The Effect of Antidepressants on Cardiovascular Morbidity and Mortality: A Population-based Cohort Study

By

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Abstract

Background: **A**ntidepressants such as selective serotonin reuptake inhibitors (SSRIs) and venlafaxine have the potential to exert beneficial effects on the heart via serotonin mediated antiplatelet activity. However, previous evidence regarding the cardiovascular effects of these agents has been conflicting. There is a need for further investigation into the risks and benefits of these drugs.

Objective: To assess the risk of acute MI and cardiac death associated the use of various classes of antidepressants, and determine whether this risk is modified by the presence of predisposing factors.

Methods: We identified a population-based, retrospective cohort study of 71,253 elderly persons initiating treatment with an antidepressant between 1997 and 2004. The cohort was analyzed using nested case-control approach with each case of acute MI or cardiac death matched with up to 20 controls according to age (±1 year), duration of follow-up, and year of cohort entry. Rate ratios for acute MI and cardiac death associated with the current use of various antidepressants were estimated using conditional logistic regression and adjusted for potential confounders.

Results: Compared with the current use of atypical antidepressants, current use of venlafaxine was associated with a significant reduction in the risk of MI and cardiac death (rate ratio [RR] 0.80 [95% CI 0.66 to 0.97]) that was more pronounced in persons with established cardiovascular disease (CVD) (RR 0.65 [CI 0.50 to 0.86]). We found no clear evidence of a benefit or harm associated with the use of SSRIs (RR 0.92 [CI 0.79 to 1.06]), although there was the suggestion of a clinically important benefit from treatment

with SSRIs for individuals who had history of MI (RR 0.68 [CI 0.44 to 1.07]). No benefit or harm was observed with other classes of antidepressants.

Conclusions: These results demonstrate a reduced risk for acute MI and cardiac death associated with current use of venlafaxine among elderly persons. This beneficial effect appears to be more pronounced in those with established cardiovascular disease. No clear evidence of benefit on CV outcomes was associated with the current use of SSRIs, although results suggest a potential benefit for use in persons with a previous MI.

Co-Authorship Statement

This thesis presents research conducted by Greg Kennedy, in collaboration with Linda Lévesque and Kristan Aronson.

Manuscript: The research question regarding the association between antidepressants and cardiovascular morbidity and mortality was provided by Linda Lévesque, with collaboration from Greg Kennedy and Kristan Aronson. The primary investigator and author of the manuscript was Greg Kennedy, who conducted the statistical analyses with guidance from Linda Lévesque. Methodology, statistical design, and interpretation were a collaboration of Greg Kennedy and supervisors Linda Lévesque and Kristan Aronson. The manuscript was written by Greg Kennedy, with editing assistance and consultation from Linda Lévesque and Kristan Aronson.

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Table of Contents

List of Tables and Figures

List of Abbreviations

CVD	Cardiovascular Disease
CV	Cardiovascular
WHO	World Health Organization
SSRI	Selective Serotonin Reuptake Inhibitor
RCT	Randomized Controlled Trial
SNRI	Serotonin Norepinephrine Reuptake Inhibitor
NSAID	Non-steroidal Anti-inflammatory Drug
MI	Myocardial Infarction
CAD	Coronary Artery Disease
IHD	Ischemic Heart Disease
CHD	Coronary Heart Disease
CHF	Congestive Heart Failure
CABG	Coronary Artery Bypass Graft
ANS	Autonomic Nervous System
SNS	Sympathetic Nervous System
HRV	Heart Rate Variability
ECG	Electrocardiogram
TCA	Tricyclic Antidepressant
5-HT	5-hydroxytryptamine (serotonin)
NE	Norepinephrine
MAOI	Monoamine Oxidase Inhibitor
ENRICHD	Enhancing Recovery in Coronary Heart Disease Trial
SADHART	Sertraline Antidepressant Heart Attack Randomized Trial
CBT	Cognitive Behavioural Therapy
ISQ	Institut de la Statistique du Québec
NAM	Numéro d'Assurance-Maladie
ICD	International Classifcation of Diseases
ACE-I	Angiotensin Converting Enzyme Inhibitor
ARB	Angiotensin Receptor Blocker
HRT	Hormone Replacement Therapy
COX-2	Cyclooxygenase-2 Inhibitor
SES	Socioeconomic Status
RR	Rate Ratio
HR	Hazard Ratio
NDRI	Norepinephrine Dopamine Reuptake Inhibitor
5-HT	5-Hydroxytryptamine
RAMQ	Régie de l'Assurance Maladie du Québec

Chapter 1: General Introduction

Background

Cardiovascular disease (CVD) is a major cause of illness, disability, and death in Canada. As such, CVD is an important public health issue both in terms of quality of life and health expenditures. Despite significant advances in the treatment and prevention of CVD, it remains the leading cause of hospitalizations and death in Canada, claiming over 75,000 lives each year.[1] CVD is also an important determinant of premature death, exceeded only by cancer and injuries in terms of person years of life lost.[2] As the largest contributor to total health care expenditures in Canada, CVD is estimated to cost the economy over $18 billion annually.[3] It is therefore not surprising that a major thrust of research in recent years has been the identification of additional cardiovascular (CV) risk factors that could potentially be modified to reduce incidence of this disease. As a result of these efforts, depression is now recognized as an important predictor of both the onset and progression of CVD.[4]

Approximately 8% of Canadians over the age of 18 will experience an episode of major depression at some point in their lives, and during any 12 month period an estimated 4% to 5% will have symptoms of major depression.[5] Depression is even more common among the elderly, with prevalence rates of 19-30%.[6, 7] According to the World Health Organization (WHO), major depression is now the leading cause of "years lived with disability" worldwide, and it is estimated that by 2020 major depression and ischemic heart disease will be the foremost contributors to the global burden of disease.[8] Depression is also four to six times more common among persons with coronary artery

disease compared to healthy individuals, and is associated with an increased risk of both cardiac morbidity and mortality.[4, 9]

For many years health professionals have recognized that individuals with heart disease are much more likely to become depressed. Several well-designed studies have confirmed that as many as 1 in 5 persons with heart disease will develop major depressive symptoms, and that these symptoms can seriously impede a person's chances of a full recovery. [4, 7, 9-13] However, it is only in recent years that depression has also been shown to be an important independent predictor of the onset and progression of cardiovascular disease and cardiac death.

It is generally believed that treatment of depression, usually done with antidepressants, will reduce cardiovascular morbidity and mortality, thus contributing to improved CV health. The majority of trials published to date have reported that a popular class of antidepressants, known as selective serotonin reuptake inhibitors (SSRIs), is well tolerated among people with CVD.[14, 15] However, a recent observational study has brought into question the safety of SSRIs, with findings of an increased risk of death from cardiovascular disease among users. As a result of the uncertainty that now exists regarding the overall risk-benefit of these agents, physicians may be reluctant to treat depression with pharmacotherapy.

Despite the large body of research evaluating the efficacy of antidepressants, evidence regarding the effects of these agents on cardiovascular endpoints is relatively sparse. Randomized controlled trials (RCTs) that have been conducted to assess antidepressant efficacy were underpowered and inadequately designed to detect clinically meaningful differences in CV outcomes. Similarly, observational studies published to

date have been plagued by methodological shortcomings and have exhibited discordant results. Most notably, all of these studies failed to control for the confounding effect of depression itself, which is likely the most important source of confounding by indication in the antidepressant-CVD association. In addition, there is no epidemiological study evaluating the cardiovascular effects of newer classes of antidepressants such as the serotonin-norepinephrine reuptake inhibitors (SNRIs).

Overview of Study Design

In this thesis, a cohort of all persons aged 66 years and older initiating therapy with an antidepressant between January 1, 1997 and December 31, 2004 was identified within an existing population-based cohort of new users of non-steroidal anti-inflammatory drugs (NSAIDs) available from a previous study of NSAID users. The source population was identified using the computerized health databases of the province of Québec. Members of the antidepressant use cohort were followed from the date of their first prescription until the earliest of one of the following dates: a) first study endpoint, b) non-cardiac death, c) end of health coverage, or d) end of study (March 31, 2005). The study outcome (acute myocardial infarction or cardiac death) was identified through record linkage of the beneficiary, hospital separations, and vital statistics databases. Given the large size of the cohort, the time-varying nature of drug exposure, and the potentially confounding effect of duration of follow-up (a proxy for duration treated depression), a time-matched nested case-control approach was used to analyze these cohort data. For each case, up to 20 controls matched on age (±1 year), days of follow-up, and year of cohort entry were randomly chosen. Using the beneficiary, prescription drugs, medical services, and hospitalizations databases, information was

obtained on exposure and covariates for all cases and matched controls. Rate ratios adjusted for potential confounders were estimated using conditional logistic regression to account for the individual level matching.

Empirical Objectives

The primary objective of this thesis is to assess the risk of acute myocardial infarction (MI) and cardiac death associated with exposure to various classes of antidepressants. More specifically to:

1. Assess and quantify the risk for the combined endpoint of acute MI and cardiac death associated with the current use of SSRI and SNRI antidepressants compared with that of atypical antidepressants.
2. Determine whether the risk of cardiovascular complications is modified by the presence of predisposing factors including: (i) age (<85 and ≥85 years of age), (ii) sex, (iii) previous myocardial infarction, (iv) cardiovascular disease, (v) history of diabetes, and vi) concomitant use of an antithrombotic.

Thesis Organization

The second chapter of this thesis is the literature review chapter which focuses on our current understanding of depression as a CV risk factor, the effects of various classes of antidepressants on CV outcomes, as well as the pharmacological and physiological factors postulated to mediate these effects. The third chapter will provide a detailed overview of the methodological considerations utilized in conducting the research. Chapter four contains the draft manuscript for publication of this research, and chapter

five is a discussion chapter that consists of study interpretations and conclusions, along with their implications for future research.

Contribution

This thesis will address an important controversy regarding the effects of antidepressants on cardiovascular morbidity and mortality. The proposed study will be the first to assess the cardiovascular effects of antidepressants independent of both the effects of depression itself, and also the duration of treated depression. The potential confounding effects of these two important factors (i.e., confounding by indication and by disease duration) will be controlled for through the use of an "all treated cohort" (i.e., all depressed individuals), a treated comparator, and a time-matched analysis. Thus, the research of this thesis is the first properly designed and sufficiently powered to address the cardiac safety of antidepressant drugs, both new and old. This information, combined with valuable insight gained through examining sub-groups, will contribute new knowledge for the management of depression vis-à-vis cardiac risk.

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Chapter 2: Literature Review

Depression as a Cardiovascular Risk Factor

For many years health professionals have recognized that individuals with heart disease are much more likely to become depressed than the general population. A number of well-designed studies have confirmed that as many as 1 in 5 persons with heart disease will develop major depressive symptoms, and that these symptoms can seriously impede a person's chances of a full recovery.[1-7] However, it is only in recent years that depression has also been shown as an important independent predictor of the onset and progression of cardiovascular disease, cardiac death, and overall mortality.

In healthy adults, the presence of depression confers a 1½ to 2-fold increased risk of developing coronary artery disease (CAD), or of dying from CAD.[1] End points that have been studied include acute myocardial infarction (MI)[8, 9], fatal ischemic heart disease (IHD)[10], and fatal coronary heart disease (CHD)[11-13]. Similarly among those with established heart disease, depression is associated with a 1½ to 2½-fold increased risk of cardiac morbidity and mortality.[1, 14] Individual studies have shown that the risk of death following an acute MI is 2 to 5-fold higher in those with depression[15, 16], and is similarly increased for congestive heart failure (CHF)[17] and among those undergoing coronary artery bypass surgery (CABG).[18] Thus, depression has detrimental effects on cardiac morbidity and mortality regardless of an individual's CV risk profile.

Other important considerations in the relationship between depression and CV risk are the potential roles of severity and duration of depression. Several studies have reported a risk gradient between depression scores, measured using various rating scales, and fatal and non-fatal CV events[5, 8, 11-13]; however, none evaluated the effect of duration

of depression on CV risks. Although a recent study reported an increased risk for CV events among patients with a longer history of treated depression,[19] a clear association between duration of depression and CV risk has yet to be established.

It is now clear that depression, depression severity, and possibly the duration of depression, are important determinants of CV events. As such, studies evaluating the association between antidepressants and CV risk need to control for the confounding effects of these factors. However, what is less clear is how depression duration contributes to cardiac morbidity and mortality.

Mediating Mechanisms: Depression and Cardiovascular Disease

Despite our increasing understanding of the underlying mechanisms leading to the development of depression, the biological processes linking depression to poor cardiovascular prognosis remain poorly understood. Postulated mechanisms include unhealthy lifestyle practices secondary to a depressed state, impaired immune and inflammatory responses, hypothalamic-pituitary-adrenal axis dysregulation, autonomic nervous system (ANS) dysregulation, and impaired platelet reactivity. Of these five proposed mechanisms, antidepressants, and SSRIs in particular, are thought to have a potential influence on the latter two only. As a result, the discussion below is limited to the effects of ANS dysregulation and impaired platelet reactivity on the cardiovascular system.

Dysregulation of the autonomic nervous system has been implicated in coronary heart disease. Reduced parasympathetic and increased sympathetic nervous system (SNS) activity has been linked to several cardiac risk factors including high blood pressure,[20] decreased vagal tone,[21] reduced heart rate recovery,[21] coronary vasoconstriction resulting

in myocardial ischemia,[22] as well as a lowered threshold for ventricular tachycardia, ventricular fibrillation, and sudden cardiac death[23]. Indicators of ANS dysregulation that have been found in depressed persons include elevated levels of plasma and urinary catecholamines[24] and increased resting heart rate[25].

Heart rate variability (HRV), a measure of fluctuation from mean heart rate, is one of the most widely used measures of cardiac autonomic activity in humans.[26] It has been repeatedly demonstrated that individuals with major depression have a reduced HRV,[27] that HRV is a strong predictor of mortality for those with CAD,[28] and it is thought to explain much of the effect of depression on cardiac mortality.[29]

Platelet reactivity is well established as a risk factor for the development and progression of atherosclerosis, acute coronary syndromes, and thrombosis, with increased reactivity increasing the risk of these outcomes.[30] Cross-sectional studies of depressed individuals have reported increased platelet reactivity in those with and without established CVD.[31, 32] Given that platelet activity is partially under the control of serotonin and that this neurotransmitter plays an important role in the development of depression, there is now a hypothesized link between platelet activity, depression, and CVD. Interestingly, the SSRIs have been shown to exert beneficial effects on serotonin-mediated platelet aggregation,[33] ANS dysregulation including HRV,[34] and elevated blood pressure [35]. On the other hand, antidepressants with differing mechanisms of action may actually have detrimental effects on the heart.

Antidepressants: Pharmacologic and Treatment Considerations

Antidepressants are classified according to their molecular structure, as is the case for the older agents known as the tricyclic and tetracyclic antidepressants (TCAs), or on the basis of their neurotransmitter activity, as is the case with newer agents (Appendix 1). Neurotransmitter activity is not only an important predictor of an agent's side effect profile, it is also indicative of the use of these agents for indications other than depression (Appendix 2).

Selective Serotonin Reuptake Inhibitors (SSRIs)

Selective serotonin reuptake inhibitors (SSRIs) inhibit neuronal reuptake of 5-hydroxytryptamine (5-HT) by blocking the serotonin transporter. SSRIs also appear to exert some minor inhibitory effects on dopaminergic and noradrenergic reuptake, although this varies across agents. The overall efficacy of SSRIs in treating depression is equivalent to that of other antidepressants, although they are often used as first-line therapy given their favourable side effect profile, including in those with established CVD.[20] The cardiovascular effects of SSRIs may include a modest slowing of the heart rate, minimal effect on blood pressure, and very little effect on electrocardiogram (ECG) intervals.[35] Currently in Canada, six SSRI agents are available for prescription.

A study evaluating the ability of an SSRI, sertraline, to facilitate the rate of recovery of cardiac autonomic function after an acute MI in 38 patients with depression found that sertraline produced a 5% increase in HRV.[34] This finding suggests that some SSRIs may exert cardioprotective effects in depressed patients. SSRIs have also been shown to reduce platelet aggregation within one week of treatment initiation,[33] thereby potentially reducing the risk of ischemic events such as acute MI and stroke.

Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs) - Venlafaxine

At daily doses exceeding 150mg, venlafaxine inhibits the reuptake of both 5-HT and NE, while at lower doses this agent is primarily an inhibitor of 5-HT reuptake.[20] For this reason, this antidepressant is classified as a dual inhibitor. Venlafaxine is believed to be less cardiotoxic than the TCAs, and together with the SSRIs and bupropion is now commonly prescribed as first-line treatment for depression. Although widely prescribed, little information is currently available on the cardiovascular effects of this agent. Although currently recommended as first-line therapy, at least one study found that venlafaxine increased diastolic blood pressure possibly due to its central noradrenergic effect,[36] while another reported increases in heart rate among elderly users[37]. In addition, a recent double-blind study of 44 depressed patients found that individuals treated with venlafaxine experienced a significant decrease in heart rate variability compared to those receiving paroxetine.[38] The cardiac effects of this new antidepressant require further study.

Tricyclic Antidepressants (TCAs)

The tricyclic antidepressants (TCAs), named on the basis of their molecular structure which shares three joined benzene rings, inhibit the reuptake of norepinephrine (NE), and to a lesser degree serotonin (5-HT). Although their efficacy equals that of other antidepressants, the TCAs tend to have more side effects, and as a result are rarely chosen as a first-line therapy. Moreover, these agents can be arrhythmogenic and epileptogenic, particularly in overdose situations.[20] The cardiovascular effects of the TCAs are well characterized and include orthostatic hypertension, slowed cardiac conduction, type 1A antiarrhythmic activity, and increased heart rate.[39] Orthostatic hypotension is of particular

concern in the elderly, and their use is considered contraindicated in persons with IHD. In addition, several studies have also demonstrated that the TCAs decrease HRV, which, as previously mentioned, is an established risk factor for adverse cardiovascular outcomes.[40]

Monoamine Oxidase Inhibitors (MAOIs)

Monoamine oxidase inhibitors (MAOIs) act by inhibiting monoamine oxidase (MAO), an enzyme found on the outer membrane of mitochondria, which catabolizes a number of monoamines including dopamine, norepinephrine, and serotonin.[20] Although the overall efficacy of MAOIs in the treatment of depression is similar to that of the other antidepressants, their use in clinical practice is severely limited by potentially life-threatening interactions with certain foods and drugs. For example, consumption of foods containing high levels of amines or the co-administration of dopaminergic agents can result in an adrenergic crisis characterized by hypertension and cardiac arrhythmias, while co-administration with other antidepressants can result in a serotonin syndrome which is characterized by alterations in cognition, ANS function, and neuromuscular activity.[20] Currently, the use of MAOIs is generally limited to a next step strategy for treatment resistant depression.

Atypical Antidepressants

Serotonin Receptor Antagonist/Agonist – Trazodone

Trazodone is a relatively weak inhibitor of 5-HT and NE uptake. This antidepressant also has an active metabolite which acts as a serotonin 5-HT2C agonist, and has the ability to release 5-HT presynaptically. The overall effect of trazodone is to increase extracellular levels of serotonin in the brain.[20] It's efficacy is comparable to that of the

SSRIs although it is less frequently used as a first-line treatment due its propensity for causing sedation, orthostatic hypotension, and headaches. Trazodone has been reported to cause premature ventricular contractions and ventricular tachycardia, although these cardiac effects are rare.[41]

Norepinephrine Dopamine Reuptake Inhibitors – Bupropion

Bupropion appears to primarily block, in a dose-dependent fashion, the uptake of dopamine (DA) and NE, although its true mechanism of action has yet to be fully elucidated.[20] The efficacy of bupropion is comparable to that of the SSRIs, and it is commonly used as a first-line treatment for major depression. This agent is generally well tolerated from a cardiovascular perspective, although one study indicated that bupropion may elevate blood pressure.[42] This study also reported no significant adverse effects on heart rate, cardiac conduction, or ventricular arrhythmias.

Tetracyclics – Maprotiline

Maprotiline exerts its pharmacological effect through strong inhibition of NE reuptake in the brain and peripheral tissues, with minimal inhibitory effect on 5-HT reuptake. When taken in high doses, tetracyclics are known to induce arrhythmias, tachycardia, and prolonged conduction time. Given previous reports of unexpected death, MI, and stroke, maprotiline is considered contraindicated in the elderly and those with history of MI or CVD.[43]

Summary

Of the antidepressants that are currently available, SSRIs, and possibly a few others with pronounced serotonin activity, appear to have the greatest potential for positively influencing CV health, independent of their effect on depression. Postulated mechanisms driving this association include serotonin mediated antiplatelet activity, and increased HRV, biological measures that have both been shown to improve within one week of treatment initiation with an SSRI.[33, 34] It is therefore not surprising that the majority of studies published to date evaluating the cardiovascular effects of the antidepressants have focused on the SSRIs.

Antidepressants and Cardiovascular Outcomes

Although numerous trials have reported that the SSRIs are safe to use in persons with CVD, to date only four randomized controlled trials have evaluated the effects of SSRI antidepressants using cardiovascular outcomes as their primary endpoint (Appendix 3).[34, 44-46] Of these, only one study used CV endpoints of MI and cardiac death, while the remaining three evaluated surrogate endpoints to quantify CV safety. Given the small sample size of two of these trials ($N \leq 27$), only the two larger studies will be discussed here.

The Enhancing Recovery in Coronary Heart Disease (ENRICHD) trial is the largest study published to date that was specifically designed to address the CV benefits of treating depression in persons with established CVD.[44] The study population consisted of 2481 individuals diagnosed with depression or "low perceived social support" following an acute MI. These were randomized to cognitive behavioural therapy (CBT), supplemented with the SSRI sertraline where indicated, or to usual medical care, and

followed for a mean of 29 months. Despite small but significant improvements for psychosocial endpoints favouring the combination of CBT and antidepressants, there was no difference for the primary endpoint of reinfarction or death (HR 1.01, 95% CI 0.86-1.18). However, a post-hoc analysis by the authors found that SSRI use was associated with a 43% risk reduction for the primary endpoint of recurrent MI or death compared to nonusers (HR 0.57, 95% CI 0.38-0.85). It is important to note that the latter analysis did not take into account the treatment group to which an individual was originally allocated.

By contrast, the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART) was designed to address the CV effects of antidepressants themselves, rather than that of CBT, but used surrogate measures of cardiac effects as primary endpoints.[45] This trial randomized 369 individuals with major depression who were hospitalized for acute MI or unstable angina to sertraline 50-200mg/day or placebo for 6 months. Sertraline had no detrimental effect on left ventricular ejection fraction, the study's primary indicator of cardiac effect, or on other surrogate measures of cardiac function. Although not statistically significant, the authors reported a marked difference in cardiovascular events between the sertraline (14.5%), and placebo group (22.4%). This post-hoc analysis was based on a total of 73 events, where 77% were angina endpoints. The results of this small trial suggest that the SSRI sertraline is safe for the treatment of depression in cardiac patients and may even exert a beneficial effect.

Several additional trials have evaluated the efficacy of various antidepressants in cardiovascular populations (Appendix 3).[47-53] However, since these studies were designed to assess antidepressant efficacy and included fewer than 100 participants, they were significantly underpowered to detect differences in the rates of CV events. Moreover, the

majority of these assessed cardiac safety using surrogate endpoints or did not report on CV endpoints at all.

Since 2000, 11 observational studies have been published to investigate the relationship between antidepressant use and cardiovascular outcomes, including eight case-control[54-61] and three cohort[62-64] studies (Appendix 4). The results of these studies are conflicting and non-definitive. For example, six of the case-control studies assessed cases of a first MI[54-58, 60]and, although five of these reported a protective effect for the use of SSRIs compared to non-users,[55-58, 60] only two of these associations were statistically significant[56, 58]. The remaining two case-control studies found an increased risk of ischemic events but these results were also statistically non-significant.[60, 61] The results of the three cohort studies are also discordant with only one of these reporting a statistically significant protective effect for the SSRIs compared to non-users[62].

A recent, as of yet unpublished, observational study has once again called into question the cardiac safety of the SSRIs.[65] Using data collected from a prospective cohort study examining the effects of anxiety and depression on CV outcomes among individuals undergoing coronary angiography, researchers found that users of antidepressants, primarily SSRIs, were twice as likely to die as nonusers even after adjusting for multiple potential confounders and depression scores (21.4% vs 12.5% respectively; $p<0.01$).

Limitations of Research to Date

Randomized controlled trials published to date have been largely undertaken to evaluate the efficacy of various antidepressants, and not their potential effect on CVD. Consequently, these trials have generally been underpowered to detect small but clinically important differences in the rates of cardiovascular events and mortality. In addition, such studies have typically excluded individuals with common comorbidities and those receiving concomitant medications, and were carried out under highly controlled conditions. As such, the results of trials are not easily generalizable to routine practice.

A major methodological shortcoming of observational studies published to date is their failure to control for the potential confounding effects of depression itself. Most studies compared users of antidepressants to nonusers in the general population or within cohorts of individuals with CVD. As such, it is difficult to discern whether the observed associations were due to antidepressant use or the presence of depression itself. This is likely the most important source of potential confounding by indication in the antidepressant-CVD association. This source of bias may also explain why several studies failed to observe a risk gradient across various classes of antidepressants, despite important pharmacological differences between these. Moreover, none of these studies controlled for the potentially confounding effects of severity and duration of depression, and most were underpowered from a statistical point of view. In addition, since the antidepressant cardio-protection hypothesis is relatively new, little or no information is

available on the cardiovascular effects of newer antidepressants including the SNRIs and NDRIs.

This thesis will address the methodological limitations of previously published studies by evaluating the cardiac effects of various antidepressants using a large, population-based cohort of elderly persons newly treated with an antidepressant.

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Chapter 3: Methods

Empirical Objectives

The primary objective of this thesis is to assess the risk of acute myocardial infarction and cardiac death associated with exposure to various classes of antidepressants. More specifically to:

3. Assess and quantify the risk for the combined endpoint of acute MI and cardiac death associated with the current use of SSRI and SNRI antidepressants compared with that of atypical antidepressants.
4. Determine whether the risk of cardiovascular complications is modified by the presence of predisposing factors including: (i) age (<85 and ≥85 years of age), (ii) sex, (iii) previous myocardial infarction, (iv) cardiovascular disease, (v) history of diabetes, and vi) concomitant use of an antithrombotic.

To address the uncertainty regarding the cardiovascular effects of the SSRIs and newer classes of antidepressants, we conducted a population-based, retrospective cohort study.

Cohort Formation

The source population for the study consisted of all elderly Québec residents who initiated treatment with an NSAID between January 1st, 1997 and March 31, 2005 (N=463,558), due to the availability of data granted for a previous study. Within this population, a sub-cohort of all 'depressed' individuals aged 66 years and over who were dispensed an antidepressant between January 1st, 1997 and December 31, 2004 were identified, and the date of this prescription was taken as cohort entry (*time zero*). Individuals were excluded from the sub-cohort if they had not been enrolled in the

provincial health plan for a period of at least one year preceding cohort entry (baseline period), or if they had been dispensed an antidepressant within this 1-year period. This permitted the establishment of medical and drug histories, as well as health services utilization profiles for each cohort member at the time they initiated therapy with an antidepressant. The remaining individuals represented an inception cohort of elderly persons initiating treatment with an antidepressant and at risk of an event for the outcome under study. The *exit date* was the earliest of the following dates: a first study endpoint, non-cardiac death, end of health coverage (due to death or emigration from the province), or end of study (March 31, 2005). Except for the event date, all other dates were censored. Age 66 was chosen as the age at entry to ensure that all cohort members had at least one year of health coverage (and hence medication use history) prior to cohort entry, given the restriction of the universal drug program to residents 65 years of age and older.

Sources of Data

The computerized health insurance databases of Québec constituted the primary source of data. These administrative databases were developed as a result of the universal health care programs offered to residents of this province and are now extensively used for research. The health databases used included: (1) the beneficiary database for socio-demographics and dates of coverage; (2) the prescription drugs database for information on prescribed medications dispensed on an outpatient basis to those aged 65 years and over; (3) the medical services and procedures database for information on all medical visits, services, and procedures provided by health professionals; and (4) the hospital separations database for information on primary and up to 15 discharge diagnoses. Depending on age at cohort entry and year of residency, information was available for a

minimum of 1 year and up to 12 years preceding cohort entry, as well as for the duration of follow-up. In addition, the vital statistics database of the *Institut de la Statistique du Québec* (ISQ) was also used for information on dates and causes of deaths occurring in and out of province. A detailed description of the data utilized in this study and its use is provided in Appendix 5.

Residents are represented in each of the health databases by a unique identifier, the *Numéro d'Assurance-Maladie* (NAM). Since all data entries require the use of this unique identifier, complete record linkage at the level of the individual was possible across all health databases. To maintain an individual's anonymity, the NAM was encrypted by the source agency prior to data transfer (Appendix 6).

The completeness and accuracy of the prescription drugs database has previously been demonstrated with 98% of elderly residents being registered, <1% of the information being missing or out of range, and 99% of prescriptions written to patients attending an internal medicine clinic, and recorded as being filled, correctly identifying the individual as well as the drug[1](Appendix 7). The accuracy of hospital discharge diagnoses for identifying cases of MI has been previously demonstrated in the Quebec database with this diagnosis having 96.9% agreement (95% CI, 94-98) with the medical chart.[2] In addition, the completeness, consistency, and apparent validity of these data were evaluated prior to undertaking any analyses (see Appendix 8 for details). Finally, since the variables obtained are required fields for reimbursement of services, missing data for the variables of interest was non-existent in these databases.

Ascertainment of Outcomes

The outcome of interest was myocardial infarction (nonfatal and fatal) and cardiac death. All cases of the study outcome occurring anytime after cohort entry were identified by linking cohort members to hospitalizations and vital statistics databases using their unique identifier (encrypted NAM). The case-defining event was either the first hospitalization with a primary or secondary discharge diagnosis of myocardial infarction (International Classification of Diseases, version 9 (ICD-9) code 410) or a cardiac death (ICD-9 codes 410.x-414.x or ICD-10 120.x-125.x): the latter captured fatal events occurring outside of hospital (i.e., sudden death). For each of these outcomes, the date of admission or death (event date) was used as the index date. The study's composite endpoint was chosen to facilitate comparability with the results of previously published studies, while also representing the event which is most relevant for the postulated pharmacologic effects of the antidepressant drugs under study.

Ascertainment and Classification of Exposure

Information on relevant exposures was obtained from the prescription drugs database for cases and controls. Antidepressants available during the study period were classified according to their mechanism of action and known cardiac effects with the more seldom prescribed classes pooled to achieve adequately sized groups. The exposure categories were as follows: (i) SSRIs; (ii) SNRIs – venlafaxine; (iii) TCAs and maprotiline; (iv) MAOIs; (v) atypical antidepressants; (vi) SSRI-based combinations; and (vii) other combinations. Combination therapy was defined as receiving at least two antidepressants from different exposure categories. All of these agents were available

without prescribing restrictions. Due to the time constraints of a Master's thesis, only dosing for users of venlafaxine was investigated.

Covariates

Well-established risk factors for acute MI include age, sex, hypertension, diabetes, hyperlipidemia, history of ischemic heart disease (previous MI, coronary artery disease (CAD), cerebrovascular disease, peripheral vascular disease), abdominal obesity, smoking, alcohol consumption, and physical inactivity.[3-5] Several medications are also known to modify the risk of MI including aspirin[6, 7], lipid lowering drugs[8, 9], antiplatelets[10], anticoagulants[11], angiotensin converting enzyme inhibitors (ACE-Is)[12], angiotensin receptor blockers (ARBs), hormone replacement therapy (HRT)[13, 14], cyclooxygenase-2 (COX-2) inhibitors[15-17], and possibly NSAIDs[17]. Moreover, depression is now recognized as an important predictor of CV events and death.[18-23] Finally, depression severity has been shown to contribute to the risk of adverse CV outcomes[20, 22, 24-26], while a robust link between duration of depression and CV risk has yet to be established.

