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Risk of Arrhythmia and Mortality from Macrolide Antibiotic Prescription: A Population-Based Cohort Study

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A thesis submitted in partial fulfillment of the requirements for the degree in Master of Science
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RISK OF ARRHYTHMIA AND MORTALITY FROM MACROLIDE ANTIBIOTIC PRESCRIPTION: A POPULATION-BASED COHORT STUDY

(Thesis format: Monograph)

by

Mai Trac

Graduate Program in Epidemiology and Biostatistics

A thesis submitted in partial fulfillment
of the requirements for the degree of
Master of Science

The School of Graduate and Postdoctoral Studies
The University of Western Ontario
London, Ontario, Canada

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Abstract

Many respiratory tract infections are treated with macrolide antibiotics. Regulatory agencies warn that these antibiotics increase the risk of ventricular arrhythmia. This population-based retrospective cohort study examined the 30-day risk of a hospital encounter with ventricular arrhythmia and all-cause mortality in 503,612 matched pairs of older adults who received a new outpatient prescription for an oral macrolide antibiotic and those prescribed referent antibiotics from 2002 to 2013 in Ontario. Conditional logistic regression was used to measure the association between macrolide exposure and outcomes. Macrolide antibiotics compared with referent antibiotics were not associated with a higher 30-day risk of ventricular arrhythmia (0.03% vs. 0.03%, relative risk [RR] 1.06, 95% confidence interval [CI] 0.83-1.36), and were associated with a lower risk of 30-day all-cause mortality (0.62% vs. 0.76%, RR 0.82, 95% CI 0.78-0.86). These findings suggest that current warnings from Health Canada and the U.S. Food and Drug Administration may be overstated.

Keywords

Macrolide, antibiotic, ventricular arrhythmia, all-cause mortality, QT prolongation, azithromycin, clarithromycin, erythromycin

Dedication

This thesis is dedicated to my parents, in-laws, Bojan, Ivan, Nicolas and Joseph for their unwavering love, support and encouragement.

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Parts of this material are based on data and information compiled and provided by the Canadian Institute for Health Information (CIHI). However, the analyses, conclusions, opinions and statements expressed herein are those of the author, and not necessarily those of CIHI.

Table of Contents

Abstract ii

Dedication iii

Acknowledgments iv

Table of Contents v

List of Tables vii

List of Figures viii

List of Appendices ix

List of Abbreviations x

Chapter 1 1

1 Introduction 1

Chapter 2 2

2 Literature Review 2

2.1 Outpatient macrolide antibiotic prescribing 2

2.2 Mechanism of macrolide antibiotic action 2

2.3 Mechanism of macrolide-induced QT interval prolongation 3

2.4 Search strategy and quality assessment of prior studies 3

2.5 Summary of previous literature 4

2.6 Macrolide antibiotics and risk of ventricular arrhythmia 5

2.7 Macrolide antibiotics and risk of all-cause mortality 5

Chapter 3 12

3 Rationale and Research Questions 12

3.1 The need for research 12

3.2 Research questions and hypotheses 12

3.2.1 Primary research question 12

3.2.2 Secondary research questions 13
Chapter 4 14
4 Methods 14
4.1 Study design and setting 14
4.2 Data sources 15
4.3 Patients 17
4.4 Matching 18
4.5 Baseline characteristics 19
4.6 Outcomes 19
4.7 Statistical analyses 20
Chapter 5 22
5 Results 22
5.1 Cohort characteristics 22
5.1.1 Unmatched cohort 22
5.1.2 Matched cohort 23
5.2 Main analysis 23
5.3 Subgroup analysis 24
5.4 Additional analyses 24
Chapter 6 38
6 Discussion 38
6.1 Summary and interpretation of study results 38
6.2 Study strengths and limitations 39
6.3 Study implications 41
References 42
Appendices 53
Curriculum Vitae 81

List of Tables

Table 1. Literature summary of ten published studies describing cardiovascular events and mortality associated with macrolide use compared with other classes of antibiotics or antibiotic non-use for the treatment of respiratory tract infections..... 7

Table 2. Baseline characteristics of macrolide antibiotic (azithromycin, clarithromycin or erythromycin) users and non-macrolide antibiotic (amoxicillin, cefuroxime or levofloxacin) users pre- and post-match 26

Table 3. 30-day risk for hospital encounter with ventricular arrhythmia and all-cause mortality in matched cohort of patients prescribed macrolide antibiotics compared to referent non-macrolide antibiotics..... 35

List of Figures

Figure 1. Flow diagram of cohort selection 25

Figure 2. The association between macrolide antibiotic prescription (azithromycin, clarithromycin or erythromycin) and 30-day hospital encounter with ventricular arrhythmia examined in subgroups defined by CKD, CHF, CAD and QT-prolonging drug use 36

Figure 3. The association between macrolide antibiotic prescription (azithromycin, clarithromycin or erythromycin) and 30-day all-cause mortality examined in subgroups defined by CKD, CHF, CAD and QT-prolonging drug use 37

List of Appendices

Appendix A. Modified Downs and Black checklist for the assessment of the methodological quality of both randomized and non-randomized studies 53

Appendix B. Checklist of recommendations for reporting of observational studies using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines 57

Appendix C. Coding definitions for demographics and comorbid conditions 60

Appendix D. Coding definitions for hospital encounter with ventricular arrhythmia and all-cause mortality 67

Appendix E. Coding definitions for cause of death data in Ontario Registrar General Vital Statistics Database 68

Appendix F. Standard daily drug doses for the treatment of respiratory tract infections 71

Appendix G. Variables included in the propensity score 72

Appendix H. QT-prolonging drugs included in subgroup analysis 75

Appendix I. 30-day cause of death in matched cohort of patients prescribed macrolide antibiotics (azithromycin, clarithromycin or erythromycin) compared to referent non-macrolide antibiotics (amoxicillin, cefuroxime or levofloxacin) 79

Appendix J. 14-day risk for hospital encounter with ventricular arrhythmia and all-cause mortality in matched cohort of patients prescribed macrolide antibiotics compared to referent non-macrolide antibiotics..... 80

