of increased risk. The estimates for current sotalol use still showed a strong protective relationship for this exposure definition.

Appendix 8 describes risk of death for patients who were not hospitalised during the 30 days before index. In this subgroup, current use of sotalol was once again associated with a significant decrease in likelihood of mortality (RR_{adj} 0.32 (0.12, 0.84). This estimate was even more protective than that from the main analysis. However there was no evidence of an association between current amiodarone use and mortality within this group (RR_{adj} 1.01 (0.57, 1.78)).

Changing the index date to the hospital admission date for case-patients who died in hospital and their respective controls had very little effect on the results (Appendix 9).

Possible effect measure modification by sex and by renal failure was also assessed though there was not sufficient statistical power to explore this fully and almost all estimates were not significant (Appendix 10, Appendix 11). Notwithstanding the lack of power, females who were current users of amiodarone appeared to have an elevated risk of mortality compared to females who were not current users of either drug (RR_{adj} 1.69 (1.01, 2.82)). This elevated risk was not seen in male current users of amiodarone (RR_{adj} 0.85 (0.47,1.53)).

The association between current sotalol and amiodarone use and any cardiovascular hospitalisation was also explored. 1992 cases who experienced a cardiovascular hospitalisation were identified and matched to 9944 controls. After exposure assessment 2 controls were excluded due to simultaneously being exposed to both study drugs. As with the death cases and controls, cases were generally less healthy than those who did not experience the outcome, having more comorbidities and more exposure to other medications in the year before cohort

entry (Appendix 12). There were 1370 and 1042 subjects considered currently exposed to sotalol and amiodarone respectively (Appendix 13**)**. Sotalol users in this cohort were similarly healthier than amiodarone users. As with mortality, current amiodarone use was associated with a higher probability of having the outcome, in this case any cardiovascular hospitalisation (RR_{adj} 1.31 (1.09, 1.57)) (Appendix 14). However current sotalol use did not have any effect (RR_{adj} 1.07 (0.91, 1.27)).

An additional nested case control analysis was done using the base cohort to test the general functionality of the cohort and nested case control methods. To do this, the association between current lorazepam use and MI was investigated **(**Appendix 15, Appendix 16, Appendix 17). As expected, no evidence of an association between exposure to lorazepam and MI was found (RR_{adj} 0.91 (0.62, 1.33)).

5. Discussion

This retrospective population-based study with nested case-control analysis assessed the association between use of sotalol and amiodarone and mortality for individuals over 65 who developed POAF after CABG surgery. The results from this study provide some evidence that current use of sotalol may decrease the likelihood of mortality in this population compared to those who are not exposed to sotalol or exposed to amiodarone during the same time window. Sotalol was shown to be protective in the main analysis as well as all sensitivity analyses with mortality as the outcome. The only exception appeared to be a trend towards increased mortality among sotalol users with chronic renal failure. This result is expected as sotalol is renally excreted and it has been recognized that the drug is contraindicated in this population due to the risk of accumulation leading to the potentially malignant arrhythmia known as torsade des pointes [11]. Of note, despite the strong and consistent protective effect of current sotalol use on mortality, no association was found between sotalol use and reduced hospitalisation for any cardiovascular condition. This lack of consistency calls for caution when interpreting the mortality results, although decreased mortality may occur without mediation of reduced cardiovascular hospitalisations via, for example, an impact on sudden cardiac death.

The rate ratios for the association between current amiodarone use and death suggested a harmful relationship. Though the association was significant in the primary analysis, the results were not consistent across sensitivity analyses which leads us to question the main findings. Interestingly an increased risk of mortality was found in female amiodarone users compared to female users of neither drug. This increased risk was not demonstrated in male amiodarone users suggesting a possible issue with dose as females tend to be smaller than males yet recommended doses do not vary by sex. Unfortunately our study was not powered to explore dose-response

relationships. When the association between current amiodarone use and any cardiovascular hospitalisation was explored, an increased risk between 10% and 60% was found.

The body of literature regarding the safety of sotalol and amiodarone remains inconclusive and is especially limited in the context of the management of POAF. A recent retrospective cohort study was conducted looking at the safety of sotalol and amiodarone in a similar population consisting of people with atrial fibrillation and coronary artery disease[20]. As with our study, sotalol users were healthier than amiodarone users. When duration of exposure was taken into consideration sotalol was shown to be protective against mortality in comparison to amiodarone but harmful in comparison to no antiarrhythmics. One clinical trial directly compared sotalol and amiodarone for the prevention of POAF following cardiac surgery[14]. There were 2 deaths in the sotalol group and none in the amiodarone group but as the study was not powered to investigate effects on mortality the association was not significant. The number of patients who discontinued therapy due to an adverse effect was also similar between groups. A Cochrane review on interventions to prevent atrial fibrillation following cardiac surgery was also conducted and included data on mortality for 25 RCTs with amiodarone, and 8 RCTs with sotalol[9]. Meta-analysis results showed an OR of 1.08 (0.74, 1.56) for amiodarone as compared to control (placebo or other treatment) and were also inconclusive with regards to the association between sotalol and mortality (OR 0.65 (0.08, 5.37)) as few studies had any events. Given the inconclusive nature of the literature regarding the safety of sotalol and amiodarone in individuals with coronary artery disease in general, and those who have undergone revascularisation procedures, it difficult to draw conclusions about our results based on published research findings.

This study demonstrated a number of strengths, many of which derived from the use of a nested case-control analysis and conditional logistic regression. Use of the nested case-control framework decreased exposure misclassification by allowing exposure to be captured at the time of the outcome ensuring that we were measuring an effect during a pharmacologically plausible time frame. Additionally the nested-case controlled strategy allowed for cases and controls to be sampled from the same large source population enhancing generalizability and ensuring more comparability between cases and controls thus somewhat limiting selection bias. If the distribution of drug use and mortality in the study population was not representative of our target population (selection bias), this could have made study drugs seem artificially protective or harmful. The risk-set sampling approach also enabled matching based on cohort entry month and year, which controlled for the effects of calendar time. This was important as positive outcomes for more recent cohort members could be due to the overall improvement in healthcare over time and because of time-trends in prescribing practices. By using conditional logistic regression rather than a traditional cox regression model we were able to obtain similar results with a less complex and more computationally efficient analysis as well as minimise misclassification of time and exposure[35].