Age was matched on at the design stage and adjusted for in the analysis, while the potentially confounding effect of sex was controlled for in the analysis. The computerized health databases previously described made it possible to statistically adjust for the influence of various comorbid conditions, concomitant drug use, and several indicators of health status including measures of health care utilization and comorbidity indices such as the Chronic Disease Score[27], the Charlson Index[28], and the number of unique drugs.[29] Apart from health care utilization and the indices of health status which we evaluated in the year preceding index, all other covariates were evaluated at baseline.

Medications were identified using the prescription drugs database and comorbid conditions using hospital discharge diagnoses and corresponding drug treatments.

The time-matched analysis controlled for the potentially biasing effects of duration of follow-up and calendar time, while restricting the cohort to users of antidepressants controlled for one of the most important sources of confounding by indication (i.e., confounding by the presence of depression itself). If being prescribed an antidepressant is a marker of more severe depression, then studying an 'all treated' cohort controlled for one aspect of depression severity, while accounting for use of antidepressants as mono- versus combination therapy (i.e., a measure of treatment intensity) further controlled for confounding by severity.

Socioeconomic status (SES) is known to be an important determinant of various health outcomes but this factor was not available at an individual level in the administrative data files. Therefore, estimates of social and material status for an individual were obtained by attributing the neighbourhood level median household income and social deprivation from census data to all persons living in that neighbourhood. This was done using the individual's postal code at cohort entry and matching it to census data at the level of the forward selection area. These ecologic-level variables were available in the beneficiary file. Consequently, all analyses were adjusted for these measures of material and social status.

Information on smoking, physical activity, obesity and alcohol consumption was not captured by these databases. While these factors are known determinants of the outcomes under study, they could only confound the relationship of interest if a physician's choice of an antidepressant were influenced by these factors. Although

previous research has not reported on physical activity, obesity, or alcohol consumption patterns across individuals prescribed various antidepressant classes, rates of tobacco use have been shown to be slightly elevated in those prescribed an antidepressant other than an SSRI (77% vs. 69%, $p<0.001$).[30] Conversely, studies have also demonstrated that the distribution of most CV risk factors do not differ across antidepressant class.[31, 32] Nonetheless, since the possibility of confounding due to missing information on these risk factors cannot be ruled out, this will need to be taken into consideration when interpreting the study results.

Statistical Analysis

Descriptive analysis

The analysis began by generating a description of the cohort and the variables under study. Tables were generated for the proportion of individuals treated with the various categories of antidepressants at cohort entry, and for the duration of follow up. In order to search for evidence of selective or preferential prescribing, an examination of the distribution of covariates across exposure categories was undertaken.

Primary analysis

The choice and use of drug treatments often change over time. Consequently, drug exposure needs to be analyzed as a time-dependent variable. In order to assess exposure to antidepressants in relation to the time of the event (i.e., the etiologically relevant window of exposure) while simultaneously controlling for the potentially confounding effects of duration of treated depression and changes in prescribing trends over time (i.e., calendar time), a time-matched, nested case-control analysis of the cohort was

undertaken.[33, 34] This approach provides unbiased estimates of the rate ratios that would be obtained from a traditional time-to-event analysis of the full cohort, with little or no loss in precision but significant gains in computational efficiency particularly when analyzing time-varying exposures within large cohorts.[35-37]

The event date of each case (i.e., index date) was used to define the "risk sets" from which individuals who were still at risk of the event (i.e., non-cases or controls) were chosen. In this way, controls had the possibility of becoming future cases. For each case up to 20 controls matched on age (±1 year), duration of follow-up, and year of cohort entry were randomly selected and assigned an index date that corresponded to the case's duration of follow-up added to the control's date of cohort entry. Twenty controls per case were chosen to obtain adequate power for detecting small risk differences, while also preserving computational manageability.

The choice of a clinically appropriate or etiologically relevant exposure time-window requires an understanding of the possible underlying mechanisms through which antidepressants may exert their cardiovascular effects, as well as consideration of the pharmacodynamic properties of these agents. Antidepressants have the potential to exert both direct pharmacological effects on the cardiovascular system and indirect effects secondary to improvement of the depression itself. The focus of this thesis was on the direct pharmacological effects of these agents. Pharmacological effects, manifested through previously discussed mechanisms (i.e., improved heart rate variability and decreased platelet aggregation for 5-HT selective agents, and pro-arrhythmic activity for the TCAs) are likely to be acute in nature. Thus, for the primary analysis it was hypothesized that use immediately preceding an event (i.e., current exposure) would be

the etiologically relevant exposure. As a result, persons for whom the duration of the last prescription dispensed in the year preceding the index date overlapped with this date were considered *currently* exposed; otherwise they were categorized as *past users* (Appendix 9). Those not having received at least one prescription in that year were classified as *non users* during this time period. These definitions were also applied to the use of combination therapy.

For the analysis of monotherapy, the risk of MI and cardiac death for current users of various antidepressants was compared with that of current users of atypical antidepressants. The latter was chosen a priori as the reference category because these agents are known to have little or no serotonin activity. Atypical agents were first examined individually using bupropion as a reference category, then recombined for the final analysis on the basis of comparable point estimates, and similar pharmacology (low serotonin selectivity) with regards to the pharmacological hypothesis under study. For the analysis of combination therapy, the comparator group was users of combinations not containing an SSRI. Using an exposed group as the reference category minimized the potential for confounding by indication. In addition, since those who become unexposed during follow-up (e.g., treatment withdrawal, discontinuation, resolution of depression) may be different from those who continued their treatment in ways that may have been related to their probability of the outcomes under study, this group would not have been an appropriate comparator for the association under study. Because controls were individually matched to the cases, conditional logistic regression was used for all analyses.[38, 39] Initially, unadjusted rate ratios (RR) for the association under study were estimated, then multivariable conditional logistic regression was conducted to obtain rate

ratios and 95% confidence intervals adjusted for the effect of potential confounders. In these analyses, the decision to retain a potential confounder was based on an assessment of the magnitude of confounding using the "change in estimate" method proposed by Greenland[40]. Briefly, starting with a fully adjusted model, any independent variable that changed the estimate of the RR by 10% or more was retained in the model using a backwards selection approach. None of the covariates tested met the definition of a confounder. However, since no appreciable gain in precision was obtained from a parsimonious model, risk estimates were adjusted for all aforementioned covariates.

Subgroup analysis

To investigate the potential risk modifying effect of important predisposing factors and comorbid conditions, an interaction term for each of these factors with the exposure groups (one at a time) was included in subsequent models. In this way, the effect of both SSRIs and venlafaxine were compared among those with and without these factors. The results of this interaction or subgroup analysis were assessed in terms of both its clinical significance (i.e., magnitude of the difference) and statistical significance. All subgroup analyses were carried out using a two-sided test of interaction at a significance level of $\alpha = 0.05$.

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Chapter 4: Manuscript

The Effect of Antidepressants on Cardiovascular Morbidity and Mortality: A Population-based Cohort Study

Background

According to the World Health Organization (WHO), it is estimated that by 2020 major depression and ischemic heart disease (IHD) will be the foremost contributors to the global burden of disease.[1] This is not surprising given that cardiovascular disease (CVD) remains the leading cause of hospitalizations and death in most developed countries, including Canada,[2] that the prevalence of depression is high, particularly in the elderly,[3, 4], and that the two diseases often coexist.

Depression is now well established as an important and independent predictor of both the onset and progression of CVD. For example, in healthy adults, the presence of depression has been shown to confer a 1½ to 2-fold increased risk of developing coronary artery disease (CAD), or of dying from CAD.[5] Similarly, in those with established heart disease, depression has been associated with a 1½ to 2½-fold increased risk of cardiac morbidity and mortality.[5, 6] These findings have generated considerable interest regarding the possible cardiovascular benefits of antidepressants, particularly the selective serotonin reuptake inhibitors (SSRIs).

The majority of trials published to date have reported that SSRIs are well tolerated in persons with CVD,[7-10] although evidence regarding their effects on cardiovascular endpoints is relatively sparse. Clinical trials have primarily been powered to address antidepressant efficacy, while observational studies have reported discordant results. In

addition, a recent cohort study has raised concerns about the cardiovascular safety of the SSRIs with findings of an increased risk of death from cardiovascular disease.[11]

We conducted a population-based, retrospective cohort study to address the uncertainty regarding the cardiovascular effects of the SSRIs and serotonin and norepineprine reuptake inhibitors (SNRIs), a new and increasingly prescribed class of antidepressants. Using a large and unselected population of elderly persons initiating treatment with an antidepressant we assessed the risk for myocardial infarction and cardiac death associated with the use of various antidepressants and evaluated factors that may modify this risk.

Methods

Study Population and Data Source

We identified a cohort of all persons aged 66 years and older initiating therapy with an antidepressant using the computerized health insurance databases of Québec. These administrative databases were developed as a result of the universal health care programs offered to residents of this province and are now extensively used for research. The health databases used included: (1) the beneficiary database for socio-demographics and dates of coverage; (2) the prescription drugs database for detailed information on prescribed medications dispensed on an outpatient basis to those aged 65 years and over; (3) the medical services and procedures database for information on all medical visits, services, and procedures provided by health professionals; and (4) the hospital separations database for information on the primary and up to 15 discharge diagnoses. We also used the vital statistics database of the *Institut de la Statistique du Québec* (ISQ) for information on dates and causes of death occurring in and out of province. Each

resident is represented in each of the databases by a unique identifier, the *Numéro d'Assurance-Maladie* (NAM). Since all data entries require the use of the NAM, complete record linkage at the level of the individual was possible across all databases. To maintain an individual's anonymity, the NAM was encrypted by the source agency prior to data transfer.

Study Design

We conducted a population-based, retrospective cohort study which was analyzed using a time-matched nested case-control approach[12, 13]. The source population for the study consisted of all elderly Québec residents who initiated treatment with an NSAID between January 1st, 1997 and March 31, 2005 (N=463,558), available from a previous study of NSAID users. Within this population, a cohort of all individuals aged 66 years and over who were dispensed an antidepressant between January 1st, 1997 and December 31, 2004 was identified, and the date of the first prescription was taken as cohort entry. Individuals were excluded from the study if they had not been enrolled in the provincial health plan for a period of at least one year preceding cohort entry (baseline period), or if they had been dispensed an antidepressant within this 1-year baseline period. Age 66 was chosen as the age at entry to ensure that all cohort members had at least one year of health coverage (and hence medication use history) prior to cohort entry, given the restriction of the universal drug program to residents 65 years of age and older. The remaining individuals were followed until the earliest of the following dates: a first study endpoint (acute MI or cardiac death), non-cardiac death, end of health coverage (due to death or emigration from the province), or end of study (March 31, 2005).

Study End Point

The study endpoint was a first hospitalization with a primary or secondary discharge diagnosis of acute MI (International Classification of Diseases (ICD) version 9, code 410) or a cardiac death (ICD-9 codes 410.x-414.x or ICD-10 120.x-125.x) occurring anytime after cohort entry. This diagnostic code has been previously validated in the Québec database for identifying cases of MI and shown to have 96.9% (95% CI, 94-98) agreement with the medical chart.[14] To be considered a valid endpoint, the hospital length of stay had to be at least 3 days unless the patient had died, been transferred to another facility, or had undergone coronary angioplasty. Cardiac death was used to capture fatal out of hospital events. For each of these endpoints, the date of admission or death (event date) was used as the index date.

Antidepressant Exposure

All antidepressants available during the study period were identified using the prescription drugs database and classified according to; a) their mechanism of action (namely serotonin activity) and known cardiac effects, and b) their pattern of use (mono- vs. combination therapy) to account for depression severity. The more rarely prescribed agents were pooled to achieve adequately sized groups. The mutually exclusive categories were as follows: (i) selective serotonin reuptake inhibitors (SSRIs); (ii) serotonin and norepinephrine reuptake inhibitors (SNRIs) – venlafaxine; (iii) tricyclic antidepressants and maprotiline (TCAs/maprotiline); (iv) monoamine oxidase inhibitors (MAOIs); (v) atypical antidepressants; (vi) SSRI-based combinations; and (vii) other combinations (Figure 1). The completeness and accuracy of the prescription drugs

database has previously been demonstrated with 98% of elderly residents being registered, and <1% of the information being missing or out of range.[15]

Statistical Analysis

Treatment choices and use of antidepressant drugs frequently change over time (switches, add-ons, and discontinuation secondary to the resolution of depression). Consequently, drug exposure needs to be analyzed as a time-dependent variable. In order to assess the effects of individual antidepressants in relation to the time of the event (i.e., the etiologically relevant window of exposure) while simultaneously controlling for the potentially confounding effects of duration of follow-up and calendar time, a time-matched, nested case-control analysis of the cohort was undertaken.[12, 13] This approach has been shown to provide unbiased estimates of the rate ratios that would be obtained from a traditional time-to-event analysis of the full cohort, with little or no loss in precision but significant gains in computational efficiency particularly when analyzing time-varying exposures within large cohorts.[16-18]

Primary Analysis

The event date of each case was used to define the "risk sets" from which individuals who were still at risk of the event were chosen. For each case, up to 20 controls matched on age (±1 year), days of follow-up, and year of cohort entry were randomly selected and assigned an index date that corresponded to the case's duration of follow-up added to the control's cohort entry date.

The SSRIs have been show to exert serotonin-mediated antiplatelet activity within 7 days of treatment initiation.[19] As such, we hypothesized that use immediately

preceding an event (i.e., current exposure) would represent etiologically relevant exposure. As a result, persons for whom the duration of the last prescription dispensed in the year preceding the index date overlapped with this date were considered *currently* exposed; otherwise they were categorized as *past user*. Those not having received at least one prescription in that year were classified as *non users* during this time period. These definitions were also applied to the use of combination therapy.

To control for the confounding effect of depression severity, we carried out separate analyses for mono- and combination therapy. For the analysis of monotherapy, we compared the risk for an acute MI and cardiac death for current users of mono-therapy of the various classes of antidepressants with that of current users of atypical antidepressants. The atypicals were chosen a priori as a reference category because of their low serotonin selectivity. For the analysis of combination therapy, current users of SSRI-based combinations were compared with current users of non-SSRI containing combinations. We estimated rate ratios (RRs) for these associations using conditional logistic regression to account for individual case-control matching.[20, 21] Initially, unadjusted rate ratios (RR) were estimated, then multivariable regression was conducted to obtain rate ratios and 95% confidence intervals adjusted for the potentially confounding effects of socio-demographics, cardiovascular comorbidities, other comorbidities, concomitant medications, health care utilization, and indices of health status. Apart from health care utilization and indices of health status which we evaluated in the year preceding index, all other covariates were evaluated at baseline. In these analyses, the decision to retain a potential confounder was based on the "change in estimate" method proposed by Greenland[22]. None of these risk factors met the 10%

change in estimate criteria for confounding. Therefore, all reported measures of effect are adjusted for all factors as their exclusion provided no significant gain in precision. Medications were identified using the prescription drugs database, while comorbid conditions were identified using the medical services database, hospital discharge diagnoses, and corresponding drug treatments.

Secondary Analysis

To investigate the potential risk modifying effect of important predisposing factors including age, sex, previous MI, CVD, history of diabetes, and concomitant use of an antithrombotic, we included an interaction term for each of these factors with the exposure groups (one at a time) in the regression model. In this way, the effect of both SSRIs and venlafaxine were compared among those with and without these factors. All subgroup analyses were carried out using a two-sided test of interaction at a significance level of $\alpha = 0.05$.

Ethics

This study received ethics approval from the Queen's University Health Sciences Research Ethics Board.

Results

The cohort consisted of 71253 elderly persons initiating treatment with an antidepressant, with a mean age (± SD) of 74.6 ± 5.5 years at cohort entry (figure 2). At cohort entry, the majority of individuals were receiving an SSRI (46.6%), followed by TCA/Maprotiline (35.8%), atypical antidepressants (10.2%), venlafaxine (5.6%), and the remainder (1.8%) receiving an MAOI or combination therapy (Table 1). With the

exception of a slightly higher proportion of females receiving SSRIs as compared to atypical antidepressants, users of these two drug classes showed striking similarities with regards to socio-economic status (SES), cardiovascular profiles, use of concomitant medications, health care utilization, and indices of health status. Likewise, venlafaxine users were similar in age, SES, cardiovascular profiles, health care utilization, and indices of health status compared with atypical antidepressants, but had a slightly increased occurrence of stroke, and were somewhat more likely to be receiving selected concomitant CV medications.