List of Abbreviations

ACE = angiotensin-converting enzyme

ARB = angiotensin II receptor blocker

BMI = body mass index

CAD = coronary artery disease

CCI = Canadian Classification of Health Interventions

CCP = Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures

CHF = congestive heart failure

CI = confidence interval

CIHI-DAD = Canadian Institute for Health Information Discharge Abstract Database

CKD = chronic kidney disease

CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration

CT = computed tomography

CORR = Canadian Organ Replacement Register

CV = cardiovascular

DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th edition

DVT/PE = deep vein thrombosis/pulmonary embolism

ECG = electrocardiogram/electrocardiography

EEG = electroencephalography

eGFR = estimated glomerular filtration rate

FDA = U.S. Food and Drug Administration

GP/FP = general practitioner/family practitioner

HR = hazard ratio

H2RA = histamine H2-receptor antagonist

ICD-9 = International Classification of Diseases, Ninth Revision

ICD-10 = International Classification of Diseases, Tenth Revision

ICES = Institute for Clinical Evaluative Sciences

IFN = interferon

I_{Kr} = rapid delayed rectifier current

IL = interleukin

IPDB = Institute for Clinical Evaluative Sciences Physician Database

IQR = interquartile range

K^+ = potassium ion

LHIN = Local Health Integration Network

LQTS = long QT syndrome

MI = myocardial infarction

NACRS = National Ambulatory Care Reporting System

NHS = National Health Service

NSAID = non-steroidal anti-inflammatory drug

ODB = Ontario Drug Benefit

OHIP = Ontario Health Insurance Plan

OMHRS = Ontario Mental Health Reporting System

OR = odds ratio

ORGD = Ontario Registrar General Vital Statistics Database

PPV = positive predictive value

PSA = prostate-specific antigen

RPDB = Registered Persons Database of Ontario

RR = relative risk

SCr = serum creatinine

SD = standard deviation

SES = socioeconomic status

STROBE = Strengthening the Reporting of Observational Studies in Epidemiology

TdP = torsades de pointes

TIA = transient ischemic attack

TNF = tumour necrosis factor

VA = Department of Veterans Affairs

Chapter 1

1 Introduction

Macrolide antibiotics (e.g. azithromycin, clarithromycin and erythromycin) are a common class of medications used to treat community-acquired respiratory tract infections (1–4). In 2010, over 57 million outpatient prescriptions were written for macrolide antibiotics in the United States (U.S.) (5). A recent observational study prompted Health Canada and the U.S. Food and Drug Administration (FDA) to issue warnings about the risk of QT interval prolongation and fatal ventricular arrhythmia with azithromycin use (6,7). This study showed a higher risk of cardiovascular death and all-cause mortality in patients prescribed azithromycin as compared with other antibiotic prescriptions (amoxicillin) or antibiotic non-use (8). Findings from this study were supported by prior case reports and published studies (9–15).

Other recent studies suggest these regulatory warnings may be overstated (16–19). Mortensen *et al.* showed the risk of 90-day mortality was no higher (and rather was lower) in older patients who received azithromycin compared with other guideline-concordant antibiotics (16). In the same study, there was no difference between the two groups in the risk of arrhythmia, heart failure or any cardiac event. Another study showed no higher 5-day risk of cardiovascular death with azithromycin compared with penicillin V (17). In a study of patients with radiologically confirmed community-acquired pneumonia, clarithromycin compared with antibiotic non-use was associated with a higher risk of cardiovascular events, but not cardiovascular mortality or all-cause mortality (18).

Given these conflicting findings, we conducted this large propensity-matched population-based cohort study of older adults in the outpatient setting to investigate whether azithromycin, clarithromycin or erythromycin compared with non-macrolide referent antibiotics (amoxicillin, cefuroxime or levofloxacin) is associated with higher 30-day risks of ventricular arrhythmia and all-cause mortality.

Chapter 2

2 Literature Review

2.1 Outpatient macrolide antibiotic prescribing

Community-acquired respiratory tract infections are common and potentially serious, especially in older adult patients and those with significant comorbidities (3). Macrolide antibiotics, such as azithromycin, clarithromycin and erythromycin, are often used in the treatment of such infections (4).

In Canada and the U.S., influenza and pneumonia were the eighth leading cause of death in 2011 (20,21). In 2013, over $20 million was spent on outpatient macrolide prescriptions in Canada (2). In 2010, over 57 million outpatient prescriptions were written for macrolide antibiotics in the United States (5).

2.2 Mechanism of macrolide antibiotic action

Azithromycin and clarithromycin are derivatives of the older macrolide, erythromycin, although the mechanism of action of all three macrolides is similar. They bind reversibly to the 50S subunit of bacterial ribosomes, leading to inhibition of transpeptidation, translocation, chain elongation and bacterial protein synthesis (22,23). Macrolides are actively concentrated within leukocytes and are transported directly into the site of infection (24). Azithromycin and clarithromycin are more acid stable than erythromycin, providing improved oral absorption, tolerance, pharmacokinetic properties and a broader spectrum of antibacterial activity than erythromycin (22,23).

2.3 Mechanism of macrolide-induced QT interval prolongation

The repolarization phase of cardiac muscle cells (myocytes) is driven predominantly by outward movement of potassium ions (K^+). The rapid delayed rectifier current (I_{Kr}) is an important K^+ current participating in ventricular repolarization (25). Blockade of this outward potassium current can prolong the cardiac action potential (25,26). Macrolide antibiotics are known to interfere with the I_{Kr} current, which results in accumulation of K^+ in cardiac myocytes thereby delaying cardiac repolarization (26–28). This disturbance of myocardial repolarization is characterized by a prolonged QT interval on the electrocardiogram (ECG) known as long QT syndrome (LQTS) (29,30). LQTS is associated with an increased risk of cardiac arrhythmia referred to as torsades de pointes (31,32). The primary symptoms in patients with LQTS include palpitations, syncope, seizures and sudden cardiac death. This disorder may be either genetic or acquired (33,34).

Erythromycin was the first macrolide to be associated with QT interval prolongation, but subsequent reports and studies have also described QT interval prolongation with azithromycin and clarithromycin use (14,15,35).

2.4 Search strategy and quality assessment of prior studies

We searched both MEDLINE (inception to June 2015) and Google Scholar (inception to June 2015) for relevant articles to include in our literature review. The purpose of our literature search was to identify prior studies that examined the association between macrolide antibiotic use and the outcomes of ventricular arrhythmia and mortality. For both databases, the final search strategy consisted of keywords such as macrolide, antibiotic, arrhythmia, mortality, respiratory tract infection, pneumonia, azithromycin, clarithromycin and erythromycin. We also used the related articles option in Google Scholar to search for additional articles and searched relevant review articles and reference lists of included articles.

Inclusion and exclusion criteria were developed a priori. Studies were included if they met the following criteria: (1) full-text English article, (2) randomized controlled trial (RCT) or cohort study, (3) more than 1,000 patients, (4) mean age 18 years or more and (5) reported ventricular arrhythmia (including composite outcomes) or mortality (all-cause or cardiovascular). We excluded the following studies from our review: (1) no incidence of main outcomes (ventricular arrhythmia or mortality) reported and (2) insufficient information on the antibiotic exposure. Ten studies were identified as meeting our inclusion criteria. For purposes of our literature review, the term 'antibiotic non-use' refers to no antibiotic use of any kind.

We evaluated the quality of individual studies using the Downs and Black quality assessment method, which is a list of 27 criteria to evaluate both randomized and non-randomized trials (Appendix A) (36). This scale assesses the completeness and clarity of study reporting, external validity, internal validity (e.g. bias and confounding) and power. The tool was modified slightly for use in our review. Specifically, the scoring for question 27 dealing with statistical power was simplified to a choice of awarding either 1 or 0 points depending on whether there was sufficient power to detect a clinically important effect. On the modified scale, we gave all included studies a score from 0 to 28, grouped into the following four quality levels: excellent (26 to 28), good (20 to 25), fair (15 to 19) and poor (14 or less).

Two reviewers (M.T. and R.J.) independently assessed the quality of the included articles. Discrepancies between the two reviewers were resolved through re-evaluation and discussion. We did not perform a meta-analysis because the studies were too heterogeneous.

2.5 Summary of previous literature

The findings of ten published studies (summarized in Table 1) describing the risk of ventricular arrhythmia or death with macrolide antibiotic use compared with other classes of antibiotics or antibiotic non-use are inconsistent. These studies vary in patient age, sex

and comorbidity. Our assessment of study quality using the Downs and Black quality checklist determined that six of the reviewed studies were of fair quality (8–10,16,18,37) and four were of good quality (11,12,17,19).