Further strengths were gained through the use of the RAMQ databases. These datasets are representative of the Canadian population[27,28], thus their use greatly increases the external generalizability of results. This is especially pertinent considering that the majority of drug safety data comes from clinical trials, which utilise highly selected populations, are not powered to detect safety signals, and often do not report adverse affects such as cardiovascular hospitalisations. Furthermore, use of these databases allowed for creation of a relatively large cohort and therefore more power to detect potentially rare safety signals. The data itself includes

a primary diagnosis and up to 15 secondary diagnoses for each hospitalisation which allowed for substantial controlling of confounding. Moreover, this data has been shown to be highly correlated to data from medical charts[25].

Beyond the nested case-control approach and use of the RAMQ databases, this study also included several advantageous design elements. Firstly, entry into the cohort was limited to individuals with new-onset atrial fibrillation. Limiting the cohort only to people who had atrial fibrillation for the first time after surgery ensured that we were not combining the effects from different subgroups. Similarly, only those who were naïve to the study drugs of interest were allowed into the cohort, minimising the potential for survivor bias. Additionally, using a hard outcome like mortality as the outcome of interest greatly reduced the potential for bias from misclassification of outcome. In addition, numerous sensitivity analyses were run which provided more understanding and perspective on the main study results. In comparison to other studies, our study had the advantage of a long follow-up period. This allowed for exposure and outcome data collection well beyond the initial few months following CABG meaning that non-proximal safety signals could be captured. Additionally, most published studies on POAF focus on prevention rather than treatment; therefore our study contributes to the limited literature on the treatment of this condition. Finally, through simultaneous investigation of sotalol and amiodarone exposure, a direct comparison can be made on the safety of these two antiarrhythmics.

Despite the numerous strengths of our study, there were some limitations. There was a lack of comparability between sotalol and amiodarone users. Sotalol users were much healthier than amiodarone users as demonstrated by differences in comorbidities and medication use at baseline. Though these factors were controlled for in the model it is possible that the groups

differed in other unmeasured ways and residual confounding was present. Although the RAMQ databases contain detailed information on comorbidities and use of medications, they lack information on certain important potential confounders such as smoking status, obesity, physical activity, frailty and family history. Some unmeasured confounding could also have been time-varying as comorbid conditions, exposure to medications, and other factors likely changed for subjects during their follow-up. However, these time-varying potential confounders were not controlled for as they likely lie along the causal pathway and methods to responsibly account for them, such as marginal structural models, were beyond the scope of our study.

The two unmeasured potential confounders of greatest concern in this study are glomerular filtration rate (GFR) and left ventricular ejection fraction (LVEF) at the time of anti-arrhythmic initiation. Though we controlled for renal failure in the year before cohort entry (which includes renal failure developed immediately after surgery) there was likely residual confounding due to impaired renal function as renal function is better represented as a continuous variable (i.e. GFR). GFR would have influenced both choice of antiarrhythmic and likelihood of mortality with those with a low GFR being less likely to receive sotalol and more likely to die. Similarly, there was probable residual confounding due to impaired LVEF that was not accounted for when controlling for congestive heart failure in the year before cohort entry. Impaired LVEF is also associated with a lower likelihood of receiving sotalol and a higher likelihood of mortality. It is possible that an imbalance in these factors, or the above-mentioned potential confounders, is responsible for the protective association observed between sotalol and mortality. If these factors varied across exposure groups, results could be biased due to confounding by indication. Propensity score methodologies could be implemented to try and increase comparability between exposure groups but this was beyond the scope of our study.

An additional limitation of our study, and of all studies conducted using the Quebec administrative databases, was that the RAMQ databases do not contain data on medications prescribed while in hospital. This means that subjects could have been exposed to the study drugs while hospitalised and we would have considered them unexposed resulting in immeasurable time bias[34]. As cases were sicker than controls, they were more likely to be hospitalised therefore we would have artificially increased the risk of death in the unexposed group. This is especially problematic considering the high frequency of hospitalisations in this population. However, to explore this issue, we conducted a sensitivity analysis where we restricted the cohort to only those not hospitalised in the 30 days before index. In this analysis sotalol appeared even more protective than in the main analysis but the harmful association between amiodarone and death was not replicated.

Measuring exposure was also challenging in that there were many possible ways to define it. We only considered current exposure to sotalol or amiodarone however recent, or past use of the study drugs could have been pertinent. Because past use was not measured, we did not treat "switchers" and those that were only exposed to one medication differently. The cohort was naïve to both study drugs before cohort entry though, so the percentage of "switchers" would likely have been small. Cumulative exposure and dose were also not in measured in our study. It could be beneficial in future research to explore a broader range of exposure definitions to determine if the association between sotalol and mortality still stands.

Additional study limitations include lack of power to explore possible effect measure medication and subgroup effects by sex and renal failure. Additionally, identification of POAF patients could have been incomplete because only those diagnosed with atrial fibrillation in hospital were included in the cohort. Therefore any patients diagnosed during an outpatient visit

would have been missed. As with all studies utilising drugs claim data, our study was limited by the assumption that dispensation of medications is equivalent to consumption. Though as the data represents filled prescriptions rather than written prescriptions it is more likely that patients were compliant. Noncompliance in our study however, would be non-differential misclassification of exposure and would have biased results towards the null.

To our knowledge, our study is the only study looking at the safety of sotalol and amiodarone in the context of management of POAF. As such our study provides valuable evidence regarding the safety of sotalol and amiodarone for treatment in this population. As this study was conducted using the Quebec health administrative databases the results can be generalised for the entire Quebec and Canadian population of individuals over 65 with POAF following CABG. Though our study suggests a possible protective association between current sotalol use and mortality in this population, these results need to be interpreted with caution given that sotalol users were healthier than their study counterparts, and given the totality of the evidence which remains inconclusive regarding sotalol. Our study also found a harmful association between amiodarone and mortality, but this association was not consistently replicated in sensitivity and subgroup analyses. More research further exploring the association between sotalol and amiodarone and mortality is needed so that there will be increased understanding of the potential benefits and risks of these medications in those with POAF. We believe that a network meta-analysis of RCTs with both direct and indirect comparators would be a beneficial next step towards providing the necessary power to answering this important clinical question.

6. Conclusion

Few studies have examined the safety of medications for the treatment of POAF following CABG. Our study was designed to explore the safety profiles of two such medications, sotalol and amiodarone, in this population. We found that sotalol therapy was more frequently used in patients with fewer comorbidities. Our results provide evidence that the use of sotalol to treat those over 65 with POAF could decrease the risk of mortality in this population. There was no association found between current use of sotalol and risk of cardiovascular hospitalisation. Amiodarone was found to be associated with increased mortality but results were not consistent across sensitivity and subgroup analyses. Amiodarone was associated with an increased risk of cardiovascular hospitalisation. We believe that additional research is required to gain further understanding of the safety profiles of these two medications in individuals with POAF.