Cohort members were followed for an average (± SD) of 3.7 ± 2.1 years. During this time, 5217 (7.3%) experienced a study endpoint of acute MI or cardiac death and were matched to 104337 controls. Table 2 describes the characteristics of the cases and their matched controls, all of which were controlled for in the analysis. As expected, cases were more likely to be males, and appeared sicker as indicated by an increase in cardiovascular comorbidities, inferior health status, and increased use of concomitant medications and health care services.

In the year preceding index, 52.3% of individuals were classified as current users of antidepressants, while 23.2% met the definition for past users, and 24.5% were non-users. The majority of current users were receiving an SSRI (47.2%), followed by TCA/Maprotiline (28.7%), atypical antidepressants (8.0%), venlafaxine (9.3%), and MAOI or combination therapy (6.9%). It should be noted that the mean daily dose for venlafaxine use in our study was 75mg and that only 289 (6.3%) of the 4580 current users of atypical antidepressants were using bupropion, a drug also prescribed for smoking cessation.

Following adjustment for the aforementioned risk factors, current users of venlafaxine monotherapy had a 20% lower risk of MI and cardiac death than users of atypical agents (RR 0.80 [0.66-0.97]) (Table 3). We found no clear evidence of a benefit or harm associated with the use of SSRIs (RR 0.92 [0.79-1.06]), nor with TCAs and maprotiline (RR 0.92 [0.78-1.07]) or MAOIs (RR 1.07 [0.67-1.69]). Past users of SSRIs were at a significantly greater risk for MI and cardiac death than current users of atypical agents (RR 1.21 [1.03-1.42]), but not past users of venlafaxine (RR 1.15 [0.89-1.48]), TCAs and maprotiline (RR 1.10 [0.93-1.30]), and MAOIs (RR 1.30 [0.95-1.48]).

Treatment with SSRI-based combinations appeared to be associated with an increased risk for MI and cardiac death compared with users of other antidepressant combinations (RR 1.34 [0.94-1.91]), although this did not reach significance (Table 4). However, past users of SSRI-based combinations and other antidepressant combinations were both at significantly increased risk of the events under study (RR 1.67 [1.10-2.53] and RR 1.66 [1.18-2.34] respectively).

Age, sex, a history of CVD and diabetes, and the concomitant use of an antithrombotic did not appear to modify the risk of MI or cardiac death associated with the use of SSRI monotherapy (Figure 3). However, there was the suggestion of a clinically important benefit from treatment with SSRIs for individuals who had a previous MI (RR 0.68 [0.44-1.07]).

Individuals with a history of CVD experienced significantly greater benefit from the use of venlafaxine (RR 0.65 [0.50-0.86]) than those without CVD (RR 0.81 [0.67-0.98]; p=0.04 for test of interaction) (Figure 4). The risk of MI and cardiac death was not

modified by age, sex, previous MI, a history of diabetes, and the concomitant use of antithrombotics.

Discussion

In this population-based cohort study, treatment with venlafaxine was associated with a significant reduction in the risk of MI and cardiac death as compared with users of atypical antidepressants. Furthermore, this protective association was more pronounced for persons with a history of cardiovascular disease than those without, and possibly also for those with a previous MI compared with those with no such history. While there was no clear evidence of benefit associated with the current use of SSRIs, the possibility of increased harm was ruled out. In addition, there was the suggestion of a clinically important benefit with the use of SSRIs for persons with a history of MI.

An important limitation of previously published observational studies has been the lack of control for the potentially confounding effects of the depression for which antidepressants were indicated (confounding by indication), as well as the lack of information on the cardiac safety of venlafaxine, a relatively new but commonly prescribed antidepressant with pronounced serotonin activity at low doses.[23-33] Our study is not only the first to control for the biasing effects of confounding by depression with the use of an "all-treated" design, it is also the first to report a significant reduction for the risk of MI and cardiac death associated with the use of venlafaxine. On the other hand, we did not observe a clear cardiovascular benefit with the use of SSRIs, even with the use of improved methodology, but the lower limit of the 95% confidence interval does not rule out the possibility of a clinically important effect.

Our findings for SSRIs are consistent with the results of the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART), the only randomized controlled trial published to date specifically designed to assess the cardiovascular benefits of treating depression with an SSRI compared with placebo in persons hospitalized for MI or unstable angina.[7] Like us, this trial found that sertraline is not associated with an increased risk in cardiac patients, and that it may even exert a beneficial effect. Indeed, our adjusted risk estimate 0.68 (CI, 0.44-1.07) for SSRIs use in persons with a previous MI is compatible with that reported for major cardiovascular events for SADHART participants assigned to sertraline (RR 0.77 [0.51-1.16]). Our results are also consistent with those of the Enhancing Recovery in Coronary Heart Disease (ENRICHD) trial.[8] Although this trial was designed to assess the cardiovascular benefits of treating depression in persons with established CVD with cognitive behavioural therapy supplemented with an SSRI as needed, compared with usual medical care, a post-hoc analysis reported that SSRI use compared to non use was associated with a 43% risk reduction for (HR 0.57, 95% CI 0.38-0.85).

A number of previously published observational studies have reported increased risks of cardiovascular morbidity and mortality with SSRIs compared with no use of antidepressants but none controlled for confounding by indication.[23, 28, 30] We found no such risk with the use of a design that controlled for the confounding effects of depression itself.

SSRIs inhibit the reuptake of 5-HT by blocking the serotonin transporter in the neural synapse, an effect which is also occurs on the surface of platelets resulting in decreased aggregation.[19] As a result, it has been suggested that SSRIs may confer

beneficial effects on the cardiovascular system.[19] While these antiplatelet effects have not yet been demonstrated for venlafaxine, this agent nonetheless exhibits high serotonin inhibitory activity at low doses.[34] This may explain the unexpected risk reductions observed with venlafaxine in our study, including those among individuals with previous MI or CVD. The serotonin-antiplatelet hypothesis is further supported by the observation that in our study venlafaxine users received an average dose of 75 mg per day; a dose at which this agent predominantly inhibits the reuptake of serotonin.

This study is not without limitations. First, information obtained on dispensed medications is not necessarily representative of biological exposure. However, there is no reason to believe that such misclassification would be differential as this would require individuals who fill their prescriptions, yet not consume them, and to do so differentially across exposure categories. As a result, any misclassification would be non-differential and bias the results towards the null. Second, we did not have information on the indication for the use of the antidepressant. Individuals receiving such an agent for an indication other than depression could be at lower risk of cardiovascular events. It is possible that a greater proportion of users of the atypical agents may have received these agents for anxiety or insomnia thus decreasing our ability to detect a protective association for users of SSRIs who are more likely to be depressed. However, we detected a significant risk reduction for users of venlafaxine who were also compared with users of an atypical agent. Finally, we did not have information on smoking, physical activity, obesity or alcohol consumption. While these factors are known determinants of cardiovascular morbidity and mortality, they could only bias our results if a physician's choice of an antidepressant was influenced by these factors. Our analysis

of baseline characteristics demonstrated no appreciable differences in the cardiovascular risk profiles of users of SSRIs, venlafaxine and atypical agents. However, the possibility of residual confounding by unmeasured factors cannot be completely ruled out.

In the spectrum of conflicting evidence surrounding the CV safety of antidepressant drugs, many physicians may be reluctant to treat depression with pharmacotherapy in patients with heart disease. The results of this study provide further evidence that treating depression with both SSRIs and venlafaxine is not associated with adverse cardiac events, even in those with established cardiovascular disease. Furthermore, the two classes of antidepressants may even confer a benefit with regards to cardiovascular morbidity and mortality. Indeed, several randomized controlled trials are currently underway to address more clearly the issue of benefit but it will be several years before these results are available. In the interim, physicians should continue to treat depression using an SSRI or venlafaxine, particularly in persons with heart disease, not only for their potential impact on CV health, but also for their profound implications on a patient's quality of life.

Figure 1: Exposure Categories and Pharmacology of the Antidepressants †

Exposure Category	Agent	Receptor Site Activity	
		5-HT	5-HT Selectivity
Selective Serotonin Reuptake Inhibitors (SSRIs)	Citalopram	√	3696
	Escitalopram	√	
	Fluoxetine	√	301
	Fluvoxamine	√	586
	Paroxetine	√	320
	Sertraline	√	1423
Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)	Venlafaxine	√	116
Tricyclics (TCAs) & Maprotiline (Tetracyclic)	Amitriptyline	√	7.97
	Amoxapine		
	Clomipramine	√	132
	Desipramine		
	Doxepin	√	
	Imipramine	√	26.2
	Nortriptyline		
	Protriptyline		
	Trimipramine	√	264
	Maprotiline		
Monoamine Oxidase Inhibitors (MAOIs)	Phenelzine ‡	√	
	Tranylcypromine ‡	√	
	Moclobemide §		
Atypical Antidepressants (reference category)	Bupropion	√	5.78
	Mirtazapine	√	
	Nefazodone	√	1.80
	Trazadone	√	51.9

† Adapted from: [35].
‡ Non-selective MAOI.
§ Selective MAOI.

Figure 2: Study Population Flow Diagram

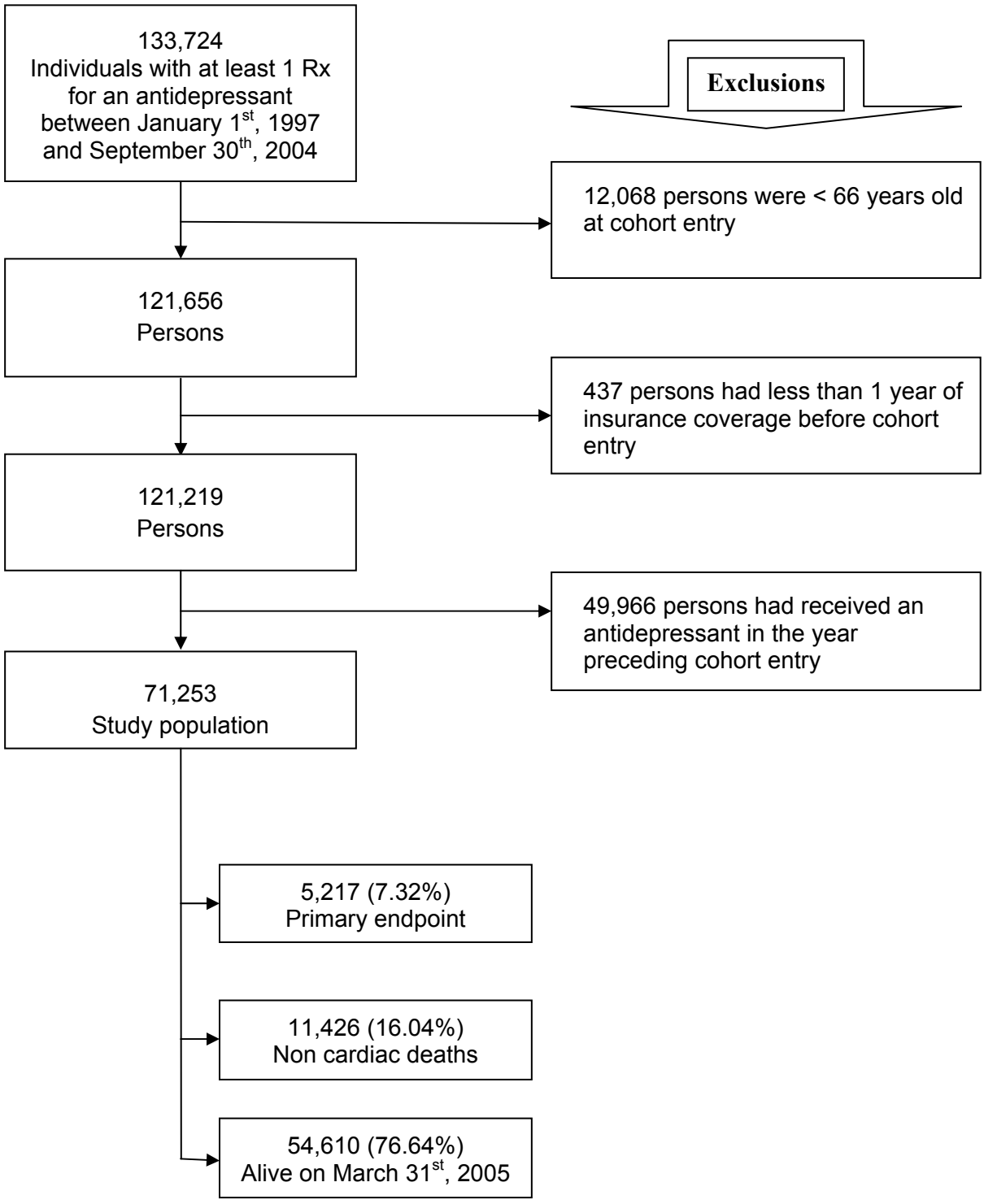

Table 1: Baseline Characteristics of Individuals Initiating Treatment with an Antidepressant

	SSRI (n=33,200)	SNRI (Venlafaxine) (n=4,023)	TCA's & Tetracyclics (Maprotiline) (n=25,532)	MAOI (n=624)	Atypicals (n=7,256)	SSRI-based combinations (n=471)	Other Combinations (n=147)
Socio-Demographics							
Age, yrs (mean ± SD)	75.0 ± 5.6	74.9 ± 5.6	74.1 ± 5.3	73.9 ± 5.0	74.5 ± 5.6	74.2 ± 5.7	74.0 ± 5.4
Sex, female	73.5	68.7	75.5	76.0	68.0	66.7	73.5
Income Quintiles							
1	17.6	16.4	17.2	17.2	16.7	17.2	17.3
2	15.9	16.3	15.7	16.7	16.7	17.2	15.9
3	18.7	19.3	18.6	20.8	18.4	17.2	18.7
4	20.4	20.5	20.2	18.8	20.2	20.6	20.3
5	21.2	21.9	22.1	19.4	21.7	22.3	21.6
Missing	6.3	5.6	6.2	7.2	6.3	5.5	6.2
Social Network							
1	12.8	14.5	13.3	11.4	12.3	15.7	13.0
2	15.3	17.0	15.0	13.6	15.2	14.9	15.2
3	17.9	18.4	17.6	18.1	18.0	17.8	18.9
4	22.1	21.4	22.6	21.0	21.7	22.1	22.2
5	25.6	23.2	25.3	28.7	26.6	24.0	25.5
Missing	6.3	5.6	6.2	7.2	6.3	5.5	6.2
History of CV Disease (%)							
Previous MI	2.6	3.0	1.7	1.9	2.4	2.8	1.4
Hypertension	56.6	58.3	53.9	46.3	56.3	54.8	52.4
Ischemic heart disease	27.0	26.5	23.1	22.3	25.3	30.8	27.2
Stroke	3.8	4.3	2.2	2.6	2.8	5.7	4.1
Peripheral vascular disease	2.1	2.8	2.1	2.4	2.3	2.1	5.4
Congestive heart failure	10.5	10.4	8.8	10.4	9.6	9.8	10.9
Diabetes	14.7	15.4	16.2	13.5	15.6	17.0	18.4
Angioplasty	0.4	0.7	0.4	0.3	0.4	1.3	0.7
Rheumatoid Arthritis	1.0	1.2	1.4	0.5	1.2	1.9	1.4