2.6 Macrolide antibiotics and risk of ventricular arrhythmia

One study included in our literature review reported an increased risk of 7-day ventricular arrhythmia with azithromycin use compared to amoxicillin-clavulanate treatment (odds ratio [OR] 4.32, 95% confidence interval [CI] 2.95-6.33) though the authors found no such risk with clarithromycin (OR 0.72, 95% CI 0.48-1.08) (12).

Despite multiple case reports demonstrating evidence of QT prolongation with macrolide antibiotic use (13–15), two studies included in our literature review reported no significant increase in the risk of ventricular arrhythmia associated with macrolide use relative to other antibiotics (9,16). Rao *et al*. found no statistically different risk of arrhythmia with azithromycin compared with amoxicillin within 6 to 10 days (hazard ratio [HR] 1.37, 95% CI 0.91-2.05), though an increased risk was observed within 5 days of follow-up (HR 1.77, 95% CI 1.20-2.62) (9). Similarly, Mortensen *et al.* found no significantly different 90-day risk of cardiac arrhythmia when comparing azithromycin with other antibiotic use (OR 0.99, 95% CI 0.95-1.02) (16). The seven remaining studies did not examine arrhythmia risk (8,10,11,17–19,37).

2.7 Macrolide antibiotics and risk of all-cause mortality

Two studies included in our literature review reported a higher risk of all-cause mortality with macrolide antibiotic use (8,11) while four other studies reported no risk or a decreased risk of death from any cause (9,16,18,19). In an RCT of five Copenhagen cardiology departments, clarithromycin use relative to antibiotic non-use was associated with an increased risk of all-cause mortality during three years of follow-up (HR 1.27, 95% CI 1.03-1.54) (11). Ray *et al.* found an increased 5-day risk of death from any cause

when comparing azithromycin with antibiotic non-use (HR 1.85, 95% CI 1.25-2.75) and amoxicillin (HR 2.02, 95% CI 1.24-3.30) (8).

A population-based prospective cohort study of 2,779 outpatients with community-acquired pneumonia assessed at seven Emergency Departments in Edmonton, Alberta found significantly lower 30-day mortality in patients receiving macrolides compared to another antibiotic (fluoroquinolone) (OR 0.28, 95% CI 0.09-0.86) (19). Three observational studies showed no risk or a decreased risk of all-cause mortality when comparing macrolides to other classes of antibiotics or antibiotic non-use at 6 to10 days (HR 1.14, 95% CI 0.81-1.62) (9), 30 days (OR 0.76, 95% CI 0.73-0.80) (16), 90 days (OR 0.73, 95% CI 0.70-0.76) (16) and one year of follow-up (HR 1.13, 95% CI 0.85-1.51) (18).

Table 1. Literature summary of ten published studies describing cardiovascular events and mortality associated with macrolide use compared with other classes of antibiotics or antibiotic non-use for the treatment of respiratory tract infections

Author	Study Type / Patient Description	Observations	Potential Risk Factors	Dose / Exposure Time / Study Limitations	Quality Score[a]
Randomized Controlled Trials					
Jespersen *et al.*, 2006 (11)	-Five Copenhagen University cardiology departments and a coordinating centre -2,172 participants who had a discharge diagnosis of MI or angina pectoris from 1993 to 1999 randomized to clarithromycin (mean age 65.4 years) and 2,200 to placebo (mean age 65.2 years)	-Clarithromycin group: *n* = 2,172; placebo group: *n* = 2,200 -No significant effects of clarithromycin on the primary outcome (344 [15.8%] vs. 307 [13.8%], HR 1.15, 95% CI 0.99-1.34) or secondary outcome (249 [11.5%] vs. 218 [9.9%], HR 1.17, 95% CI 0.98-1.40) -All-cause mortality (212 [9.8%] vs. 172 [7.8%], HR 1.27, 95% CI 1.03-1.54) and CV mortality (111 [5.1%] vs. 78 [3.5%], HR 1.45, 95% CI 1.09-1.92) were significantly higher in the clarithromycin arm	-Age, sex, previous CV disease and risk factors, smoking status, concurrent use of certain drugs	-Two-week treatment with clarithromycin 500 mg/day or matching placebo; follow-up period 2-3 years -Primary outcome: composite of all-cause mortality, MI or unstable angina pectoris during 3-year follow-up; Secondary outcome: composite of CV mortality, MI or unstable angina pectoris -Limitation: more smokers were randomized to the clarithromycin arm	24
Population-Based Studies					
Asadi *et al.*, 2012 (19)	-Population-based prospective cohort study of 2,779 outpatients with community-acquired pneumonia assessed at 7 Emergency Departments in Edmonton, Alberta, Canada prescribed macrolide (mean age 46.1 years) or fluoroquinolone (mean age 61.9) enrolled from 2000 to 2002 and followed until 2007	-Macrolide group: *n* = 1,832; fluoroquinolone group: *n* = 947 -30-day mortality was significantly lower in the macrolide group relative to the fluoroquinolone group (4 [0.2%] vs. 25 [3%], adjusted OR 0.28, 95% CI 0.09-0.86)	-Age, sex, clinical radiographic severity of illness at presentation, nursing home status	-10 days of any one of the following: doxycycline 200 mg initially then 100 mg/day, levofloxacin 500 mg/day, azithromycin 500 mg initially then 250 mg/day, clarithromycin 500 mg/day or erythromycin 500 mg/day -Limitations: confounding by indication, physician bias, no post-discharge microbiologic data available, generalizability	20

Chou *et al.*, 2015 (12)	-Retrospective cohort study of Taiwan National Health Insurance data comparing patients prescribed oral amoxicillin-clavulanate (mean age 43.9 years), azithromycin (mean age 44.7 years), clarithromycin (mean age 47.1 years), ciprofloxacin (mean age 46.9 years), levofloxacin (mean age 50.6 years) or moxifloxacin (mean age 52.3 years) between January 2001 and November 2011	-Amoxicillin-clavulanate users: *n* = 1,102,358; azithromycin users: *n* = 66,745; clarithromycin users: *n* = 393,243; ciprofloxacin users: *n* = 205,205; levofloxacin users: *n* = 117,352; moxifloxacin users: *n* = 38,833 -Compared with amoxicillin-clavulanate treatment, the use of azithromycin was associated with significantly higher 7-day risks of ventricular arrhythmia (OR 4.32, 95% CI 2.95-6.33) and CV death (OR 2.62, 95% CI 1.69-4.06) -Compared with amoxicillin-clavulanate treatment, the use of clarithromycin was associated with similar 7-day risk of ventricular arrhythmia (OR 0.72, 95% CI 0.48-1.08) and decreased risk of CV death (OR 0.51, 95% CI 0.33-0.80)	-Age, sex, calendar date, concomitant medications, health resource utilization, indications for antibiotic use	-Limitations: interethnic differences and generalizability, reliance on ICD-9 codes, true incidence of TdP unknown, residual confounding, confounding by indication, precise risk estimates for subgroups of patients with certain characteristics could not be determined	20
Mortensen *et al.*, 2014 (16)	-Retrospective cohort study of VA data comparing 31,863 patients hospitalized with pneumonia from 2002 to 2012 prescribed azithromycin (mean age 77.8 years) to 31,863 patients who received other guideline-concordant antibiotics (mean age 77.8 years)	-Azithromycin users: *n* = 31,863; non-azithromycin users: *n* = 31,863 -90-day mortality significantly lower in the azithromycin group (17.4% vs. 22.3%, OR 0.73, 95% CI 0.70-0.76) -30-day mortality significantly lower in the azithromycin group (OR 0.76, 95% CI 0.73-0.80) -Significantly increased odds of 90-day MI (5.1% vs. 4.4%, OR 1.17, 95% CI 1.08-1.25) but not any cardiac event (43.0% vs. 42.7%, OR 1.01, 95% CI 0.98-1.05), cardiac arrhythmias (25.8% vs. 26.0%, OR 0.99, 95% CI 0.95-1.02) or heart failure (26.3% vs. 26.2%, OR 1.01, 95% CI 0.97-1.04)	-Tobacco use, alcohol use, liver disease, multiple classes of medications, SES, race	-At least 1 outpatient medication from a VA pharmacy within 90 days prior to admission; at least 1 dose of antimicrobial therapy within the first 48 hours of admission -Limitations: few female patients, only patients 65 and older, reliance on ICD-9 diagnosis of CV events rather than clinical information, ICD-9 codes not validated in VA administration data, undetermined duration of azithromycin therapy	18
Rao *et al.*, 2014 (9)	-Retrospective cohort study of US veterans (mean age 56.5 years) who received an outpatient prescription of	-During treatment days 1 to 5, patients receiving azithromycin had significantly increased risk of death (HR 1.48, 95% CI 1.05-2.09) and serious arrhythmia (HR 1.77,	-Race, age, sex, indication for antibiotics cardiac	-Follow-up times were separated into the first 5 days and days 6 through 10 after antibiotics were dispensed, with day 1 being the first	18