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Appendices

Appendix 1 ICD-9 Codes for atrial fibrillation and comorbidities

Comorbidity	ICD-9 Codes	Description
Atrial fibrillation	427.31, 427.32,	427.31 Atrial fibrillation 427.32 Atrial flutter
Diabetes	250.0-250.9	250.0 Diabetes mellitus without mention of complication, 250.1 Diabetes with ketoacidosis, 250.2 Diabetes with hyperosmolarity, 250.3 Diabetes with other coma, 250.4 Diabetes with renal manifestations, 250.5 Diabetes with ophthalmic manifestations, 250.6 diabetes with neurological manifestations, 250.7 Diabetes with peripheral circulatory disorders, 250.8 Diabetes with other specified manifestations, 250.9 Diabetes with unspecified complication
Hypertension	401.0-405.9	401 Essential hypertension, 402 Hypertensive heart disease, 403 Hypertensive chronic kidney disease, 404 Hypertensive heart and chronic kidney disease, 405 Secondary hypertension
Acute myocardial infarction	410.0-410.9, 412.0-412.9	410 Acute myocardial infarction 412 Old myocardial infarction * ICD-9 412 was not considered when defining cases of acute myocardial infarction
Congestive heart failure	428.0-428.9	428.0 Congestive heart failure unspecified, 428.1 Left heart failure, 428.2 Systolic heart failure, 428.3 Diastolic heart failure, 428.4 Combined systolic and diastolic heart failure, 428.9 Heart failure unspecified
Stroke	430-431, 433-434, 436	430 Subarachnoid hemorrhage, 431 Intracerebral hemorrhage, 433 Occlusion and stenosis of precerebral arteries 434 Occlusion and stenosis of cerebral arteries 436 Acute, but ill-defined, cerebrovascular disease
Chronic obstructive pulmonary disease (COPD)	491.0-492.9, 496.0-496.9	491 Chronic bronchitis, 492 Emphysema, 496 Chronic airway obstruction, not elsewhere classified
Acute or chronic renal failure	584.0-586.9	584 Acute kidney failure, 585 Chronic kidney disease, 586 Renal failure unspecified
Hyperthyroidism	240.0-243.9	240 Simple and unspecified goiter, 241 Nontoxic nodular goiter, 242 Thyrotoxicosis with or without goiter
Cerebrovascular disease	430.0-437.9	430 Subarachnoid hemorrhage, 431 Intracerebral hemorrhage, 432 Other and unspecified intracranial hemorrhage, 433 Occlusion and stenosis of precerebral arteries, 434 Occlusion of cerebral arteries, 435 Transient

Comorbidity	ICD-9 Codes	Description
		cerebral ischemia, 436 Acute but ill-defined cerebrovascular disease, 437 Other ill-defined cerebrovascular disease
Peripheral vascular disease	440.2-440.8, 443.1, 443.8-443.9, 444.2,	440.2 Atherosclerosis of native arteries of the extremities, 440.3 Atherosclerosis of bypass graft of the extremities, 440.4 Chronic total occlusion of artery of the extremities, 440.8 Atherosclerosis of other specified arteries, 443.1 Thromboangiitis obliterans, 443.8 Other specified peripheral vascular diseases, 443.9 Peripheral vascular disease unspecified, 444.2 Arterial embolism and thrombosis of arteries of the extremities
Cancer	140.0-209.6	140-149 Malignant neoplasm of lip, oral cavity, and pharynx, 150-159 Malignant neoplasm of digestive organs and peritoneum, 160-165 Malignant neoplasm of respiratory and intrathroacic organs, 170-176 Malignant neoplasm of bone, connective tissue, skin, and breast, 179-189 Malignant neoplasm of genitourinary organs, 190-199 Malignant neoplasm of other and unspecified sites, 200-208 Malignant neoplasm of lymphatic and hematopoietic tissue, 209 Neuroendocrine tumors
Unstable angina	411.0-411.1, 411.81, 411.89	411.0 Postmyocardial infarction syndrome, 411.1 Intermediate coronary syndrome, 411.81 Acute coronary occlusion without myocardial infarction, 411.89 Other (coronary insufficiency (acute), subendocardial ischemia)
Other arrhythmias (excl. atrial fibrillation)	426.0-427.2, 427.4-427.9	426.0 Atrioventricular block, complete, 426.1 Atrioventricular block, other and unspecified, 426.2 Left bundle branch hemiblock, 426.3 Left bundle branch block, 426.4 Right bundle branch block, 426.5 Bundle branch block, other and unspecified, 426.6 Other heart block, 426.7 Anomalous atrioventricular excitation, 426.8 Other specified conduction disorders, 426.9 Conduction disorder, unspecified, 427.0 Paroxysmal supraventricular tachycardia, 427.1 Paroxysmal ventricular tachycardia, 427.2 Paroxysmal tachycardia, unspecified, 427.4 Ventricular fibrillation and flutter, 427.5 Cardiac arrest, 427.6 Premature beats, 427.8 Other specified cardiac dysrhythmias, 427.9 Cardiac dysrhythmia, unspecified