Renal Disease	1.2	1.4	1.1	0.8	1.0	2.3	2.0
Respiratory Illness	23.2	22.8	21.3	23.4	25.8	25.7	20.4
Other Comorbidities (%)							
Thyroid Disorder	19.3	20.8	18.3	19.2	18.3	17.8	17.7
Cancer	5.9	8.0	5.8	5.0	5.8	6.2	4.8
Cardiovascular Drugs (%)							
Antiplatelets	2.7	4.8	1.9	0.8	2.5	1.3	2.0
Aspirin	32.3	33.4	28.7	27.2	31.3	29.3	27.2
Anticoagulants	5.6	7.4	4.5	4.8	5.5	6.6	6.8
ACE-inhibitors	22.3	23.2	20.6	19.4	21.7	20.6	15.7
Angiotensin receptor blockers	6.7	8.7	4.7	2.6	7.4	6.8	7.5
Lipid lowering drugs	23.6	29.4	21.6	13.9	26.1	21.7	25.2
Other Drugs (%)							
Hormone replacement therapy	20.9	21.9	22.4	19.2	21.3	19.4	22.2
COX-2 Inhibitors	15.8	27.4	13.0	1.9	20.3	19.8	19.1
NSAIDs	20.3	15.1	26.8	25.6	18.5	19.5	15.7
Oral Corticosteroids	17.4	18.4	16.8	15.7	18.4	18.1	15.7
Health Care Utilization							
No. unique drugs (mean ± SD)	9.1 ± 5.4	9.4 ± 5.4	9.4 ± 5.3	9.6 ± 5.2	9.2 ± 5.4	9.7 ± 5.8	9.6 ± 6.5
Outpatient Medical Visits (mean ± SD)	15.0 ± 11.4	14.7 ± 10.4	15.4 ± 12.1	17.1 ± 11.7	14.1 ± 10.6	16.2 ± 13.7	15.3 ± 12.0
No. of Hospitalizations							
0	67.2	62.9	71.9	68.9	69.1	52.2	54.4
1	21.7	23.8	19.0	19.9	20.4	31.0	25.2
≥2	11.1	13.3	9.1	11.2	10.5	16.8	20.4
Psychiatry Visits (%)	9.7	11.4	6.1	26.0	7.6	26.5	33.3
Indices of Health Status							
Charlson Index							
≤1	89.7	87.6	91.9	94.2	90.4	84.5	87.1
≥2	10.3	12.5	8.1	5.8	9.6	15.5	12.9
Chronic Disease Score (mean ± SD)	5.1 ± 3.6	5.4 ± 3.6	5.0 ± 3.5	4.73 ± 3.36	5.2 ± 3.6	5.1 ± 3.7	4.7 ± 4.0

Table 2: Characteristics of Cases and Controls

	Cases (n=5,217)	Controls (n=104,337)
Socio-Demographics		
Age, yrs (mean ± SD)	79.8 ± 5.9	79.8 ± 5.9
Sex, female	66.4	77.3
Income Quintiles		
1	17.6	16.0
2	15.8	15.8
3	18.3	17.8
4	19.8	20.7
5	21.2	22.1
Missing	7.3	7.6
Social Network		
1	12.5	12.4
2	14.8	14.4
3	17.2	18.0
4	22.3	21.9
5	25.9	25.7
Missing	7.3	7.6
History of CV Disease (%)		
Previous MI	2.4	2.0
Hypertension	62.7	54.8
Ischemic heart disease	40.1	25.4
Stroke	4.8	2.9
Peripheral vascular disease	4.2	1.8
Congestive heart failure	19.1	9.5
Diabetes	24.1	13.7
Angioplasty	0.7	0.3
Rheumatoid Arthritis	1.4	1.0
Renal Disease	2.1	0.9
Respiratory Illness	28.8	21.3
Other Comorbidities(%)		
Thyroid Disorder	18.4	19.2
Cancer	5.6	5.0
Cardiovascular Drugs (%)		
Antiplatelets	3.1	1.8
Aspirin	40.7	30.5
Anticoagulants	7.6	4.7
ACE-inhibitors	29.0	20.4
Angiotensin receptor blockers	5.3	4.7
Lipid lowering drugs	20.7	19.4
Other Drugs (%)		
Hormone replacement therapy	14.5	19.0
COX-2 Inhibitors	10.4	10.0
NSAIDs	25.7	24.6
Oral Corticosteroids	21.5	15.8

Health Care Utilization		
No. unique drugs (mean ± SD)	14.2 ± 7.5	11.2 ± 6.0
Outpatient Medical Visits (mean ± SD)	16.0 ± 13.9	13.4 ± 10.8
No. of Hospitalizations		
0	51.6	70.1
1	25.8	19.8
≥2	22.6	10.1
Psychiatry Visits (%)	10.7	8.3
Indices of Health Status		
Charlson Index		
≤1	77.3	91.5
≥2	22.7	8.5
Chronic Disease Score (mean ± SD)	7.5 ± 4.1	5.9 ± 3.7

Table 3: Unadjusted and Adjusted Rate Ratios of Acute Myocardial Infarction or Cardiac Death for Monotherapy Use of Various Antidepressant Agents

	Cases [†] (n =5,217)	Controls [†] (n =104,337)	Unadjusted rate ratio	Adjusted [‡] rate ratio with 95% CI
Current use (%)				
Atypicals	235 (4.5)	4,323 (4.1)	1.00	1.00 (Reference)
SSRIs	1,247 (23.9)	25,784 (24.7)	0.89	0.92 (0.79-1.06)
Venlafaxine	220 (4.2)	5,089 (4.9)	0.79	0.80 (0.66-0.97)
TCAs	701 (13.4)	15,737 (15.1)	0.82	0.92 (0.78-1.07)
MAOIs	21 (0.4)	385 (0.4)	1.00	1.07 (0.67-1.69)
Past use [§] (%)				
SSRIs	610 (11.6)	9,687 (9.3)	1.16	1.21 (1.03-1.42)
Venlafaxine	90 (1.7)	1,438 (1.4)	1.16	1.15 (0.89-1.48)
TCAs	414 (7.9)	7,432 (7.1)	1.03	1.10 (0.93-1.30)
MAOIs	9 (0.2)	146 (0.1)	1.14	1.30 (0.65-2.61)
Atypicals	135 (2.6)	2,235 (2.1)	1.12	1.18 (0.95-1.48)
No use * (%)	1,140 (21.9)	25,678 (24.6)	0.81	0.95 (0.82-1.10)

SSRIs = Selective Serotonin Reuptake Inhibitors; TCAs = Tricyclic Antidepressants; MAOIs = Monoamine Oxidase Inhibitors; CI = confidence interval.

[†] An additional 177 cases and 3371 controls were current users of combination therapy, while an additional 218 cases and 3032 were past users of this therapy.

[‡] Adjusted for age at index (continuous variable); sex, income, social network, diabetes, ischemic heart disease, hypertension, congestive heart failure, cerebrovascular disease, previous myocardial infarction, peripheral vascular disease, renal disease, respiratory illness, rheumatoid arthritis, angioplasty, thyroid disorders, and cancer, in the year preceding cohort entry; use of concomitant therapy including lipid lowering agents, antiplatelets, aspirin, anticoagulants, hormone replacement therapy, cox-2 inhibitors, non-steroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and oral corticosteroids in the year preceding cohort entry; health care utilization including number of unique drugs, outpatient medical visits to any physician, outpatient psychiatry visits, and hospitalizations in the year preceding the index date and; chronic disease score and charlson index in the year preceding the index date.

***** No use in the year preceding the index date.

[§] Past users are those who were currently unexposed but had received at least one prescription for an antidepressant in the year preceding the index date.

Table 4: Unadjusted and Adjusted Rate Ratios of Acute Myocardial Infarction or Cardiac Death for Use of Various Antidepressant Combination Therapy

	Cases [†] **(n =5,217)**	**Controls** [†] **(n =104,337)**	**Unadjusted rate ratio**	**Adjusted** [‡] **rate ratio with 95% CI**
Current use (%)				
Other Combinations	45 (0.9)	1,004 (1.0)	1.00	1.00 (Reference)
SSRI-based Combinations	132 (2.5)	2,367 (2.3)	1.24	1.34 (0.94-1.91)
Past use [§] **(%)**				
Other Combinations	55 (1.1)	719 (0.7)	1.72	1.67 (1.10-2.53)
SSRI-based Combinations	163 (3.1)	2,313 (2.2)	1.59	1.66 (1.18-2.34)

SSRIs = Selective Serotonin Reuptake Inhibitors; CI = confidence interval.

[†] An additional 2424 cases and 51318 controls were current users of mono-therapy, while an additional 1258 cases and 20938 were past users of this therapy, with 1140 cases and 25678 controls being non-users.

[‡] Adjusted for age at index (continuous variable); sex, income, social network, diabetes, ischemic heart disease, hypertension, congestive heart failure, cerebrovascular disease, previous myocardial infarction, peripheral vascular disease, renal disease, respiratory illness, rheumatoid arthritis, angioplasty, thyroid disorders, and cancer, in the year preceding cohort entry; use of concomitant therapy including lipid lowering agents, antiplatelets, aspirin, anticoagulants, hormone replacement therapy, cox-2 inhibitors, non-steroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and oral corticosteroids in the year preceding cohort entry; health care utilization including number of unique drugs, outpatient medical visits to any physician, outpatient psychiatry visits, and hospitalizations in the year preceding the index date and; chronic disease score and charlson index in the year preceding the index date.

[§] Past users are those who were currently unexposed but had received at least one prescription for an antidepressant in the year preceding the index date.

	Cases (n=1,247)	Controls (n=25,784)	Adjusted RR (95% CI)	P-value ‡
Age, years				
<85	908	19,263	0.90 (0.77-1.05)	0.43
>85	339	6,521	0.96 (0.80-1.15)	
Sex				
Male	423	5,789	0.92 (0.77-1.10)	0.90
Female	824	19,995	0.91 (0.78-1.06)	
Previous MI				
Yes	29	632	0.68 (0.44-1.07)	0.18
No	1,218	25,152	0.92 (0.80-1.07)	
CVD				
Yes	582	7,907	0.92 (0.78-1.08)	0.90
No	665	17,877	0.91 (0.78-1.06)	
Diabetes				
Yes	310	3,587	0.98 (0.81-1.18)	0.28
No	937	22,197	0.90 (0.77-1.04)	
Anti-thrombotic				
Yes	652	9,896	0.94 (0.80-1.10)	0.51
No	595	15,888	0.90 (0.76-1.05)	

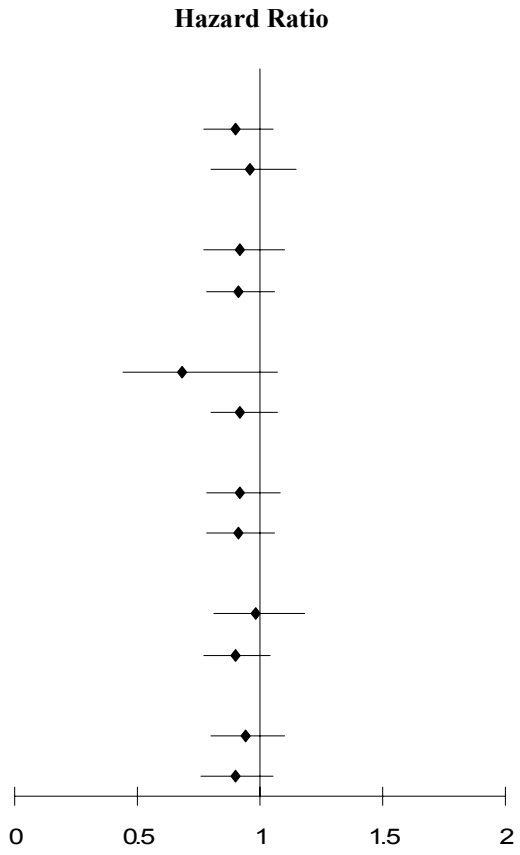

Figure 3: Adjusted Rate Ratios of Acute Myocardial Infarction and Cardiac Death for Current Use of Selective Serotonin Reuptake Inhibitors According to Various Prognostic Factors

‡ P-value for two-sided test of interaction comparing those with and without the prognostic factor at a significance level of $\alpha = 0.05$.

	Cases (n=220)	Controls (n=5,089)	Adjusted RR (95% CI)	P-value ‡
Age, years				
<85	174	3,959	0.81 (0.66-0.99)	0.70
>85	46	1130	0.75 (0.54-1.05)	
Sex				
Male	76	1,291	0.75 (0.57-0.99)	0.58
Female	144	3,798	0.82 (0.66-1.02)	
Previous MI				
Yes	3	125	0.38 (0.12-1.25)	0.22
No	217	4,964	0.81 (0.67-0.98)	
CVD				
Yes	77	1,405	0.65 (0.50-0.86)	0.04
No	143	3,684	0.89 (0.72-1.11)	
Diabetes				
Yes	52	716	0.76 (0.55-1.05)	0.71
No	168	4,373	0.81 (0.66-0.99)	
Anti-thrombotic				
Yes	113	1,842	0.84 (0.66-1.07)	0.43
No	107	3,247	0.75 (0.59-0.95)	

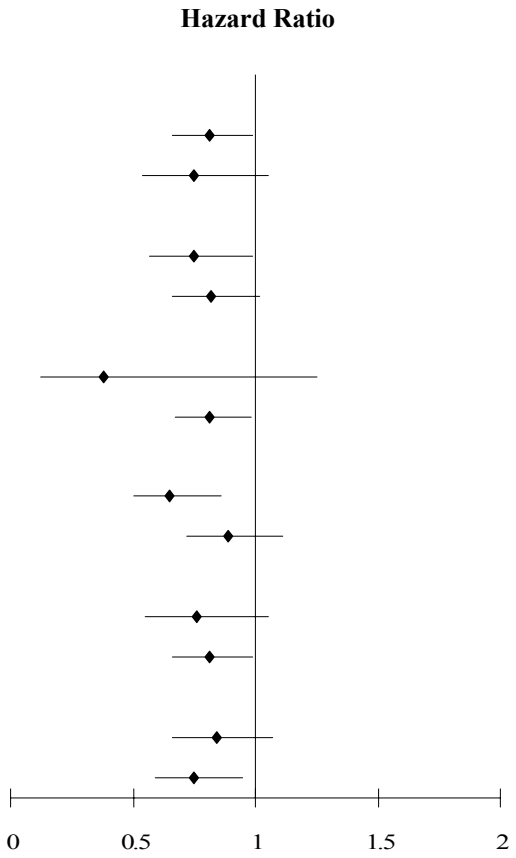

Figure 4: Adjusted Rate Ratios of Acute Myocardial Infarction and Cardiac Death for Current Use of Venlafaxine According to Various Prognostic Factors

‡ P-value for two-sided test of interaction comparing those with and without the prognostic factor at a significance level of $\alpha = 0.05$.

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Chapter 5: General Discussion

Main Findings

In this population-based cohort study, treatment with venlafaxine was associated with a significant reduction in the risk of MI and cardiac death as compared with users of atypical antidepressants. This association was more pronounced for persons with a history of cardiovascular disease than for those without, and possibly also for those with a previous MI compared with those with no such history, though the latter difference did not reach statistical significance. While, there was no clear evidence of benefit associated with the current use of SSRIs, the possibility of increased harm was nonetheless ruled out. Moreover, there was the suggestion of a clinically important benefit for SSRIs among persons with a history of MI. On the other hand, individuals who had stopped taking their SSRI prior to their index date (past users), were at greater risk of MI and cardiac death than current users of atypical agents, possibly due to the ongoing presence of depression. No benefit or harm was observed with current or past use of other antidepressants.

This study is the first to report a reduction for the risk of MI and cardiac death associated with the use of venlafaxine, a relatively new antidepressant with pronounced serotonin-activity at low doses. Despite the use of improved methodology, no benefit with the use of SSRIs was observed, although the lower limit of the 95% confidence interval does not rule out the possibility of a clinically important effect. In contrast with three case-control studies reporting increased risks of cardiovascular morbidity with SSRIs compared with no use of antidepressants,[1-3] no such risk was observed with the use

of a design that controlled for the confounding effects of depression itself and an analysis that controlled, at least in part, for the influence of duration and severity of depression.

Our findings for SSRIs are consistent with the results of the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART), the only randomized controlled trial published to date specifically designed to assess the cardiovascular benefits of treating depression with an SSRI compared with placebo in persons hospitalized for MI or unstable angina.[4] Like us, this trial found that sertraline is not associated with an increased risk of cardiac events in individuals with cardiovascular disease, and that it may even exert a beneficial effect. Indeed, our adjusted risk ratio of 0.68 (CI, 0.44-1.07) for SSRIs use in persons with a previous MI is compatible with that reported for major cardiovascular events for SADHART participants assigned to sertraline (RR 0.77 [0.51-1.16]). Our results are also consistent with those of the Enhancing Recovery in Coronary Heart Disease (ENRICHD) trial.[5] Although this trial was designed to assess the cardiovascular benefits of treating depression in persons with established CVD with cognitive behavioural therapy supplemented with an SSRI as needed, compared with usual medical care, a post-hoc analysis reported that SSRI use compared to non use was associated with a 43% risk reduction for (HR 0.57, 95% CI 0.38-0.85).