	either amoxicillin (*n* = 979,380), azithromycin (*n* = 594,792) or levofloxacin (*n* = 201,798) between September 1999 and April 2012	95% CI 1.20-2.62) compared with patients receiving amoxicillin -On treatment days 6 to 10, when comparing azithromycin with amoxicillin, risks were not statistically different for death from any cause (HR 1.14, 95% CI 0.81-1.62) and arrhythmia (HR 1.37, 95% CI 0.91-2.05)	morbidities, laboratory findings, medication	day the drug was dispensed -Azithromycin, levofloxacin or amoxicillin (including amoxicillin with clavulanate potassium) within 30 days after a VA outpatient visit -Limitations: residual confounding, baseline differences between antibiotic groups, exclusion criteria	
Ray *et al.*, 2004 (10)	-Retrospective cohort study of Tennessee Medicaid patients between January 1988 and December 1993 -5,305 person-years of current use of erythromycin (mean age 41.4 years) and 111,779 person-years of former use (mean age 42.2 years) compared to 1,126,013 person-years of antibiotic non-use (mean age 45.0 years) and 6,846 person-years of current use of amoxicillin (mean age 41.7 years)	-Rate of sudden death from cardiac causes was twice as high among current users of erythromycin compared to antibiotic non-users (10 vs. 1,358 deaths, adjusted incidence-rate ratio 2.01, 95% CI 1.08-3.75) -No significant increase for former users of erythromycin (100 vs. 1,358 deaths, adjusted incidence-rate ratio 0.89, 95% CI 0.72-1.09) or current users of amoxicillin (8 vs. 1,358 deaths, adjusted incidence-rate ratio 1.18, 95% CI 0.59-2.36)	-Smoking, higher BMI, high consumption of saturated fats, lack of physical activity, pre-existing CV disease (heart failure, angina and MI), concurrent use of CYP3A4 inhibitors	-Current use: days of supply from the day the prescription was filled; antibiotic non-use: no use of any study antibiotics within the previous 365 days; former use: some use of a study medication that was not current but had occurred within the previous 365 days -Limitations: drug compliance, no information on a number of behavioural risk factors	19
Ray *et al.*, 2012 (8)	-Retrospective cohort study of Tennessee Medicaid patients between 1992 and 2006 comparing patients who took azithromycin (347,795 prescriptions, mean age 48.6 years), no antibiotics (1,391,180 prescriptions, mean age 48.6 years), amoxicillin (1,348,672 prescriptions, mean age 47.7 years), ciprofloxacin (264,626	-Increased risk of 5-day CV death (HR 2.88, 95% CI 1.79-4.63) and death from any cause (HR 1.85, 95% CI 1.25-2.75) from azithromycin (adjusted) relative to no antibiotics (adjusted) -Relative to amoxicillin (unadjusted), azithromycin (adjusted) was associated with an increased risk of CV death (HR 2.49, 95% CI 1.38-4.50) and death from any cause (HR 2.02, 95% CI 1.24-3.30) -Among patients who took azithromycin, there were 29 CV deaths during the 5-day course of treatment (85.2 per 1 million	-CV disease and other behavioural risk factors associated with CV disease, indication for antibiotic therapy	-Duration of treatment: 5-day period generally recommended for azithromycin and 10-day period most commonly suggested for other study antibiotics -Limitation: misclassification	19

	prescriptions, mean age 50.5 years) or levofloxacin (193,906 prescriptions, mean age 51.5 years)	courses); for those not taking antibiotics, there were 41 CV deaths (29.8 per 1 million periods); for the amoxicillin group, there were 42 CV deaths (31.5 per 1 million courses) -Risk of CV death significantly greater with a 5-day course of azithromycin (adjusted) than with the first 5 days of a course of ciprofloxacin (unadjusted HR 3.49, 95% CI 1.32-9.26) but not significantly different from levofloxacin (unadjusted HR 1.27, 95% CI 0.66-2.47)			
Schembri *et al.*, 2013 (18)	-Secondary analysis of a prospectively collected dataset of 1,631 patients admitted to NHS Lothian Hospitals in Edinburgh, UK with radiologically confirmed community-acquired pneumonia and prescribed clarithromycin (median age 65 years) compared with patients who received non-macrolide antibiotics (median age 68 years) during their admission between 2005 and 2009	-Clarithromycin users: $n = 980$; non-macrolide users: $n = 651$ -Significant association between clarithromycin use and CV events compared with non-macrolide users after propensity matching (123 [12.6%] vs. 48 [7.4%], HR 1.58, 95% CI 1.08-2.30) -Clarithromycin use was not associated with a significant difference in all-cause mortality (adjusted HR 1.13, 95% CI 0.85-1.51) or CV mortality (adjusted HR 1.58, 95% CI 0.93-2.71)	-Age, history of CV events	-Macrolide users included all patients who received at least one dose of clarithromycin during their hospital admission -Duration of use: < 3 days, 3-6 days, 7 days, > 7 days -1-year follow-up -Limitations: bias due to unrecorded factors, patients with more severe illness were more likely to be prescribed clarithromycin and thus clarithromycin may be a marker for more severe infection and hence increased CV events	16
Svanstrom *et al.*, 2013 (17)	-Retrospective cohort study of Danish adults comparing 1,102,050 episodes of azithromycin use (mean age 39.7 years) with no use of antibiotic (mean age 39.5 years) matched in a 1:1 ratio and comparing 1,102,419 episodes of azithromycin use (mean age 39.7 years) with 7,364,292 episodes of	-With propensity score matched analysis, risk of death from CV causes significantly increased with current use of azithromycin as compared with no use of antibiotics (rate ratio 2.85, 95% CI 1.13-7.24) -With adjustment for propensity scores, current azithromycin use was not associated with an increased risk of CV death when compared with penicillin V (rate ratio 0.93, 95% CI 0.56-1.55)	-Age, sex, history of CV disease	-Current use (1-5 days), recent use (6-10 days) and past use (11-35 days) -Limitations: no information on the indication for treatment and several known risk factors (e.g. smoking and BMI), primary definition, including all CV causes of death, was broad	20