Appendix 2 Drugs used to define comorbidities

Comorbidity	**Drug or drug algorithm**
Diabetes	If any of the following: acetohexamide, chlorpropamide, gliclazide, glimepiride, glyburide, tolbutamide, metformine, metformine/rosiglitazone, acarbose, nateglinide, repaglinide, pioglitazone, rosiglitazone, insulin isophane (boeuf),insulin isophane (porc), insulin isophane (búuf et porc), insuline zinc (boeuf), insuline zinc (porc), insulin zinc (búuf et porc), insulin zinc/isophane (porc), insuline protamine zinc (boeuf), insuline protamine zinc (porc), insulin protamine zinc (búuf et porc), insulin globine zinc, insulin sulfate, insulin semi-lente (búuf et porc), insulin lente(porc), insulin lente (búuf et porc), insulin ultralente (búuf et porc), human insulin, human insulin isophane, human insulin zinc, human insulin zinc/isophane, human insulin lente, human insulin ultralente, insulin aspart, insulin lispro, insulin lispro/protamine, insulin lispro isophane, insuline glargine, aiguille jetable pour auto-injecteur d'insuline, seringue avec aiguille jetable pour insuline, rÈactif quantitatif du glucose dans le sang
Hypertension	If: -Diuretic and no digoxin -Beta blocker or timolol and no nitrate -Calcium channel blocker and no nitrate -ACE inhibitor and no loop diuretic or digoxin -ARB and no loop diuretic or digoxin -Beta blocker or timolol and no loop diuretic or digoxin -Combination diuretic -Any of: Prazosin, clonidine, hydralazine, methyldopa, minoxidil Diuretic: amiloride, amiloride/HCTZ, bendroflumethiazide, chlorthalidone, HCTZ, indapamide, methyclothiazide, metolazone, triamterene, spironolactone/HCTZ, triamterene/HCTZ Digoxin: digitoxin, digoxin Beta-blocker: acebutolol, atenolol, bisoprolol, labetalol, metoprolol, nadolol, oxprenolol, pindolol, propranolol Nitrate: isosorbide-5-mononitrate, isosorbide dinitrate, pentaerythritol tetranitrate(Peritrate), trinitrate de glyceryle Calcium channel blocker amlodipine, diltiazem, felodipine, nicardipine, nifedipine, verapamil, verapamil/trandolapril ACE inhibitors: benazepril, captopril, cilazapril, enalapril, fosinopril, lisinopril, perindopril, quinapril, ramipril, trandolapril Loop diuretic: ethacrynic acid, furosemide, torsemide ARB: candesartan, eprosartan, irbesartan, losartan, telmisartan, valsartan Combination diuretic: nadolol/bendroflumethiazide, atenolol/chlorthalidone, pindolol/HCTZ, cilazapril/HCTZ, enalapril/HCTZ, lisinoril/HCTZ, perindopril/indapamide,

	quinapril/HCTZ, candesartan/HCTZ, eprosartan/HCTZ, irbesartan/HCTZ, losartan/HCTZ, telmisartan/HCTZ, valsartan/HCTZ
Congestive heart failure	If: -Beta-blocker and loop diuretic -Loop diuretic and digoxin -ACE inhibitor and loop diuretic or digoxin -ARB and loop diuretic or digoxin - Loop diuretic and beta-blocker and ACE inhibitor - Loop diuretic and beta-blocker and ARB for CHF - Loop diuretic and ACE inhibitor and (spironolactone or diuretic) - Loop diuretic and digoxin and nitrate and hydralazine Loop diuretic: ethacrynic acid, furosemide, torsemide Beta-blockers: bisoprolol, carvedilol, metoprolol Digoxin: digitoxin, digoxin ACE inhibitors: benazepril, captopril, cilazapril, enalapril, fosinopril, lisinopril, perindopril, quinapril, ramipril, trandolapril ARB: candesartan, eprosartan, irbesartan, losartan, telmisartan, valsartan ARB for CHF: candesartan, valsartan Diuretic: amiloride, amiloride/HCTZ, bendroflumethiazide, chlorthalidone, HCTZ, indapamide, methyclothiazide, metolazone, triamterene, spironolactone/HCTZ, triamterene/HCTZ Spironolactone: spironolactone Nitrate: isosorbide-5-mononitrate, isosorbide dinitrate, pentaerythritol tetranitrate(Peritrate), trinitrate de glyceryle
Chronic obstructive pulmonary disease	If at least one of: xanthine derivative, beta 2 agonists, combination beta 2 agonists, beclomethasone, budesonide, flunisolide, fluticasone, triamcinolone acetonide, anticholinergic Xanthine derivatives: aminophylline, bufylline, diphylline, theophylline, oxtriphylline Beta 2 agonists: fenoterol, formoterol, orciprenaline, pirbuterol, procaterol, salbutamol, salmeterol, terbutaline Combination beta 2 agonists: formoterol/budesonide, salmeterol/fluticasone Anticholinergics: ipratropium, ipratropium/fenoterol, ipratropium/salbutamol, tiotropium
Acute or chronic renal failure	If: -darbepoetine alfa or epoetine and no cancer -sevelamer
Hyperthyroidism	If any of: potassium (iodure de), methimazole, propylthiouracile
Cerebrovascular disease	Nimodipine
Peripheral vascular disease	Pentoxifylline

Cancer	If any of the following: altretamine, anastrozole, bicalutamide, bleomycin, busulfan, capecitabine, carboplatin, cisplatin, cladribine, cytarabine, dactinomycine, daunorubicine, docetaxel, dacarbazine, doxorubicin, epirubicine, estramustine, etoposide, exemestane, 5-FU, fludarabine, flutamide, formestane, hydroxyurea, idarubicine, ifosfamide, irinotecan, letrozole, levamisole, lomustine, mechlorethamine, melphalan, mitomycine, mitoxantrone, nilutamide, paclitaxel, procarbazine, tamoxifene, temozolomide, thioguanine, thiotepa, topotecan, trastuzumab, vinblastine, vincristine, vindesine, vinorelbine

Appendix 3 Drug List

Type of medication	Medications included
Antiarrhythmics*	Disopyramide Flecainide Mexiletine Procainamide Propafenone Quinidine Tocainide
Calcium channel blockers	Amlopidine Diltiazem Felodipine Nicardipine Nifedipine Verapamil Verapamil/trandolapril
Beta blockers	Aceutolol Atenonlol Bisoprolol Labetalol Metoprolol Nadolol Oxprenolol Pindolol Propanolol Carvedilol Timolol (tablets)
Digoxin	Digitoxin Digoxin
Angiotensin-converting-enzyme inhibitors (ACE inhibitors)	Benazepril Captopril Cilazapril Enalapril Fosinopril Lisinopril Perindopril Quinapril Ramipril Trandolapril
Angiotensin II receptor antagonists (ARBs)	Candesartan Eprosartan Irbesartan Losartan Telmisartan Valsartan

Diuretics	Amiloride Amiloride/HCTZ Bendroflumethiazide Chlorthalidone Hydrochlorothiazide (HCTZ) Indapamide Methyclothiazide Metolazone Triamterene Spironolactone Spironolactone/HCTZ Triamterene/HCTZ
Lipid-modifying agents	Cholestyramine Colestipol Bezafibrate Clofibrate Fenofibrate Gemfibrozil Niacin Probucol Atorvastatin Cerivastatin Fluvastatin Lovastatin Pravastatin Rosuvastatin Simvastatin
Diabetes medications	Acetohexamide Chlorpropamide Gliclazide Glimepiride Glyburide Tolbutamide Metformin Metformin/rosiglitazone Acarbose Nateglinide Repaglinide Pioglitazone Rosiglitazone Insulin, isophane (bovine) Insulin, isophane (porcine) Insulin, isophane (bovine and porcine) Insulin, zinc (bovine) Insulin, zinc (porcine) Insulin, zinc (bovine and porcine)