Strengths & Limitations

A major advantage of database studies of drug effects stems from the use of prospectively collected and validated information on outcomes and treatments for an entire population of unselected individuals. Unlike the results of clinical trials that often lack generalizability because they are typically conducted in highly selected populations

and under highly controlled conditions, the results of large observational cohort studies, such as the one in this thesis, are typically generalizable to most persons treated in routine practice.

In comparison with previous observational studies assessing the relationship between antidepressant use and cardiovascular risk, the study in this thesis is the first designed to control for confounding by depression (i.e. confounding by indication). Using a design novel to the antidepressant-CVD literature, the potentially confounding effects of depression were controlled for through the use of an 'all treated' cohort of antidepressant users, as well as the use of treated individuals as the comparator group (i.e., reference category).

Due to the fact that selection bias cannot be controlled for at the analysis stage, it can be a major threat to the validity of any study. In this study, the use of an all-inclusive population-based cohort of persons prescribed an antidepressant, combined with a "hard" primary endpoint, led to very high case ascertainment, and thus reduced the possibility of selection bias. Given the nature of these data, losses to follow up were negligible as they would primarily occur as a result of emigration from the province, which is unlikely to occur at a high rate in such an elderly population. Moreover, there is no reason to believe that emigration from the province would be associated with drug availability, especially given Québec's generous drug coverage policies. Although information on outcomes of interest were not available for those lost to follow-up, it is unlikely that the losses would be differential across exposure groups, and any resulting bias would be towards the null.

A strength of using a computerized prescription drugs database is the ability to effectively reconstruct drug exposure history, a difficult task to replicate in a field study.

However, the use of these data is not free of misclassification as information obtained about dispensed medications is not necessarily representative of biological exposure. However, this limitation is not restricted to the proposed study as field studies often rely on self-reports of drug history. In this study, there is no reason to believe that such misclassification would be differential as this would require individuals who fill their prescriptions, yet not consume them, to do so differentially across exposure categories. Moreover, SSRIs and SNRIs are known to be well tolerated. As a result, any misclassification should be non-differential, with the resulting bias being towards the null. In addition, the completeness and accuracy of the prescription drugs database has previously been demonstrated with 98% of elderly residents being registered, <1% of the information being missing or out of range, and 99% of prescriptions written to patients attending an internal medicine clinic, and recorded as being filled, correctly identifying the individual as well as the drug (Appendix 7).

We did not have information on the actual indication for the use of the antidepressant. Individuals receiving such an agent for an indication other than depression could be at lower risk of cardiovascular events. It is possible that a greater proportion of users of the atypical agents may have received these agents for indications other than depression (e.g. anxiety or insomnia) thus decreasing our ability to detect a protective association for users of SSRIs who are more likely to be depressed users. However, we detected a significant risk reduction for users of venlafaxine who were also compared with users of an atypical agent. A greater proportion of users of TCAs having been treated for indications such as neuropathic pain or anxiety disorders could explain

why the TCAs appeared to have an effect similar to that of the SSRIs, despite having known adverse cardiac effects, particularly with regards to arrhythmias.

Diagnostic misclassification of the study endpoint could also have introduced bias. However, as previously discussed, the coding accuracy of hospital discharge diagnoses of MI is very high in this data source resulting in minimal misclassification for individuals classified as cases in this study. The validity of hospital discharge diagnoses for identifying cases of MI has been previously demonstrated in the Quebec database with this diagnosis having 96.9% (95% CI, 94-98) agreement with the hospital medical record. While this does not rule out the possibility that controls may have been misclassified due to experiencing an MI which went undiagnosed (silent MI), it is improbable that such misclassification would in any way be associated with exposure, and therefore would bias results towards the null.

The possibility also exists that a detection bias could have resulted in misclassification of the outcome if subjects had received a differential work-up from physicians based on the differing CV effects of the antidepressant classes. However, the only two RCTs examining the antidepressant-CVD association were published in 2002-2003, and both produced non-definitive results, making it unlikely that physicians were aware of the cardio-protection hypothesis relating to these drugs. The use of a 'hard' CV endpoint, the high accuracy of the diagnostic code, and minimal knowledge of the cardio-protection hypothesis, especially that of serotonin mediated antiplatelet activity, makes it unlikely that a detection bias is present. In order to explain our results, the known cardiac effects of the SSRIs, venlafaxine, and the TCAs would have to have led to a less intensive work-up for patients on these drugs, also a very unlikely occurrence.

Our investigation into the effects of combination therapy yielded a 34% increased risk for MI and cardiac death in users of SSRI-based combinations as compared to users of other antidepressant combinations. If combination therapy is a marker for more severe depression, this finding reinforces the need to control for severity of depression when studying the antidepressant-CVD association. Although separate analyses were conducted for mono- and combination therapy, this is only one measure of depression severity as we did not have access to properly validated measures of severity such as the Hamilton Depression Rating Scale, or the Beck Depression Inventory Score that would be ideal in future research. Consequently, our separate analyses provide us with only a crude measure of severity that does not take into account the number, or types of drugs being used, indicating that the observed risk increases with SSRI-based combinations could be explained by residual confounding due to depression severity.

The possibility of confounding by indication due to missing information on factors that are determinants of the outcome is an important threat to the validity of observational studies. Although residual confounding due to unmeasured risk factors including smoking status, family history of MI, obesity and physical activity cannot be ruled out, many known risk factors for CV morbidity and mortality are documented in these databases, and were controlled for in the analysis. Furthermore, there was no evidence of selective prescribing of venlafaxine, SSRIs or atypical agents on the basis of any of the 30 factors that were measured. Consequently, although the possibility of residual confounding cannot be ruled out, it seems unlikely that physicians would preferentially prescribe venlafaxine or an SSRI over another antidepressant on the basis of the unmeasured risk factors, or on factors correlated with these. For example, hypertension

for obesity, and respiratory illness for smoking, showed no appreciable differences between the exposure groups of primary interest.

Finally, while the results our subgroup analyses suggest that the observed risk estimates for the association under study may be dependent on the presence of certain CV comorbidities including previous MI and CVD, the study lacked the statistical power to conclusively demonstrate these associations in all but one subgroup. Nonetheless, these findings are of clinical interest and possess strong biological plausibility.

Choice a Reference Category

An important decision for the validity of any study is the choice of an appropriate comparator or reference category. Following the decision to use treated individuals as the reference group, it was determined that an appropriate comparator would be chosen on the basis of our pharmacological hypothesis that serotonin mediated antiplatelet activity would decrease the risk of cardiovascular morbidity and mortality. As a result, the referent category would need to exhibit minimal serotonin selectivity, and in order to give the most clinically meaningful estimates, would preferably possess neutral cardiovascular effects. The atypical antidepressants were chosen a priori as the group which most closely fulfilled these criteria, while at the same time enabling us to provide information on the newer classes of antidepressant agents, and SNRIs in particular.

Whereas previous studies selected non-users as a comparator which likely resulted in confounding by indication, the choice of a treated reference group to control for this source of bias introduced some complexities in the interpretation of the results, which are compounded by the lack of information on the indication for the use of the antidepressant. For example, if the reference population were at increased risk of

cardiovascular morbidity and mortality because some users of bupropion, an atypical agent, were using this for smoking cessation rather than depression, then the exposures of interest would appear falsely protective. However, bupropion use represented a small percentage of the atypical category. If, on the other hand, users of atypical antidepressants were less likely to be receiving these agents for depression (i.e., not depressed), they would be at lower risk of cardiovascular events and make users of other agents appear to be at greater risk, or more importantly in the context of this study, bias a true protective effect towards the null.

A further complexity introduced by the use of a treated comparator is that all observed associations are relative to another antidepressant drug. Without the use of a placebo or unexposed comparator, determining the absolute effects of individual antidepressants is not possible. This notion, as well as the potential scenarios presented above, were all considered in the interpretation of the results, together with a close examination of all risk factors measured at baseline.

External Validity

The results of this study cannot necessarily be generalized to unstudied younger individuals. However, the use of such a large and unselected population-based cohort of persons aged 66 years and older possesses excellent generalizability to a segment of the population commonly prescribed antidepressants and also at highest risk of cardiovascular events. The source population is quite representative of Quebec seniors due to the fact that at least 55% of seniors in this province received an NSAID at any one time. In addition, given the postulated mechanism for the beneficial cardiovascular effects of some antidepressants, that is serotonin mediated antiplatelet activity, there is no

reason to believe that younger persons would not derive equal benefit, although the net gain would be less in view of their lower baseline rate of event. Since the use of an NSAID is accompanied by an increase in bleeding time, the possibility exists that the observed results were exaggerated by the concomitant user of NSAIDs. On the other hand, since the use of NSAIDs is intermittent, it is unlikely that a large number of people would have been concurrently receiving this therapy, and the concomitant use of NSAIDs was accounted for in the analyses. Finally, the venlafaxine findings of a reduced risk of cardiac morbidity and mortality cannot be generalized to individuals receiving higher doses of this agent given that the majority of individuals in this study received average daily doses of 75mg, doses known to be sub-therapeutic for the treatment of depression.

Future Research

The results of this thesis indicate a need for additional analyses to provide further insight into the antidepressant-CVD relationship. For instance, there was a suggestion of an increased risk for past users of all antidepressants, although only that of SSRIs reached statistical significance. Repeating the analysis by stratifying past users by time since treatment discontinuation may help indicate whether this risk increase is due to the removal of a pharmacological benefit or the effects of untreated depression. For example, if the observed results were due to serotonin mediated antiplatelet activity, we would expect to find an early risk increase (i.e., among individuals with the shortest time since treatment discontinuation) which would diminish over time. An explanation for this could be serotonin discontinuation syndrome, characterized by symptoms including dizziness, anxiety, fatigue, insomnia, irritability, nausea, tremor, and potentially platelet activity rebound [6]. On the other hand, if unresolved depression was the underlying cause

for increased risk in past users, then we would expect to see an increased risk in past users with the longest time since treatment discontinuation (i.e., risk exacerbated through prolonged exposure to untreated depression) but a low or no risk soon after treatment discontinuation.

A number of sensitivity analyses could also be undertaken to verify the robustness of the study results. First, prescriptions filled *within 7 days* of the index date met the definition of *current* exposure but may not represent etiologically relevant exposure if there is insufficient time for the pharmacological actions of these agents to manifest themselves. Consequently, the primary analyses should be repeated with prescriptions dispensed within 7 days of the index date excluded.

Second, in the primary analysis current exposure was defined on the basis of the last prescription dispensed prior to the index date overlapping with this date. However, it is possible given the pharmacodynamic properties of some of the antidepressants that their pharmacological effect on platelets and other mechanisms could extend for a few days to a few weeks following treatment discontinuation. Consequently, to test the assumption of a possible residual effect, the primary analyses should be repeated using a definition of current users that permits a grace period of up to 14 days and in a separate analysis 30 days, prior to the index date.

Contribution

This thesis has addressed an important controversy regarding the effects of antidepressants on cardiovascular morbidity and mortality. This study was the first to assess the cardiovascular effects of antidepressants independent of both the effects of depression itself, and also the duration of treated depression. The results of this study

should reassure clinicians that the use of SSRIs and SNRIs is associated with no increased risk for cardiovascular events, even in persons with established cardiovascular disease, and they also provide important information regarding the choice of an appropriate design for future studies of the antidepressant-CVD association. This information, combined with valuable insight gained through the examination of clinically relevant subgroups, will contribute new knowledge on the management of depression vis-à-vis cardiac risk.

Recommendation and Conclusion

Given the widespread prevalence of depression in society today, the expected increases in major depression estimated to occur over the next 15 years, the aging of the population, and the high incidence of cardiovascular events in this population, there is a need for information on the cardiovascular effects of currently available antidepressant pharmacotherapy to enable physicians and their patients to make informed treatment decisions. With increased marketing pressures due to improved side effect profiles, accurate information on the cardiovascular safety of the newer generation drugs such as SSRIs and venlafaxine is especially important. This study demonstrates a reduced risk for cardiovascular outcomes associated with the use of venlafaxine, and suggests a potential benefit from the use of SSRIs in persons with a previous MI. Equally important, this study found no evidence of an increased risk associated with the use of two of the most commonly prescribed classes of antidepressants. There is now a need for properly designed and powered trials to confirm these findings. In the interim, physicians should continue to prescribe venlafaxine and SSRIs in the treatment of depression in

patients with heart disease, not only because of their potential impact on cardiovascular health, but also for their profound implications on a patient's quality of life.

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Appendix 1: Classification and Pharmacology of the Antidepressants [†]

Classification	Agent	Receptor site activity					Anti-cholinergic	Hypo-tension	Cardiac Effects
		NE	5-HT	DA	NE selectivity	5-HT selectivity			
Tetracyclics	Maprotiline	√			532		2+	2+	2+
Tricyclics (TCAs)	Amitriptyline	√	√			7.97	3+	3+	3+
	Amoxapine	√		√	3.63		+	2+	2+
	Clomipramine	√	√			132	3+	3+	3+
	Desipramine	√			21.1		+	2+	2+
	Doxepin	√	√		2.27		2+	3+	3+
	Imipramine	√	√			26.2	2+	3+	3+
	Nortriptyline	√			4.25		+	2+	2+
	Protriptyline	√			14.0		2+	3+	3+
	Trimipramine	√	√			264	3+	3+	3+
Monoamine Oxidase Inhibitors (MAOIs)	Phenelzine [‡]	√	√	√			0	0	0
	Tranylcypromine [‡]	√	√	√			0	0	0
	Moclobemide [§]								

Selective Serotonin Reuptake Inhibitors (SSRIs)	Citalopram		√			3696	0	0	0
	Escitalopram		√				0	0	0
	Fluoxetine		√			301	0	0/+	0/+
	Fluvoxamine		√			586	0	0	0
	Paroxetine		√			320	0/+	0	0
	Sertraline		√			1423	0	0	0
Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)	Venlafaxine	√	√			116	0	0/+	0/+
Atypical Antidepressants	Bupropion		?√	√		5.78	0	0	0
	Mirtazapine	√	√		21.0		0	0	0
	Nefazodone		√			1.80	0	0/+	0/+
	Trazadone		√			51.9	0	0/+	0/+

0=negligible; 0/+=minimal; +=mild; 2+=moderate; 3+=moderately severe; 4+=severe.
† Adapted from: [1].
‡ Non-selective MAOI.
§ Selective MAOI.

Appendix 2: Classification, Mechanism of Action, Indications, and Contraindications of Antidepressant drugs.

Drug Class	Mechanism of Action	Agents	Indications[2]	Contraindications[2]
Selective Serotonin Reuptake Inhibitors	- Inhibit neuronal reuptake of serotonin by blocking the serotonin transporter. SSRIs also appear to have minor inhibitory effects on dopaminergic and noradrenergic reuptake.[3]	Citalopram HBr	Depressive Illness.	Hypersensitivity; within 14 days of treatment with an MAOI.
		Escitalopram Oxalate	Depressive Illness.	As for Citalopram.
		Fluoxetine HCl	Depressive Illness; Bulimia Nervosa; OCD.	As for Citalopram.
		Paroxetine HCl	Depressive Illness; OCD; Panic Disorder; Social Phobia; Generalized Anxiety Disorder; Post-traumatic Stress Disorder; Premenstrual Dysphoric Disorder.	As for Citalopram.
		Sertraline HCl	Depressive Illness; OCD; Panic Disorder.	As for Citalopram.
Tricyclic Antidepressants	- Inhibit the reuptake of norepinephrine, and to a lesser degree serotonin.[3]	Amitriptyline	Depressive Illness; atypical analgesic in the management of fibromyalgia; migraine prophylaxis; rheumatoid arthritis; and various neuropathies.	Hypersensitivity; within 14 days of treatment with an MAOI; during the acute recovery phase following MI or in the presence of congestive heart failure.
		Nortriptyline	Depressive Illness; or also in the management of neuropathic pain; chronic pain; and smoking cessation.	As for Amitriptyline.
		Imipramine	Depressive Illness.	Hypersensitivity; within 14 days of treatment with an MAOI; during the acute recovery phase following MI or in the presence of congestive heart failure; in those with existing kidney or liver damage, a history of blood dyscrasias, or glaucoma.
		Clomipramine	Depressive Illness; OCD.	As for Imipramine.