	penicillin V use (mean age 42.0 years) between 1997 and 2010				
Svanstrom *et al.*, 2014 (37)	-Retrospective cohort study of Danish adults who received prescriptions for clarithromycin (*n* = 108,767, mean age 57.2 years), roxithromycin (*n* = 350,575, mean age 56.6 years) or penicillin V (*n* = 1,519,324, mean age 55.7 years)	-Compared with use of penicillin V (235 deaths, incidence rate 2.5 per 1,000 person years), use of clarithromycin was associated with a significantly increased risk of cardiac death (18 deaths, incidence rate 5.3 per 1,000 person years, adjusted rate ratio 1.76, 95% CI 1.08-2.85) but use of roxithromycin was not (32 deaths, incidence rate 2.5 per 1,000 person years, adjusted rate ratio 1.04, 95% CI 0.72-1.51)	-Sex, age, cardiac risk score, concomitant use of cytochrome P450 3A inhibiting drugs	-Treatment: 7-day course of antibiotic -Limitations: lack of information on lifestyle and health factors known to influence the risk of cardiac death (e.g. smoking and BMI), missing infection information, limited power to detect difference in subgroup analyses	16

Abbreviations: BMI = body mass index, CI = confidence interval, CV = cardiovascular, HR = hazard ratio, ICD-9 = International Classification of Diseases, Ninth Revision, IL = interleukin, MI = myocardial infarction, NHS = National Health Service, OR = odds ratio, SES = socioeconomic status, TdP = torsades de pointes, TNF = tumour necrosis factor, VA = Department of Veterans Affairs

[a]We evaluated the quality of individual studies using the Downs and Black quality assessment method, which is a list of 27 criteria to evaluate both randomized and non-randomized trials (Appendix A) (36). This scale assesses the completeness and clarity of study reporting, external validity, internal validity (e.g. bias and confounding) and power. The tool was modified slightly for use in our review. Specifically, the scoring for question 27 dealing with statistical power was simplified to a choice of awarding either 1 or 0 points depending on whether there was sufficient power to detect a clinically important effect. On the modified scale, we gave all included studies a score from 0 to 28, grouped into the following four quality levels: excellent (26 to 28), good (20 to 25), fair (15 to 19) and poor (14 or less).

Chapter 3

3 Rationale and Research Questions

3.1 The need for research

In 2013, Health Canada and the U.S. FDA warned about a higher risk of QT interval prolongation and subsequent ventricular arrhythmia among patients taking azithromycin (6,7). Although many case reports support this assertion (13–15,27), evidence from published studies is inconsistent (8–12,16–19,37). To better elucidate the safety profiles of macrolide antibiotics in the treatment of community-acquired respiratory tract infections, we conducted a population-based cohort study to investigate the risks of ventricular arrhythmia and all-cause mortality associated with azithromycin, clarithromycin or erythromycin use compared with other antibiotics for similar indications.

3.2 Research questions and hypotheses

3.2.1 Primary research question

In the outpatient setting, does a group of patients prescribed macrolide antibiotics compared with a group of patients prescribed non-macrolide antibiotics that have similar baseline characteristics have an altered 30-day risk of a hospital encounter with ventricular arrhythmia?

Hypothesis: Based on prior literature, macrolide antibiotic use may be associated with a higher risk of ventricular arrhythmia compared with non-macrolide antibiotic use. However, based on other prior literature, it is also possible that there will be no difference in risk between the two groups.

3.2.2 Secondary research questions

1) In the outpatient setting, does a group of patients prescribed macrolide antibiotics compared with a group of patients prescribed non-macrolide antibiotics that have similar baseline characteristics have an altered 30-day risk of all-cause mortality?

   Hypothesis: Based on prior literature, macrolide antibiotic use may be associated with a higher risk of all-cause mortality compared with non-macrolide antibiotic use. However, based on other prior literature, it is also possible that there will be no difference in risk between the two groups.

2) In older adults in the outpatient setting, in subgroup analyses is the association between macrolide antibiotic use (compared with non-macrolide antibiotic use) and 30-day risk of a hospital encounter with ventricular arrhythmia modified in the presence of conditions that can be responsible for ventricular arrhythmia? These four conditions are (1) chronic kidney disease, (2) congestive heart failure, (3) coronary artery disease and (4) concurrent use of a drug known to prolong the QT interval.

   Hypothesis: Compared with non-macrolide antibiotic use, macrolide antibiotic use will be associated with a higher risk of ventricular arrhythmia when the conditions that can be responsible for ventricular arrhythmia are present.

3) In older adults in the outpatient setting, in subgroup analyses is the association between macrolide antibiotic use (compared with non-macrolide antibiotic use) and 30-day risk of all-cause mortality modified in the presence of conditions that can be responsible for mortality? These four conditions are (1) chronic kidney disease, (2) congestive heart failure, (3) coronary artery disease and (4) concurrent use of a drug known to prolong the QT interval.

   Hypothesis: Compared with non-macrolide antibiotic use, macrolide antibiotic use will be associated with a higher risk of all-cause mortality when the conditions that can be responsible for mortality are present.

Chapter 4

4 Methods

4.1 Study design and setting

We conducted a population-based retrospective cohort study of older adults from April 1, 2002 to March 1, 2013 using linked healthcare databases in Ontario, Canada. Ontario has approximately 13.7 million residents, 16% of whom are 65 years of age or older (38). The Ontario Health Insurance Plan (OHIP) is the single payer for all Ontario citizens and provides universal access to hospital care and physician services. Those aged 65 years or older (approximately 2 million residents) also receive prescription drug coverage.

Ontario's administrative healthcare databases provide a rich source of information and are representative of the entire province. The use of these databases addresses problems typical of prospective studies, such as selection and information biases, and allow for large sample sizes and long periods of follow-up. Emigration out of Ontario is less than 1% per year, with little loss to follow-up (39).

We conducted this study at the Institute for Clinical Evaluative Sciences (ICES) according to a pre-specified protocol that was approved by the Research Ethics Board at Sunnybrook Health Sciences Centre (Toronto, Ontario). Participant informed consent was not required for this study. The reporting of this study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (see Appendix B) (40).

4.2 Data sources

We used the following 11 healthcare administrative databases housed at ICES to ascertain patient characteristics, drug exposure, covariate information and outcome data. These datasets were linked using unique, encoded identifiers and analyzed at ICES.

Registered Persons Database of Ontario (RPDB): We used RPDB to obtain information on patient demographics (age, sex and vital status), income (categorized into quintiles of average neighbourhood income) and location of residence (urban or rural). Moreover, we used the vital status information captured by this database to ascertain the outcome of all-cause mortality.

Ontario Drug Benefit (ODB) Database: The ODB database stores records for all outpatient drug prescriptions dispensed to patients aged 65 years and older in Ontario with a high level of accuracy (overall error rate of less than 1%) (41). We used this database to ascertain exposure to macrolide antibiotics and baseline medication use assessed in the 120 days prior to cohort entry. We also acquired information on patient residential status (community-dwelling or long-term care) and medical specialty of the physicians who prescribed study antibiotics.