	Insulin, zinc/isophane (porcine) Insulin, protamine zinc (bovine) Insulin, protamine zinc (porcine) Insulin, protamine zinc (bovine and porcine) Insulin, globine zinc Insulin, sulfated Insulin, semi-lente (bovine and porcine) Insulin, lente (porcine) Insulin, lente (bovine and porcine) Insulin, ultralente (bovine and porcine) Insulin, human Insulin, isophane (human) Insulin, zinc (human) Insulin, zinc/isophane (human) Insulin, lente (human) Insulin, ultralente (human) Insulin, aspart Insulin, lispro Insulin, lispro/protamine Insulin, lispro isophane Insulin, glargine Disposable needle for insulin auto-injector Disposable syringe with needle for insulin Quantitative reagent in blood glucose

*Amiodarone and sotalol are not included in antiarrhythmics as they are the exposure of interest

Appendix 4 Number of dispensed sotalol and amiodarone prescriptions per year for the base cohort and for all in the prescription drugs database

Year	Base Cohort		Prescription drugs database*	
	Sotalol	**Amiodarone**	**Sotalol**	**Amiodarone**
1993	407	36	7,963	1,901
1994	811	127	11,473	2,966
1995	1,545	374	15,590	4,478
1996	1,942	539	19,089	6,208
1997	2,132	648	22,629	10,119
1998	2,535	915	25,291	14,952
1999	2,826	1,788	28,023	22,029
2000	3,022	2,723	29,673	30,441
2001	2,971	3,669	29,844	39,692
2002	3,063	4,341	29,393	47,487
2003	2,867	4,336	27,906	54,040

*The prescription drugs database consists of all prescriptions for individuals who had a revascularisation procedure (CABG or PCI) between 1993 and 2003 inclusive

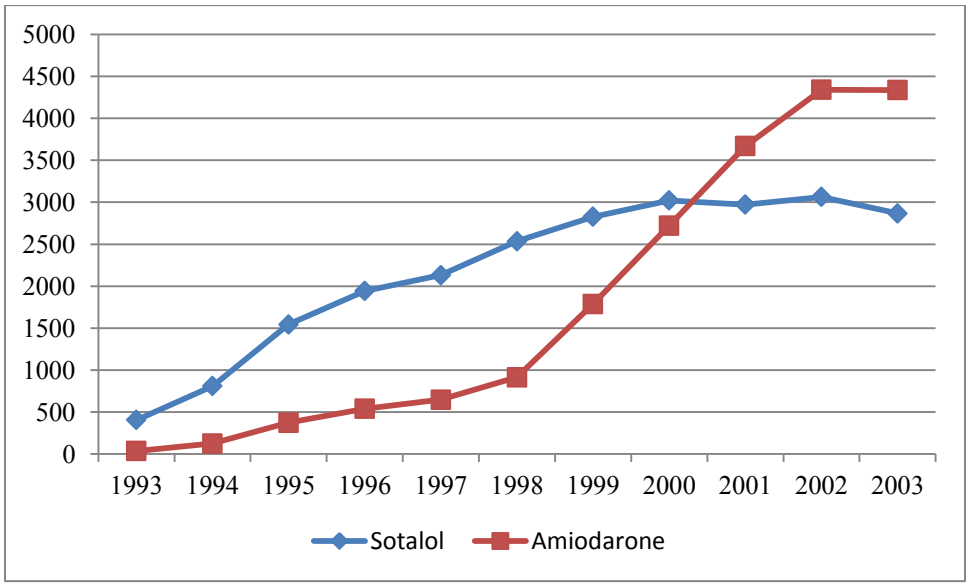

Figure 2 Number of dispensed sotalol and amiodarone prescriptions per year for the base cohort

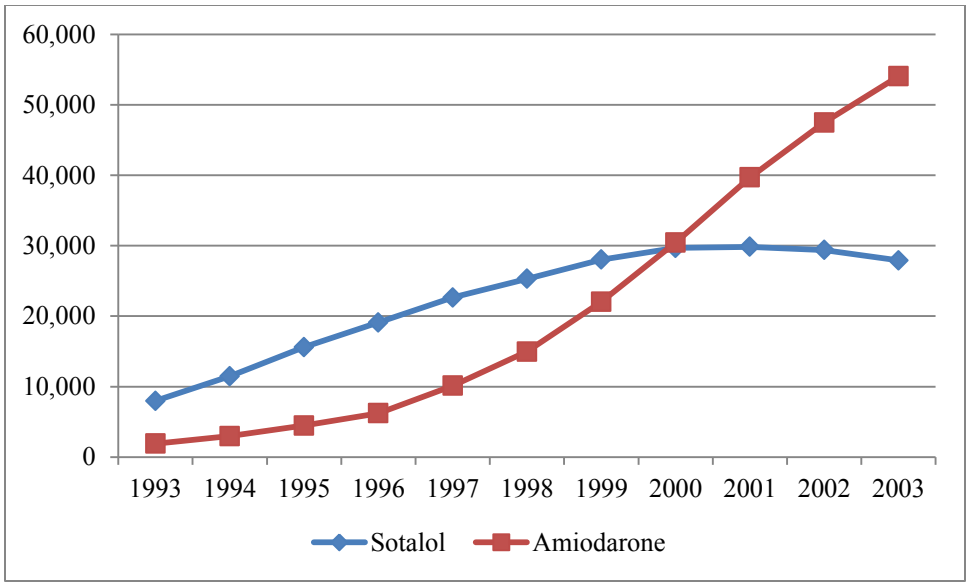

Figure 3 Number of dispensed sotalol and amiodarone prescriptions per year for everyone who had a revascularisation procedure between 1993 and 2003

Appendix 5 Sotalol and amiodarone use amongst death cases and controls (30 day lag period)

Current use of sotalol or amiodarone	Cases (n=930)	Controls (n=4648)	Crude RR (95%CI)	Adjusted (full) RR (95% CI)*	P value (full)
Neither	794(85.4)	3981(85.7)	1.00	1.00 (ref.)	Reference
Sotalol	41 (4.4)	387 (8.3)	0.52 (0.37, 0.73)	0.57 (0.41, 0.80)	.001
Amiodarone	95 (10.2)	280 (6.0)	1.74 (1.35, 2.23)	1.50 (1.15, 1.94)	.003