		Desipramine	Depressive Illness.	Hypersensitivity; within 14 days of treatment with an MAOI; during the acute recovery phase following MI or poorly controlled cardiac decomposition.
		Trimipramine	Depressive Illness.	As for Desipramine.
		Doxepin	Depressive Illness; Anxiety Disorder.	As for Imipramine.
Monoamine Oxidase Inhibitors	- Act through inhibition of monoamine oxidase (MAO), an enzyme found on the outer membrane of mitochondria which catabolizes a number of monoamines such as dopamine, norepinephrine, and serotonin.[3]	Phenelzine	Depressive illness, for patients who have failed to more commonly used drugs.	Hypersensitivity; pheochromocytoma; congestive heart failure; history of liver disease or abnormal liver function tests; combination therapy with sympathomimetic drugs, dextromethorphan, CNS depressants, MAOI's, buspirone HCl, fluoxetine, guanethidine, reserpine, or anesthesia.
		Tranyl-cypromine Sulfate	Depressive Illness, for treatment of moderate to severe depression.	Hypersensitivity; cerebrovascular or cardiovascular disorders with history of recurrent headaches; in patients beyond age of 60; liver damage or blood dyscrasias; pheochromocytoma; combination therapy with any antidepressants or sympathomimetics.
		Moclobemide	Depressive Illness.	Hypersensitivity; combination with TCA's or narcotics.
Tetracyclics	- Strong inhibition of noradrenaline reuptake in the brain and peripheral tissues, with a minimal inhibitory effect on serotonin reuptake.[2]	Maprotiline	Treatment of depressive affective disorders, dysthymic disorder, major depression and anxiety related depression, and neuropathic pain.	Hypersensitivity; within 14 days of treatment with an MAOI; during acute recovery phase following acute MI and in patients with congestive heart failure; in those with known seizure disorders, existing kidney or liver damage, a history of blood dyscrasias, or angle-closure glaucoma.

Norepinehphrine Dopamine Reuptake Inhibitor	- Appears to primarily block the uptake of dopamine and norepinephrine, although the true mechanism is not confirmed. Overall effect is a dose-dependent increase in extracellular levels of dopamine and norepinephrine in the brain.[3]	Bupropion HCl	Depressive Illness	Hypersensitivity; in patients with seizure disorder; those with a prior diagnosis of bulimia or anorexia nervosa; within 14 days of treatment with an MAOI; in combination with the antipsychotic thioridazine; in those undergoing withdrawal from alcohol, benzodiazepines, or sedatives.
Serotonin Receptor Antagonist / Agonist	- Relatively weak inhibitor of serotonin and norepinephrine reuptake, primarily blocking serotonin 5HT2A receptors. Trazodone also has an active metabolite which acts as a serotonin 5HT2C agonist, and possesses the ability to release serotonin presynaptically.[3]	Trazodone HCl	Depressive Illness.	Hypersensitivity.
Serotonin Norepinephrine Reuptake Inhibitor	- At daily doses exceeding 150 mg, venlafaxine inhibits the reuptake of both serotonin and norepinephrine, while at lower doses mostly inhibiting the reuptake of serotonin.[3]	Venlafaxine HCl	Depressive Illness; Social Phobia; Generalized Anxiety Disorder.	Hypersensitivity; within 14 days of treatment with an MAOI.

Appendix 3: Randomized controlled trials of antidepressants for psychiatric morbidity in patients with cardiovascular disease

A. Antidepressant Effects on Cardiovascular Outcomes

Trial	Study Population	Follow Up	Treatment	No. of subjects	Endpoints	Results
Berkman et al[4] (ENRICHD) 2003	MI patients with major and minor depression	Mean 29 months	Cognitive behavioural therapy supplemented with an SSRI where indicated	2481	1^0: composite end point of death or recurrent MI 2^0: change in Hamilton Depression Rating Scale, or Enrichd Social Support Instrument for low perceived social support	No significant difference in event free survival between usual care and psychosocial intervention. Antidepressant drug use was associated with a lower risk of recurrent MI or death.
Glassman et al[5](SADHART) 2002	MI and/or angina patients with major depression	24 weeks	Sertraline *v* placebo	369	1^0: change from baseline left ventricular ejection fraction (LVEF) 2^0: surrogate cardiac measures, CV events, change in depression scales	Sertraline had no significant effect on mean LVEF or other cardiac measures Non-significant trend suggesting sertraline protective against CV events In sertraline group: MI (N=5) CV death (N=2) Stroke (N=2) Sertraline superior to placebo for most depression outcomes
McFarlane et al 2001[6]	MI patients with major and minor depression	22 weeks	Sertraline *v* placebo	27	1^0: time dependent changes in both time and frequency domain parameters of heart rate variability (HRV)	Increased HRV with sertraline, and decreased HRV with placebo Sertraline superior to placebo on depression scores
Strik et al 1998[7]	MI or hypertension patients with major depression	6 weeks	Fluoxetine *v* fluvoxamine	20	1^0: LVEF, aortic flow interval, active mitral inflow, electrocardiography	Ejection fraction improved by both drugs in patients with CV disease Both drugs do not effect cardiac function adversely Both drugs effective in treating depression

B. Antidepressant Efficacy in Treating Depression

Trial	Study Population	Follow Up	Treatment	No. of subjects	Endpoints	Results
Fruehwald et al 2003[8]	Stroke patients with moderate to severe depression	12 weeks, with open label long term assessment at 18 months	Fluoxetine *v* placebo	50	1^0: change in depression rating scale	Improvement in depression scores at four weeks in both groups. Fluoxetine superior in open label follow up. No CV effects reported.

Strik et al 2000[9]	MI patients with major depression	25 weeks	Fluoxetine *v* placebo	54	1^0: efficacy of fluoxetine on various depression rating scales 2^0: cardiac function measured by echocardiography and electrocardiography	Fluoxetine superior to placebo for most depression outcomes. Non-significant trend suggesting fluoxetine reduced readmission to hospital for CV events. Fluoxetine group rehospitalization (N=1)
Wiart et al 2000[10]	Stroke patients with major depression	6 weeks	Fluoxetine *v* placebo	31	1^0: change in depression rating scale 2^0: motricity index, functional independence measure, and mini-mental state examination	Fluoxeting significantly more effected than placebo for depression. No significant CV effects reported.
Robinson et al 2000[11]	Stroke patients with major or minor depression	12 weeks	Fluoxetine *v* nortriptyline *v* placebo	56	1^0: change in depression rating scale 2^0: functional independence measure, mini-mental state exam, functional inventory, social functioning exam	Nortriptyline significantly more effective than fluoxetine and placebo for depression and anxiety symptoms Increase in heart rate significantly greater in nortriptyline group than placebo group
Roose et al 1998[12]	IHD patients with major depression	8 weeks	Paroxetine *v* nortriptyline	81	1^0: decline in scores on depression rating scale 2^0: CV outcomes -HR, BP, ECG intervals, indexes of HRV, and rate of adverse events	Paroxetine slightly but not significantly superior to nortriptyline in treatment of depression Increased HR and decreased HRV with nortriptyline Significant excess of withdrawals in nortriptyline group due to adverse cardiovascular events (18% - n=7 *v 2%* - n=1)
Dam et al 1996[13]	Stroke patients with depression	12 weeks	Fluoxetine *v* maprotiline *v* placebo	52	1^0: neurological and functional recovery, and depression rating scale	No cardiovascular effects reported; fluoxetine group superior to maprotiline and placebo groups in functional indices Fluoxetine and maprotiline associated with significant improvement in depression
Andersen et al 1994[14]	Stroke patients with moderate to severe depression	6 weeks	Citalopram *v* placebo	66	1^0: change in depression rating scale 2^0: side effect rating scale	Better outcome in citalopram group No serious CV side effects reported

Appendix 4: Antidepressant Use and Cardiovascular Outcomes – Observational Studies

CASE-CONTROL STUDIES								
Study	**Design**	**# of patients**	**Follow-up**	**Exposure**	**Primary Outcome**	**Reference Group**	**Covariates**	**Results**
Tata et al., 2005[15]	Case-control analysis, and a self controlled case series	60,000 cases of MI with 360,000 matched controls	12.3 years (1988 - 2001)	Source: UK General Practice Research Database Exposure: Antidepressant drugs Time Window: 1-7, 8-14, 15-21, 22-28, >28 days after prescription	First time myocardial infarction	360,000 age, sex, and practice matched controls	BMI, smoking, BP, anti-hypertensive & hyperlipidemic drugs, diabetes	OR (95% CI): Any SSRI 1.49 (1.43-1.56) Any TCA 1.41 (1.37-1.45) Any MAOI 1.26(1.00-1.59) Any 'other' 1.39 (1.26-1.54)
Monster et al., 2004[16]	Population based case-control	8887 cases of MI with 88,862 matched controls	8 years (1994-2002)	Source: Pharmaco-epidemiologic Prescription database of North Jutland County, Denmark Exposure: antidepressant drugs Time Window: separate analyses for <30, <90, or >90 days before hospitalization	First time myocardial infarction	Non users of antidepressants	Chronic bronchitis, or emphysema (proxy for smoking), alcoholism, DM, HT, and a variety of concomitant prescriptions	Patients with CVD adjusted OR (95% CI): SSRIs: 0.85 (0.62 – 1.16) Nonselective SRIs: 0.83 (0.50 – 1.38) Other antidepressants: 0.55 (0.31 – 0.97)

Schlienger et al., 2004[17]	Population based case-control	8688 cases of MI with 33,923 matched controls	6 years (1995 – 2001)	Source: UK General Practice Research Database Exposure: antidepressant drugs Time Window: current user if last Rx lasted until event, else recent past or past user depending on lag between end of therapy and index date	First time myocardial infarction	Non users of antidepressants	BMI, smoking, # GP visits, HT, DM, IHD, other cardiac diseases, arterial vascular diseases, kidney disease, acute respiratory diseases/infection, aspirin use	Adjusted OR (95% CI): SSRIs: 0.63 (0.43 – 0.91) Non-SSRIs: 0.92 (0.77 – 1.09) Other antidepressants: 0.59 (0.29 – 1.20)
Sauer et al., 2003[18]	Case-control	1080 cases of MI with 4256 controls	3 years (1998 – 2001)	Source: Structured telephone interview Exposure: Antidepressant drugs Time Window: Week prior to index date	First myocardial infarction	Non users of antidepressants	Age, gender, race, education, physical activity, smoking, apirin use, BMI, family hx of DM, HT, CAD, and hypercholesterolemia, a number of concomitant drugs, alcohol & caffeine intake, vitamin use, marital status, and type of insurance	Adjusted OR (95% CI): SSRIs: 0.72 (0.49 – 1.05) Tricyclics: 1.63 (0.89 – 2.88) Atypicals: 1.28 (0.75 – 2.20)
Bak et al., 2002[19]	Nested case-control study	4765 cases of stroke with 40,000 controls	5 years (1994 – 1999)	Source: Odense University Pharmaco-epidemiological database Exposure: Antidepressant drugs Time Window: If supply ended after 30 days before index date → current user; between 31-60 days → recent user; >61 days → past user	All stroke (displayed separately in analyses) 2717 Ischemic strokes	Never use of antidepressants	Age, sex, HT, DM, smoking, and other stroke risk factors (used concomitant drugs as proxy measures)	Adjusted OR (95% CI) SSRIs: 1.10 (0.9 – 1.4)

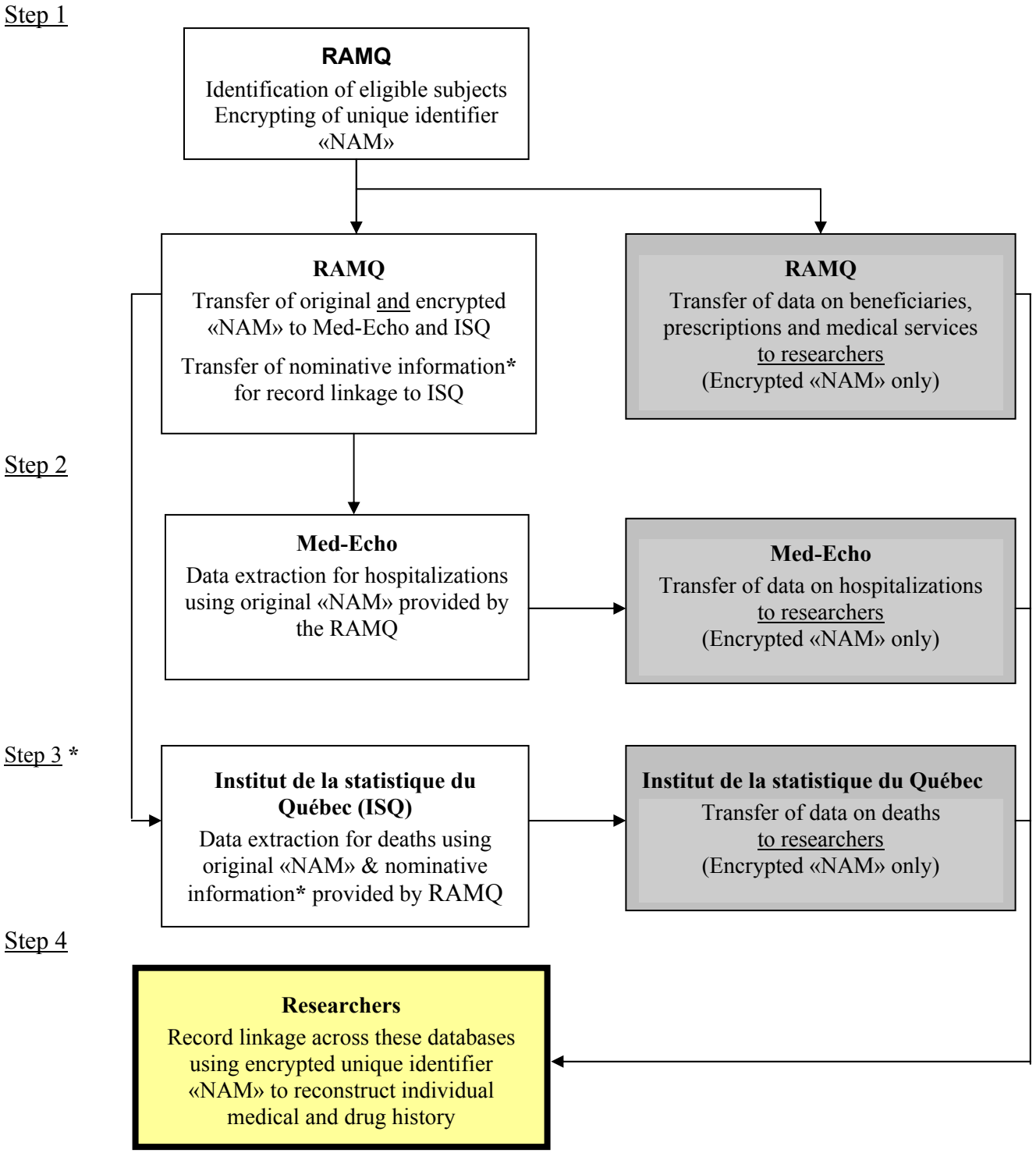
Sauer et al., 2001[20]	Case-control	653 cases of MI with 2990 control subjects; all smokers	2.3 years (1995 – 1997)	Source: Structured telephone interview Exposure: Antidepressant drugs Time Window: Week prior to index date	First myocardial infarction	Non users of antidepressants	Age, sex, race, education, exercise, smoking, BMI, # GP visits, aspirin use, family hx, hx of CAD, DM, HT, and hypercholersterolemia, income, vitamin use, marital status, caffeine and alcohol, insurance type, season during index week, and concomitant drugs	Adjusted OR (95% CI): SSRIs: 0.35 (0.18 – 0.68) Non-SSRIs: 0.48 (0.17 – 1.32)
Hippisley-Cox et al., 2001[21]	Case-control	933 incident cases of Ischemic Heart Disease with 5516 matched controls	4 years (1995 – 1999)	Source: Trent Focus Collaborative Research Network Database Exposure: Antidepressant drugs Time Window: before diagnosis	Diagnosis of Ischemic Heart Disease	Non users of antidepressants	DM, HT, BMI, smoking	Adjusted OR (95% CI): SSRI ever: 1.29 (0.89 – 1.87) TCA ever: 1.56 (1.18 – 2.05)
Meier et al., 2001[22]	Population based case-control	3319 cases of MI free of predisposing factors to IHD with 13,139 matched controls	5 years (1992 – 1997)	Source: UK General Practice Research Database Exposure: Antidepressant drugs Time Window: Current user if last Rx lasted until within 30 days of event; 31-60 days were recent users; >61 days were past	First time myocardial infarction	Non users of antidepressants	BMI, smoking status, aspirin use, HRT use, use of antibiotics, respiratory tract infection, # GP visits	Adjusted OR (95% CI): SSRIs: 0.9 (0.5 – 1.8) Non SSRIs: 0.9 (0.7 – 1.2) Other antidepressants: 1.3 (0.6 – 2.8)