Canadian Institute for Health Information Discharge Abstract Database and National Ambulatory Care Reporting System (CIHI-DAD, NACRS): CIHI-DAD and NACRS contain diagnostic and procedural information on all inpatient, emergency department and outpatient visits occurring in Ontario. The hospital diagnosis codes were based on the International Classification of Diseases, Ninth Revision (ICD-9) codes prior to 2002 and Tenth Revision (ICD-10) codes since 2002. We used both ICD-9 and ICD-10 codes to determine baseline comorbidities in the five years prior to receipt of the new antibiotic prescription (detailed in Appendix C). We used ICD-10 codes exclusively to determine hospitalized outcomes since all events occurred after the implementation of this coding system (detailed in Appendix D).

Ontario Health Insurance Plan (OHIP) Database: The OHIP database contains information on physician claims for inpatient and outpatient services using fee codes. We

used the information captured by this database to identify baseline comorbid conditions in addition to the diagnostic information obtained from CIHI-DAD.

Canadian Organ Replacement Register (CORR): This registry stores information on renal replacement therapies. CORR receives data from the Ontario Renal Network, Trillium Gift of Life Network and independent sources. We used this database to identify the number of kidney transplants occurring in our cohort for the comorbidity of chronic kidney disease.

Ontario Mental Health Reporting System (OMHRS) Database: The OMHRS database contains demographic and health information on patients admitted to adult mental health beds in Ontario. Diagnosis codes for health conditions based on the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition are recorded in this database (detailed in Appendix C). In addition to the CIHI-DAD and OHIP databases, we used the diagnostic information stored in this database to determine baseline psychiatric comorbid conditions.

Institute for Clinical Evaluative Sciences Physician Database (IPDB): IPDB reports prescriber and specialist referral data including demographics, education, location and measures of physician activity. We used this database to measure the number of general practitioner visits and nephrologist and cardiologist consults.

Ontario Registrar General Vital Statistics Database (ORGD): ICD-9 codes were used to ascertain cause of death in ORGD (see Appendix E). New variables that are coded in the database as ICD-10 are converted to ICD-9 codes to ensure consistency across all years.

Cerner and Gamma-Dynacare Laboratory Databases: A subpopulation of patients in Southwestern Ontario had outpatient serum creatinine and urine dipstick protein measurements available before cohort entry and was in the catchment area of 12 hospitals in which linked serum creatinine laboratory measurements were available through these laboratory datasets. We used the information to assess baseline kidney function.

All 11 databases have been used previously to study adverse drug events and health outcomes (42–51).

4.3 Patients

We established a cohort of older adults in Ontario who were dispensed a new outpatient prescription for a macrolide antibiotic (azithromycin, clarithromycin or erythromycin) between April 1, 2002 and March 1, 2013. The date of the prescription served as the index date (referred to as the cohort entry date or start time for follow-up).

Inherent to observational drug studies is a bias known as confounding by indication. This bias occurs when drugs are selectively used or not used by those who developed the outcome of interest (52). The assumption is that patients are exposed to drugs for particular reasons and the variables underlying these reasons may predispose patients to study outcomes of interest. A method to limit confounding by indication is to compare treatments that are interchangeable within the same indication (53). Therefore, we compared our macrolide antibiotic users to a group of older adults with similar indicators of baseline health who were prescribed non-macrolide antibiotics (amoxicillin, cefuroxime or levofloxacin).

Before matching, we excluded the following patients from both groups: (1) those who were in their first year of eligibility for prescription drug coverage (aged 65 years) to avoid incomplete medication records, (2) those with prescriptions for any antibiotic in the 180 days prior to the index date to ensure that the drug was newly prescribed, (3) those who received a prescription for more than one type of antibiotic on the index date (in order to form mutually exclusive groups), (4) those who were discharged from the hospital in the two days prior to their index date to ensure these were new outpatient antibiotic prescriptions (because in Ontario, patients continuing an antibiotic treatment initiated in the hospital would have their outpatient antibiotic prescription dispensed on the same day or the day after hospital discharge) and (5) those with daily drug doses that were not standard for the treatment of respiratory tract infections to ensure generalizability to usual prescribing (see Appendix F). Study patients could only enter the cohort once, so for patients with multiple eligible prescriptions, we restricted the information to the first eligible prescription.

4.4 Matching

We used propensity score matching to eliminate systematic differences in the measured baseline characteristics of our comparison groups. This allowed us to form a matched set of patients in our two groups with a similar probability of receiving a macrolide antibiotic given a set of measured baseline covariates (54,55). We estimated the propensity scores using a multivariable logistic regression model with 106 baseline characteristics selected because of their potential influence on the outcomes or segregation of patients between the comparison groups (Appendix G) (55–57). Subsequently, we matched a referent user to each macrolide antibiotic user on the following six characteristics: the logit of the propensity score (within calipers of width ± 0.2 standard deviations) (58), chronic kidney disease (yes or no), congestive heart failure (yes or no), coronary artery disease (yes or no), QT-prolonging drug use (yes or no) and availability of serum creatinine measurement in the year prior to the index date (yes or no). There are several types of matching techniques including individual matching and frequency matching (59). In greedy matching, a macrolide antibiotic user is first selected at random and then matched to the nearest non-macrolide antibiotic user, even if that non-user would have been a better match for a subsequent macrolide antibiotic user. This process is then repeated until non-macrolide antibiotic users have been matched to all macrolide antibiotic users or until the list of macrolide antibiotic users for whom a matched non-macrolide antibiotic user can be found has been exhausted (55). An alternative to greedy matching is optimal matching, in which matches are formed to minimize the total within-pair difference of the propensity score (60). In studies involving large administrative healthcare databases, greedy matching is simpler to implement and considerably faster to run. Additionally, it has been shown that optimal matching does not perform better than greedy matching in forming balanced groups (61). For these reasons, we selected the greedy matching technique. Study patients were matched without replacement. Those who were not matched successfully were excluded from our analysis.

We anticipated the 106 variables used in this study to be complete. We expected prescriber information would be missing in up to 25% of patients based on the results of prior studies (42,46,51,62). For income quintile, we expected up to 0.5% of patients

would have a missing value based on the results of prior studies (42,46,62), and missing values in the unmatched cohort were re-classified into the average income quintile (income quintile 3) during matching. For location of residence, we expected up to 0.2% of patients would have a missing value based on the results of prior studies (49,51), and missing values in the unmatched cohort were re-classified into the "No" category during matching.

4.5 Baseline characteristics

We assessed baseline comorbid conditions in the five years prior to the index date and concurrent medication use in the 120 days prior to the index date of each macrolide antibiotic user and referent non-macrolide antibiotic user (see Appendix C for coding information). For the subpopulation of patients whose laboratory measurements were available, we assessed their kidney function in the year prior to their index date. Chest x-ray, urinalysis and sputum tests were assessed in the seven days prior to cohort entry. We evaluated prior health care use with physician visits, and diagnostic and screening tests performed in the previous year.

4.6 Outcomes

The primary outcome of this study was a hospital encounter (presentation to the emergency room or hospital admission) with ventricular arrhythmia (ventricular tachycardia or ventricular fibrillation) in any diagnosis field. The secondary outcome was all-cause mortality. We restricted our analysis to 30 days after the index date because macrolide antibiotics are prescribed for short durations and any observed outcomes can be reasonably attributed to our study drugs over this timeframe. Furthermore, QT interval prolongation has been shown to start within hours to days of initiating macrolides, and thus, one would expect that drug-related ventricular arrhythmias would occur soon after initiating a macrolide antibiotic prescription (14,15,63–65).