* Adjusted for: age at cohort entry, sex, hospital stay, Charlson Index, diabetes, hypertension, previous MI, CHF, COPD, renal failure, cerebrovascular disease, peripheral vascular disease, previous stroke, hyperthyroidism, cancer, use of antiarrhythmics, calcium channel blockers, digoxin, ACE inhibitors, lipid modifiers, ARBs, diabetes medications, beta-blockers, diuretics, anti-coagulants, and anti-platelet agents in the year before cohort entry

Appendix 6 Sotalol and amiodarone use amongst death cases and controls (7 day lag period)

Current use of sotalol or amiodarone	Cases (n=930)	Controls (n=4648)	Crude RR (95%CI)	Adjusted (full) RR (95% CI)*	P value (full)
Neither	820 (88.2)	4134(88.9)	1.00	1.00 (ref.)	Reference
Sotalol	37 (4.0)	358 (7.7)	0.50 (0.35, 0.71)	0.55 (0.38, 0.79)	.001
Amiodarone	73 (7.9)	256 (5.5)	1.42 (1.07, 1.86)	1.20 (0.90, 1.60)	.21

* Adjusted for: age at cohort entry, sex, hospital stay, Charlson Index, diabetes, hypertension, previous MI, CHF, COPD, renal failure, cerebrovascular disease, peripheral vascular disease, previous stroke, hyperthyroidism, cancer, use of antiarrhythmics, calcium channel blockers, digoxin, ACE inhibitors, lipid modifiers, ARBs, diabetes medications, beta-blockers, diuretics, anti-coagulants, and anti-platelet agents in the year before cohort entry

Appendix 7 Sotalol and amiodarone use amongst death cases and controls (Rx dispensed within 30 days of index)

Current use of sotalol or amiodarone	Cases (n=930)	Controls (n=4648)	Crude RR (95%CI)	Adjusted (full) RR (95% CI)*	P value (full)
Neither	838 (90.1)	4092(88.0)	1.00	1.00 (ref.)	Reference
Sotalol	31 (3.3)	316 (6.8)	0.47 (0.32, 0.69)	0.52(0.35, 0.76)	<.001
Amiodarone	61 (6.6)	240 (5.2)	1.25 (0.93, 1.67)	1.01 (0.75, 1.38)	.93

*Adjusted for: age at cohort entry, sex, hospital stay, Charlson Index, diabetes, hypertension, previous MI, CHF, COPD, renal failure, cerebrovascular disease, peripheral vascular disease, previous stroke, hyperthyroidism, cancer, use of antiarrhythmics, calcium channel blockers, digoxin, ACE inhibitors, lipid modifiers, ARBs, diabetes medications, beta-blockers, diuretics, anti-coagulants, and anti-platelet agents in the year before cohort entry

Appendix 8 Sotalol and amiodarone use amongst cases and controls (restricted to those who were not hospitalised in the 30 days before index)

Current use of sotalol or amiodarone	Cases (n=240)	Controls (n=1130)	Crude RR (95%CI)	Adjusted (full) RR (95% CI)*	P value (full)
Neither	218 (90.8)	996(88.1)	1.00	1.00 (ref.)	Reference
Sotalol	5 (2.1)	68 (6.0)	0.33 (0.13, 0.84)	0.32 (0.12 0.84)	.02
Amiodarone	17 (7.1)	66 (5.8)	1.14 (0.65, 1.99)	1.01 (0.57, 1.78)	.98

* Adjusted for: age at cohort entry, sex, hospital stay, Charlson Index, diabetes, hypertension, previous MI, CHF, COPD, renal failure, cerebrovascular disease, peripheral vascular disease, previous stroke, hyperthyroidism, cancer, use of antiarrhythmics, calcium channel blockers, digoxin, ACE inhibitors, lipid modifiers, ARBs, diabetes medications, beta-blockers, diuretics, anti-coagulants, and anti-platelet agents in the year before cohort entry

Appendix 9 Sotalol and amiodarone use amongst death cases and controls (Index changed to hospital admission for cases who died in hospital and their controls)

Current use of sotalol or amiodarone	Cases (n=240)	Controls (n=1130)	Crude RR (95%CI)	Adjusted (full) RR (95% CI)*	P value (full)
Neither	218 (90.8)	996(88.1)	1.00	1.00 (ref.)	Reference
Sotalol	5 (2.1)	68 (6.0)	0.65 (0.47, 0.90)	0.71 (0.51, 0.98)	.04
Amiodarone	17 (7.1)	66 (5.8)	1.93 (1.51, 2.46)	1.66 (1.29, 2.14)	<.001

* Adjusted for: age at cohort entry, sex, hospital stay, Charlson Index, diabetes, hypertension, previous MI, CHF, COPD, renal failure, cerebrovascular disease, peripheral vascular disease, previous stroke, hyperthyroidism, cancer, use of antiarrhythmics, calcium channel blockers, digoxin, ACE inhibitors, lipid modifiers, ARBs, diabetes medications, beta-blockers, diuretics, anti-coagulants, and anti-platelet agents in the year before cohort entry

Appendix 10 Sotalol and amiodarone use amongst death cases and controls by sex

Exposure category (sex*current use)	Cases (n=930)	Controls (n=4648)	Crude RR (95%CI)	Adjusted (full) RR (95% CI)*	P value (full)
Female*neither	210 (22.6)	1110 (23.7)	1.00	1.00 (ref.)	Ref.
Female*sotalol	9 (1.0)	84 (1.8)	0.57 (0.28, 1.15)	0.65 (0.32, 1.34)	.25
Female*amiodarone	26 (2.8)	71 (1.5)	2.04 (1.25, 3.32)	1.69 (1.01, 2.82)	.04
Male*neither	588 (63.2)	2900 (61.9)	1.07 (0.90, 1.27)	1.14 (0.95, 1.37)	.16
Male*sotalol	28 (3.0)	274 (5.9)	0.87 (0.38, 1.95)	0.82 (0.36, 1.87)	.63
Male*amiodarone	69 (7.4)	209 (4.5)	0.81 (0.46, 1.43)	0.85 (0.47, 1.53)	.59

* Adjusted for: age at cohort entry, sex, hospital stay, Charlson Index, diabetes, hypertension, previous MI, CHF, COPD, renal failure, cerebrovascular disease, peripheral vascular disease, previous stroke, hyperthyroidism, cancer, use of antiarrhythmics, calcium channel blockers, digoxin, ACE inhibitors, lipid modifiers, ARBs, diabetes medications, beta-blockers, diuretics, anti-coagulants, and anti-platelet agents in the year before cohort entry