COHORT STUDIES								
Study	**Design**	**# of patients**	**Follow-up**	**Exposure**	**Primary Outcome**	**Reference Group**	**Covariates**	**Results**
Taylor et al., 2005[23]	Observational secondary analysis of ENRICHD RCT	1834 depressed patients	Mean: 29 months	Source: Enhanced Recovery in Coronary Heart Disease (ENRICHD) RCT Exposure: use of SSRIs (mainly Sertraline), or other antidepressants Time Window: antidepressant drug use treated as time dependent covariate	Death, recurrent MI 457 fatal and non-fatal CV events	Patients who did not use SSRIs	Age, baseline Beck Depression Score, Killip class, ejection fraction, left ventricular dysfunction, serum creatinine, previous MI, prior dx of stroke, TIA, CHF or DM	SSRIs Adjusted HR (95% CI): All cause mortality 0.59 (0.37 – 0.96) Recurrent MI 0.53 (0.32 – 0.90)
Ray et al., 2004[24]	Retrospective cohort	481,744	5 years (1988 – 1993)	Source: Tennessee Medicaid Database Exposure: Cyclic antidepressants Time Window: current use from day of filling Rx through end of supply, nonuse if non in past 365, recent if some in past 365 but none currently	Sudden cardiac death 1487 deaths	Non users of antidepressants	Calendar year, age, sex, race, measure of medical use and comorbidity	Rate ratio (95% CI): TCAs: (dose-dependent increase in risk) for all doses: 1.12 (0.89 – 1.40) SSRIs: 0.95 (0.45 – 2.15)
Cohen et al., 2000[25]	Prospective cohort	54,997 (2247 who received at least one Rx for antidepressants during 1991-1992)	Mean: 3.3 years Minimum: 6 months Max: 4.5 years	Source: National Prescription Administrators Inc. data tapes Exposure: Antidepressant drugs Time Window: not reported	Hospitalization or death due to myocardial infarction 16 MIs among users of antidepressants	Non users of antidepressants	Age, sex, heart disease, HT, DM, hyperlipidemia, anxiety, cancer, and stratified by use of drugs for heart disease, and HT	Adjusted RR (95% CI) SSRIs: 0.8 (0.2 – 3.5) TCAs: 2.2 (1.2 – 3.8)

Appendix 5: Details of Data to be Obtained from Various Data Sources

SOURCE / AGENCY	DATABASE	INFORMATION OBTAINED	USE OF DATA	TIME FRAME AVAILABLE
Régie de l'Assurance-maladie du Québec (RAMQ)	Population Registry (Beneficiary file)	▪ Encrypted NAM (unique identifier) ▪ Age ▪ Sex ▪ Date of death (if applicable) ▪ Indicator of area of residence ▪ Insurance coverage enrollment & termination dates ▪ Indicator of social and economic status (using 6 digit postal code)	▪ Encrypted NAM (unique person identifier) will be used to link various records across databases ▪ To obtain socio-demographic information on all cohort members	▪ At cohort entry where applicable
	Prescription Claims	▪ Encrypted NAM (unique identifier) ▪ Drug name ▪ Dose dispensed ▪ Quantity & duration dispensed ▪ Dispensing date ▪ Costs ▪ Prescription status (new or refill)	▪ Identify cohort members & date of cohort entry ▪ Exposure for drugs of interest ▪ Identification of comorbidities from corresponding drug treatments (e.g., hypertension, heart disease, diabetes)	▪ Depending on age at cohort entry or year of residency in Québec (start of coverage), a minimum of 1 year & up to 5 years preceding cohort entry ▪ Up to the end of study, death or termination of coverage
	Medical Services & Procedures	▪ Encrypted NAM (unique identifier) ▪ Medical visits/procedure ▪ Diagnostic code for service ▪ Date of service ▪ Nature of service/procedure ▪ Location of service ▪ Physician specialty	▪ Identification of certain medical procedures (e.g. angioplasty) and associated comorbid conditions (e.g., coronary artery disease) ▪ Health care utilization covariates	▪ Depending on year of residency in Québec (start of coverage), a minimum of 1 year & up to 10 years preceding cohort entry ▪ Up to the end of study, death or termination of coverage
Ministère de la santé et des services sociaux (MSSS)	Hospitalizations	▪ Encrypted NAM (unique identifier) ▪ Admission & discharge dates ▪ Type of admission (eg., acute) ▪ Hospital identification code ▪ Hospital type (eg., acute, chronic) ▪ Primary diagnosis (ICD-9) ▪ Up to 15 secondary diagnoses ▪ Length of stay ▪ Hospital mortality indicator (where applicable)	▪ Identification of study outcomes ▪ Identification of comorbidities from corresponding admissions (e.g., diabetes, heart disease, congestive heart failure) ▪ Health care utilization covariates	▪ Depending on year of residency in Québec (start of coverage), a minimum of 1 year & up to 10 years preceding cohort entry ▪ Up to the end of study, death or termination of coverage
Institut de la statistique du Québec (ISQ)	Vital Statistics	▪ Encrypted NAM (unique identifier) ▪ Date of birth and sex ▪ Date of death ▪ Cause of death (ICD-9/ICD-10)	▪ Identification of all deaths (study outcomes) and causes of deaths	▪ Anytime following cohort entry to the end of the study

Appendix 6: Data Encrypting and Data Transfer



RAMQ will communicate to the Ministère de la santé et des services sociaux (MSSS) or its agent (l'Institut de la Statistique du Québec the following information to facilitate record linkage with the vital statistics database: original NAM, encrypted NAM, full name, date of birth, sex, and when available date last known to be alive (e.g., last date service obtained or termination of insurance coverage).

Appendix 7: Results of Validation Study of Québec's Prescription Claims Database[26]

CRITERIA	VARIABLE	RESULTS	
Comprehensiveness	Proportion of elderly residents registered in the database	98%	
Completeness of data	Proportion of information missing or out of range values	Drug code	0.0%
		Drug class	0.0%
		Date dispensed	0.0%
		Quantity dispensed	0.4%
		Duration stated	0.0%
		Type of order	0.7%
		New or refill Rx	0.7%
		Prescriber identification	0.0%
		Pharmacy identification	0.0%
Accuracy of data	Proportion of information accurately recorded in database †	Written Rx captured	83.0% ‡
		Unique person identifier	99.0%
		Drug	99.0%
		Duration	72.1% §
		Quantity	69.1% §
		Prescribing physician	91.0%

† Accuracy of data recorded in the prescription claims database was based on a comparison of the information contained in the database to that of the outpatient medical record. An important assumption made by this assessment is that the medical record is error-free and that changes made to the prescription by the pharmacist in consultation with the prescriber would be captured by the clinic's medical record.

‡ Not necessarily indicative of errors as individuals may choose not to fill a prescription that has been given to them. Available data indicate that this occurs at least 10% of the time.

§ 88% of the time for a quantity or duration that was less than that indicated on the written prescription. It is important to recognize that these do not necessarily represent documentation errors as pharmacists in Québec are permitted to reduce the quantity and duration authorized by a physician.

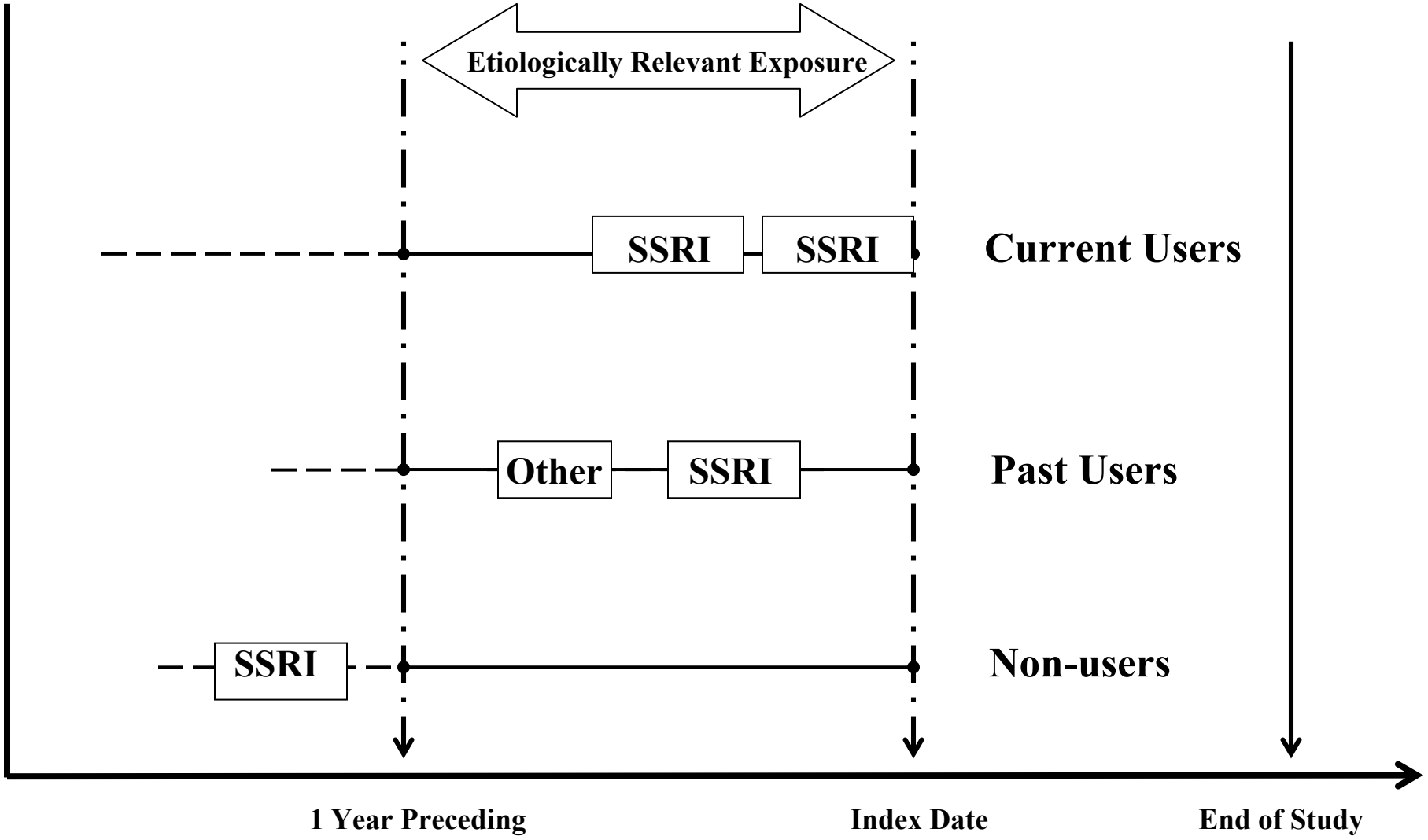
Appendix 8: Description of data verification

DATASET	CRITERIA
Beneficiary file	Check for duplicate lines (all variables identical)
	Check for duplicate "NAMs" (duplicates due to changes in coverage/plan are appropriate)
	If duplicates, verify: a) number and proportion (%) of subjects with duplicate observations b) if duplicate observations have different insurance plans/coverage («code de plan»)
	Verify that date of "start" of coverage always before "end" date: a) within observations (same line) b) across observations for same 'NAM"
	Check for gaps in coverage for each subject ("NAM")
	If gaps in coverage identified: a) quantify # and % of subjects ("NAMs") with any gap b) quantify # days for gaps & examine distribution (proc means/proc freq) c) quantify # gaps per subject ("NAM") & examine distribution (proc means/proc freq)
	Check each variable for missing or out-of-range values (i.e., proc freq for each variable)
	Examine frequency of subjects where insurance plan («code de plan») = DE (date of death) on start date; repeat for end date
	Examine distribution of start dates and end dates by month and by year
	Examine distribution of beneficiaries by age, sex, and both combined (age*sex)
	Examine distribution of date of death by month and by year & compare to that in death file
	Verify if all subjects with a date of death here are also documented in death file
	Compare date of death documented here with that documented in death file
	Compare date of death documented here with start date where insurance plan («code de plan») = DE in beneficiary file
Health professionals file	Check for duplicate lines (all variables identical)
	Verify that encrypted identifiers are not duplicated (i.e., unique identifiers)

	Check each variable for missing or out-of-range values (i.e., proc freq for each variable)
Prescription drugs file	Check for duplicate lines (all variables identical)
	Compare "NAMs" listed here against those in beneficiary file
	Compare encrypted prescriber ID listed here against those in health professionals file
	Check each variable for missing or out-of-range values (i.e., proc freq for each variable)
	Check the following drug variables for apparent validity: a) drug codes («dénomination commune») consistent with RAMQ list of codes b) dosage form codes («code de forme») consistent with RAMQ list of codes c) drug strength codes («code de dosage») consistent with RAMQ list of codes d) correct strength and dosage form for each drug (proc freq for drug*strength*form) e) correct duration (quantity dispensed/known or typical dosing frequency)
	Check that prescriptions dispensed same day to an individual are for different drugs
	Check the "dispensing date" variable for apparent validity: a) range of dates vs study period requested b) "dispensing date" vs dates of insurance coverage (chronology) c) distribution of dispensing "month" by calendar year (proc freq month*year) d) "dispensing date" ≤ date of death (chronology)
	Check each subject for important gaps (>6 months) in service utilization (any prescription) to identify potentially missed deaths
Medical services file	Check for duplicate lines (all variables identical)
	Compare "NAMs" listed here against those in beneficiary file
	Compare encrypted prescriber ID listed here against those in health professionals file
	Check each variable for missing or out-of-range values (i.e., proc freq for each variable)

	Check the following variables for apparent validity: a) professional speciality («spécialité») consistent with RAMQ list of codes b) service codes («code S2») consistent with RAMQ list of codes c) diagnostic codes («code diagnostic») consistent with ICD-9
	Check the "service date" variable for apparent validity: a) range of dates vs study period requested b) "service date" vs dates of insurance coverage (chronology) c) distribution of service "month" by calendar year (proc freq month*year) d) "service date" ≤ date of death (chronology)
	Check each subject for important gaps (>6 months) in service utilization (any service) to identify potentially missed deaths
	Check service dates where location = hospital against dates of hospitalizations
Hospitalizations file	Check for duplicate lines (all variables identical)
	Compare "NAMs", age and sex listed here against those in beneficiary file
	Check each variable for missing or out-of-range values (i.e., proc freq for each variable)
	Check the "admission date" variable for apparent validity: a) range of dates vs study period requested b) "admission date" vs dates of insurance coverage (chronology) c) distribution of admissions by month, by year, both combined d) "admission date" + length of stay ≤ date of death (chronology) e) discharge date – admission date = length of stay f) admission date ≤ discharge date (chronology)
Death file	Check for duplicate lines (all variables identical)
	Compare "NAMs", age and sex listed here against those in beneficiary file
	Check "NAMs" of those listed here against those who died in hospital
	Check each variable for missing or out-of-range values (i.e., proc freq for each variable)
	Check the "date of death" variable for apparent validity: a) range of dates vs study period requested b) date of death ≥ date of any service (prescription or medical) (chronology) c) distribution of deaths by age, by sex, by month, and by year

Appendix 9: Exposure Definitions



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