The diagnosis codes used to identify ventricular arrhythmia are presented in Appendix D. Trained personnel enter these codes into the databases based only on physician-recorded diagnoses in a patient's medical chart. The ICD-10 codes for ventricular arrhythmia have not been fully validated; however, we would expect their sensitivity to be low as true ventricular arrhythmias frequently go undetected in routine healthcare (because they often occur outside hospital settings, in unmonitored patients in hospital or in a setting of multi-organ medical illness). In previous studies assessing the accuracy of ICD-9 and ICD-10 codes for cardiac arrhythmia (ventricular and supraventricular), the positive predictive value (PPV; truly have the condition when code present) exceeded 80% (66–69). We performed a manual review of 202 charts in our region and confirmed a PPV of 92% (95% CI 87-95%) for the set of codes used in this study to detect ventricular arrhythmia. All-cause mortality vital statistics are coded accurately in our data sources with a sensitivity of 97.8% and specificity of 100% for the finding of death (70).

4.7 Statistical analyses

We compared baseline characteristics between those prescribed macrolide antibiotics and those prescribed non-macrolide antibiotics using standardized differences. This metric describes differences between group means relative to the pooled standard deviation and is considered a meaningful difference if greater than 10% (71). The use of standardized differences is preferred over statistical hypothesis testing (using *P* values) for assessing balance in baseline characteristics between propensity score matched groups (72–74). The standardized difference is not influenced by sample size and thus, one can compare balance in the unmatched sample to that in the matched sample (73,74).

We estimated the OR and 95% CIs for the primary and secondary outcomes using conditional logistic regression, which accounted for matching (75). The non-macrolide antibiotic group was the referent group. Each OR was approximated to be the relative risk (RR), which was appropriate given the incidences observed.

We also evaluated the association between macrolide antibiotic and our outcomes in four specified subgroups, defined by the presence or absence of the following conditions: (1) chronic kidney disease, (2) congestive heart failure, (3) coronary artery disease and (4) concurrent use of a drug known to prolong the QT interval (Appendix H). We hypothesized that any RR of ventricular arrhythmia with macrolide antibiotic use compared to referent antibiotic might be greater when these conditions were present than when they were absent. For example, the dose of clarithromycin should be reduced by 50% in chronic kidney disease due to impaired clearance, but in practice this seldom occurs (76). Similarly, in prior reports, ventricular arrhythmia with macrolide antibiotic use frequently occurred in patients with pre-existing risk factors such as congestive heart failure (77), cardiovascular disease (14,78–80) and those taking other QT-prolonging medications (81,82). We determined interaction *P* values by including interaction terms in the regression models.

Chronic kidney disease was identified using an algorithm of hospital diagnosis codes validated in our region for older adults (83). The algorithm identified patients with a median estimated glomerular filtration rate (eGFR) of 38 mL/min/1.73 m^2 (interquartile range [IQR] 27-52 mL/min/1.73 m^2), whereas its absence identified patients with a median eGFR of 69 mL/min/1.73 m^2 (IQR 56-82 mL/min/1.73 m^2). The algorithm for chronic kidney disease had a sensitivity of 32% and specificity of 94% using an eGFR of 45 mL/min/1.73 m^2 as the reference standard (83). Due to its limited sensitivity, the algorithm underestimated the true prevalence of chronic kidney disease.

To provide insights for any observed difference in all-cause mortality between our two groups, we also conducted a post hoc analysis to determine the various causes of death in our matched cohort. Finally, we conducted an additional analysis of our outcomes at 14 days of follow-up rather than 30 days.

We conducted all analyses with SAS version 9.4 (SAS Institute, Cary, North Carolina, 2011). In all outcome analyses, we interpreted two-tailed *P* values less than 0.05 as statistically significant.

Chapter 5

5 Results

5.1 Cohort characteristics

5.1.1 Unmatched cohort

Cohort selection is presented in Figure 1 and baseline characteristics before and after matching are presented in Table 2. We identified 616,359 older adults with prescriptions for macrolide antibiotics (azithromycin, clarithromycin or erythromycin) and 705,132 patients with prescriptions for the referent antibiotics (amoxicillin, cefuroxime or levofloxacin) before matching. The mean age of the unmatched cohort was 73.9 years and 56.7% were women.

Prior to matching, patients prescribed macrolide antibiotics compared to those prescribed referent antibiotics were more likely to receive their prescription from a general practitioner (77.0% vs. 56.6%), have chronic lung disease (28.8% vs. 23.8%), were less likely to use warfarin (4.6% vs. 7.4%) and were less likely to have a urinalysis test (1.5% vs. 4.9%) (Table 2). Information on income was not available for 2,160 (0.4%) macrolide antibiotic users and 2,468 (0.4%) non-macrolide antibiotic users. Location of residence could not be ascertained for 647 (0.1%) macrolide antibiotic users and 708 (0.1%) non-macrolide antibiotic users. Local Health Integration Network (LHIN), which refers to health authorities responsible for regional administration of public healthcare services in Ontario, was unavailable for 619 (0.1%) macrolide antibiotic users and 684 (0.1%) non-macrolide antibiotic users. Prescriber information was not available for 100,111 (16.2%) macrolide antibiotic users and 262,915 (37.3%) non-macrolide antibiotic users in the unmatched cohort.

5.1.2 Matched cohort

A total of 503,612 macrolide antibiotic users were successfully matched to 503,612 non-macrolide antibiotic users. The two groups were well-balanced and showed no meaningful differences in the 106 measured baseline characteristics: age, sex, income, year of cohort entry, location of residence, residential status, LHIN, prescribing physician, 30 comorbid conditions, use of 37 medications, general practitioner visits, nephrology consults, cardiology consults, 25 prior investigations and treatments, baseline serum creatinine concentration, eGFR and urine dipstick protein (Table 2). The mean age of the matched cohort was 74.0 years and 57.3% of patients were women. Clarithromycin and azithromycin were the most frequently prescribed macrolide antibiotics (48.4% and 48.3%, respectively), followed by erythromycin (3.3%). The median starting daily dose for clarithromycin was 1,000 mg (IQR 500 to 1,000 mg), for azithromycin was 300 mg (IQR 300 to 300 mg) and for erythromycin was 1,000 mg (IQR 999 to 1,000 mg). The median day supply for clarithromycin, azithromycin and erythromycin was 10 days (IQR 7 to 10 days), 5 days (IQR 5 to 5 days) and 7 days (IQR 7 to 10 days), respectively. LHIN information was unavailable for 500 (0.1%) macrolide users and 480 (0.1%) non-macrolide antibiotic users in the matched cohort. Prescriber information was not available for 100,093 (19.9%) macrolide antibiotic users and 95,973 (19.1%) non-macrolide antibiotic users in the matched cohort. General practitioners were the most frequent prescribers (73.1%).

5.2 Main analysis

The primary and secondary outcomes are shown in Table 3. Across the entire cohort, in the 30-day follow-up period, 260 patients (0.03%) had a record of a hospital encounter with ventricular arrhythmia and 6,977 (0.69%) died.

The 30-day risk of ventricular arrhythmia with macrolide antibiotic use compared to referent antibiotic use was not statistically different (0.03% vs. 0.03%, RR 1.06, 95% CI 0.83-1.36, *P* value 0.62). Macrolide antibiotic compared with referent antibiotic was

associated with a lower 30-day risk of all-cause mortality (0.62% vs. 0.76%, RR 0.82, 95% CI 0.78-0.86, *P* value < 0.0001).