Appendix 11 Sotalol and amiodarone use amongst death cases and controls by renal failure

Exposure category (renal status*current use)	Cases (n=930)	Controls (n=4648)	Crude RR (95%CI)	Adjusted (full) RR (95% CI)*	P value (full)
No renal failure*neither	668 (71.8)	3608 (77.0)	1.00	1.00 (ref.)	Ref.
No renal failure*sotalol	35 (3.8)	334 (7.1)	0.25 (0.06, 1.08)	0.33 (0.08, 1.41)	.14
No renal failure*amiodarone	74 (8.0)	233 (5.0)	1.35 (0.77, 2.37)	1.22 (0.68, 2.19)	.51
Renal failure*neither	130 (14.0)	402 (8.6)	1.77 (1.42, 2.20)	1.08 (0.82, 1.42)	.58
Renal failure*sotalol	2 (<0.1)	24 (<0.1)	2.18 (0.49, 9.77)	1.80 (0.39, 8.20)	.45
Renal failure*amiodarone	21 (2.3)	47 (1.0)	1.30 (0.69, 2.43)	1.30 (0.67, 2.49)	.44

* Adjusted for: age at cohort entry, sex, hospital stay, Charlson Index, diabetes, hypertension, previous MI, CHF, COPD, renal failure, cerebrovascular disease, peripheral vascular disease, previous stroke, hyperthyroidism, cancer, use of antiarrhythmics, calcium channel blockers, digoxin, ACE inhibitors, lipid modifiers, ARBs, diabetes medications, beta-blockers, diuretics, anti-coagulants, and anti-platelet agents in the year before cohort entry

Appendix 12 Characteristics of any CV hospitalisation cases and controls

Characteristic	Cases (n=1992)	Controls (n=9944)	P value
Age (mean (SD))			
At cohort entry	73.2(4.6)	72.5(4.6)	<.001
At index date	75.4(4.9)	74.7(4.9)	<.001
Sex (%)			<.001
Female	30.7	26.1	
Male	69.3	73.9	
Follow-up (mean(SD) days)	802(881)	802(879)	>.99
Comorbid conditions (%)*			
Hypertension	74.1	71.9	.045
Cerebrovascular disease	16.0	10.3	<.001
Peripheralvascular disease	13.3	9.1	<.001
Previous MI	47.8	43.8	<.001
Congestive heart failure	36.2	24.7	<.001
Previous stroke	13.5	8.3	<.001
Diabetes	30.4	23.0	<.001
COPD	29.9	21.8	<.001
Acute or chronic renal disease	15.1	9.4	<.001
Hyperthyroidism	1.0	0.8	.38
Cancer	4.0	4.0	.91
Charlson Comorbidity Index*			
Mean (SD) Charlson Index score	2.3(1.8)	1.8(1.5)	<.001
Charlson Index score (%)			<.001
0	13.5	19.6	
1	25.5	32.4	
2	22.3	21.7	
≥ 3	38.7	26.3	
Use of concomitant treatment (%)*			
Antiarrhythmics†	2.0	1.3	.02
Calcium channel blockers	64.6	57.8	<.001
Beta blockers	56.5	52.2	<.001
Digoxin	12.3	7.2	<.0001
Lipid modifying agents	37.2	39.4	.06
ACE inhibitors	34.2	25.5	<.001
ARBs	3.5	4.5	.03
Diuretics	20.7	17.7	.002
Anticoagulants	6.0	8.8	<.001
Anti-platelet agents	63.0	64.3	.29
Diabetes medications	25.1	18.3	<.001

Length of post-surgical hospital stay			
Mean (SD) hospital stay	12.6(6.2)	11.3(5.7)	<.001
Hospital stay (%)			<.001
≤ 10 days	49.2	59.2	
> 10 days	50.8	40.8	

*In the year before cohort entry
†Except amiodarone or sotalol

Appendix 13 Characteristics of sotalol and amiodarone users in the 'any CV hospitalisation' cohort

Characteristic	Sotalol (n=1370)	Amiodarone (n=1042)	Neither (n=9522)	P value
Age (mean (SD))				
At cohort entry	71.9(4.5)	73.2(4.9)	72.6(4.6)	
At index date	73.4(4.9)	73.9(5.0)	75.01(4.9)	
Sex (%)				.95
Female	27.1	26.5	26.9	
Male	72.9	73.5	73.1	
Follow-up (mean(SD) days)	516(780)	273 (591)	901(890)	
Comorbid conditions (%)*				
Hypertension	73.0	76.9	71.7	.001
Cerebrovascular disease	12.3	15.7	10.6	<.001
Peripheralvascular disease	8.4	12.0	9.7	.01
Previous MI	41.2	51.2	44.2	<.001
Congestive heart failure	24.0	39.9	25.5	<.001
Previous stroke	10.4	12.7	8.7	<.001
Diabetes	23.9	32.2	23.5	<.001
COPD	17.9	30.1	23.1	<.001
Acute or chronic renal disease	7.2	16.9	10.1	<.001
Hyperthyroidism	0.6	1.0	0.8	.56
Cancer	3.1	5.1	4.0	.04
Charlson Comorbidity Index*				
Mean (SD) Charlson Index score	1.7(1.5)	2.4(1.8)	1.8(1.6)	
Charlson Index score (%)				<.001
0	22.1	10.3	19.0	
1	32.8	24.8	31.8	
2	21.3	23.6	21.6	

≥ 3	23.8	41.4	27.6	
Use of concomitant treatment (%)*				
Antiarrhythmics†	1.2	2.8	1.3	<.001
Calcium channel blockers	58.1	55.5	59.4	.04
Beta blockers	65.4	52.4	54.7	<.001
Digoxin	8.5	7.7	8.0	.77
Lipid modifying agents	42.1	48.3	37.5	<.001
ACE inhibitors	27.3	35.2	26.0	<.001
ARBs	2.2	7.7	3.4	<.001
Diuretics	18.1	22.7	17.7	<.001
Anticoagulants	4.2	7.4	6.7	.001
Anti-platelet agents	65.0	63.9	62.9	.29
Diabetes medications	18.5	26.4	18.8	<.001
Length of post-surgical hospital stay				
Mean (SD) hospital stay	10.7(5.3)	13.1(6.4)	11.5(5.8)	
Hospital stay (%)				<.001
≤ 10 days	63.8	42.9	58.3	
> 10 days	36.2	57.1	41.8	

*In the year before cohort entry
†Except amiodarone or sotalol

Appendix 14 Sotalol and amiodarone use amongst any CV hospitalisation cases and controls

Current use of sotalol or amiodarone	Cases (n=1991)	Controls (n=9940)	Crude RR (95%CI)	Adjusted (full) RR (95% CI)*	P value (full)
Neither	1557(78.2)	7962(80.1)	1.00	1.00 (ref.)	Reference
Sotalol	213 (10.7)	1157 (11.6)	0.95 (0.81, 1.12)	1.07 (0.91, 1.27)	.41
Amiodarone	221 (11.1)	821 (8.3)	1.47(1.23, 1.75)	1.31 (1.09, 1.57)	.004

*Adjusted for: age at cohort entry, sex, hospital stay, Charlson Index, diabetes, hypertension, previous MI, CHF, COPD, renal failure, cerebrovascular disease, peripheral vascular disease, previous stroke, hyperthyroidism, cancer, use of antiarrhythmics, calcium channel blockers, digoxin, ACE inhibitors, lipid modifiers, ARBs, diabetes medications, beta-blockers, diuretics, anti-coagulants, and anti-platelet agents in the year before cohort entry

Appendix 15 Characteristics of MI cases and controls

Characteristic	Cases (n=343)	Controls (n=1715)	P value
Age (mean (SD))			
At cohort entry	72.6(4.5)	72.3(4.6)	.27
At index date	75.8(5.1)	75.5(5.1)	.32
Sex (%)			.01
Female	33.5	26.9	
Male	66.5	73.1	
Follow-up (mean(SD) days)	1163 (1008)	1164(1007)	>.99
Comorbid conditions (%)*			
Hypertension	77.0	68.9	.003
Cerebrovascular disease	16.0	11.6	.02
Peripheralvascular disease	18.1	9.5	<.001
Previous MI	50.4	41.8	.003
Congestive heart failure	33.5	24.0	.002
Previous stroke	12.8	9.5	.06
Diabetes	32.4	23.2	<.001
COPD	29.7	23.0	.008
Acute or chronic renal disease	12.5	10.6	.28
Hyperthyroidism	0.9	0.5	.34
Cancer	3.5	4.0	.68
Charlson Comorbidity Index*			
Mean (SD) Charlson Index score	2.3(1.8)	1.8(1.6)	<.001
Charlson Index score (%)			<.001
0	12.8	19.2	
1	27.1	32.3	
2	21.9	22.9	
≥ 3	38.2	25.6	
Use of concomitant treatment (%)*			
Antiarrhythmics†	2.3	1.5	.28
Calcium channel blockers	67.1	59.4	.008
Beta blockers	55.1	55.6	.87
Digoxin	11.4	7.8	.03
Lipid modifying agents	35.6	38.1	.37
ACE inhibitors	32.7	24.9	.003
ARBs	2.6	3.5	.41
Diuretics	18.4	16.1	.30
Anticoagulants	8.2	5.4	.04
Anti-platelet agents	63.3	63.2	.97
Diabetes medications	27.7	18.0	<.001

Length of post-surgical hospital stay			
Mean (SD) hospital stay	12.4(6.2)	11.4(5.6)	.008
Hospital stay (%)			.03
≤ 10 days	51.3	57.7	
> 10 days	48.7	42.3	

*In the year before cohort entry
†Except amiodarone or sotalol

Appendix 16 Characteristics of lorazepam users and non-users in the MI cohort

Characteristic	Lorazepam user (n=233)	Lorazepam non-users (n=1825)	P value
Age (mean (SD))			
At cohort entry	72.6(4.3)	72.4(4.6)	.41
At index date	75.7(4.6)	75.6(5.1)	.68
Sex (%)			<.001
Female	42.5	26.1	
Male	57.5	73.9	
Follow-up (mean(SD) days)	1126(1032)	1168 (1004)	.55
Comorbid conditions (%)*			
Hypertension	74.7	69.6	.11
Cerebrovascular disease	9.4	12.7	.15
Peripheralvascular disease	12.0	10.7	.56
Previous MI	47.2	42.7	.19
Congestive heart failure	26.2	25.5	.83
Previous stroke	7.7	10.3	.22
Diabetes	18.9	25.5	.03
COPD	24.9	24.1	.78
Acute or chronic renal disease	9.0	11.1	.33
Hyperthyroidism	0.4	0.56	.81
Cancer	3.9	3.9	.98
Charlson Comorbidity Index*			
Mean (SD) Charlson Index score	1.9(1.4)	1.9(1.7)	.50
Charlson Index score (%)			.06
0	12.5	18.	
1	31.3	31.5	
2	27.5	22.1	
≥ 3	28.8	27.6	

Use of concomitant treatment (%)*			
Antiarrhythmics†	2.2	1.6	.53
Calcium channel blockers	63.1	60.3	.42
Beta blockers	55.4	55.5	.97
Digoxin	10.3	8.1	.26
Lipid modifying agents	48.1	36.4	<.001
ACE inhibitors	23.6	26.5	.34
ARBs	4.3	3.2	.40
Diuretics	20.2	16.0	.11
Anticoagulants	6.9	5.7	.47
Anti-platelet agents	67.0	62.7	.20
Diabetes medications	15.9	20.1	.13
Length of post-surgical hospital stay			
Mean (SD) hospital stay	11.6(5.7)	11.6(5.7)	.96
Hospital stay (%)			.66
≤ 10 days	57.9	56.4	
> 10 days	42.1	43.6	

*In the year before cohort entry
†Except amiodarone or sotalol

Appendix 17 Current lorazepam use amongst MI cases and controls

Current use of lorazepam	Cases (n=343)	Controls (n=1785)	Crude RR (95%CI)	Adjusted (full) RR (95% CI)*	P value (full)
Non-user	305(88.9)	1520(88.6)	1.00	1.00 (ref.)	Reference
Lorazepam	38 (11.1)	195 (11.4)	0.97 (0.68, 1.40)	0.91 (0.62, 1.33)	.62

*Adjusted for: age at cohort entry, sex, hospital stay, Charlson Index, diabetes, hypertension, previous MI, CHF, COPD, renal failure, cerebrovascular disease, peripheral vascular disease, previous stroke, hyperthyroidism, cancer, use of antiarrhythmics, calcium channel blockers, digoxin, ACE inhibitors, lipid modifiers, ARBs, diabetes medications, beta-blockers, diuretics, anti-coagulants, and anti-platelet agents in the year before cohort entry