5.3 Subgroup analysis

Subgroup analyses for ventricular arrhythmia and all-cause mortality are shown in Figures 2 and 3. The presence or absence of chronic kidney disease, congestive heart failure, coronary artery disease or concurrent use of a QT-prolonging drug did not significantly modify the relative association between antibiotic exposure and the risk of ventricular arrhythmia (*P* values for interaction ranged from 0.28-0.80). Across all subgroups, use of macrolide antibiotics compared to referent antibiotics was associated with a lower risk of all-cause mortality, with no modification of the relative association across subgroups (*P* values for interaction ranged from 0.11-0.67).

5.4 Additional analyses

First, using ORGD, we conducted a post hoc analysis to determine the various causes of death in our matched cohort. Specific codes are listed in Appendix E. There were no significant differences in the cause of death between the two groups. The most common cause of 30-day mortality among older adults prescribed macrolide antibiotics was cardiovascular disease (*n* = 638, 20.3% of deaths), followed by cancer (*n* = 569, 18.1%). Among older adults prescribed referent antibiotics, the most common causes of death were cancer (*n* = 785, 20.5%) and cardiovascular disease (*n* = 755, 19.7%) (Appendix I).

Second, we examined our outcomes at 14 days of follow-up. Similar to our 30-day follow-up analysis, macrolide antibiotic use compared to referent antibiotic use was associated with no different risk in ventricular arrhythmia (0.01% vs. 0.01%, RR 0.99, 95% CI 0.71-1.37, *P* value 0.93) and a lower risk of all-cause mortality (0.34% vs. 0.41%, RR 0.82, 95% CI 0.77-0.87, *P* value < 0.0001) (Appendix J).

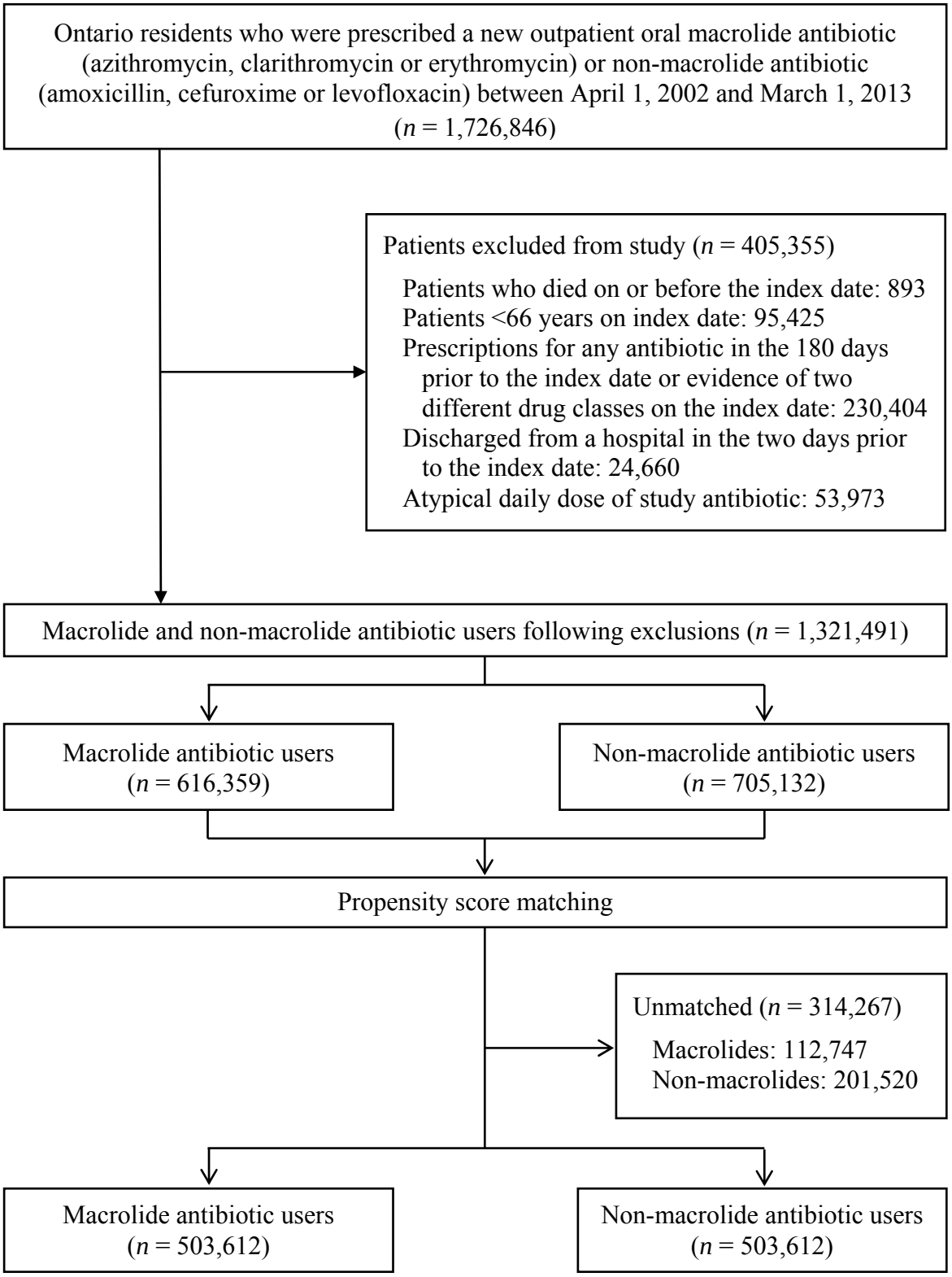

Figure 1. Flow diagram of cohort selection

Table 2. Baseline characteristics of macrolide antibiotic (azithromycin, clarithromycin or erythromycin) users and non-macrolide antibiotic (amoxicillin, cefuroxime or levofloxacin) users pre- and post-match[a]

Variable	Unmatched			Matched		
	Macrolide (*n* = 616,359)	Non-Macrolide (*n* = 705,132)	Standardized Difference[b]	Macrolide (*n* = 503,612)	Non-Macrolide (*n* = 503,612)	Standardized Difference[b]
Demographics						
Age, mean (SD), years	73.7 (7.1)	74.1 (7.3)	6%	73.9 (7.2)	74.0 (7.2)	2%
Women	359,895 (58.4)	389,520 (55.2)	6%	288,515 (57.3)	288,473 (57.3)	0%
Income quintile[c]						
1 (low)	120,433 (19.5)	135,873 (19.3)	1%	99,340 (19.7)	100,535 (20.0)	1%
2	128,791 (20.9)	147,680 (20.9)	0%	106,101 (21.1)	106,738 (21.2)	0%
3 (middle)	121,353 (19.7)	139,156 (19.7)	0%	101,012 (20.1)	101,455 (20.1)	0%
4	120,224 (19.5)	138,126 (19.6)	0%	97,895 (19.4)	97,247 (19.3)	0%
5 (high)	123,398 (20.0)	141,829 (20.1)	0%	99,264 (19.7)	97,637 (19.4)	1%
Year of cohort entry						
2002	71,875 (11.7)	71,491 (10.1)	5%	56,548 (11.2)	56,434 (11.2)	0%
2003	89,014 (14.4)	86,440 (12.3)	6%	69,300 (13.8)	68,989 (13.7)	0%
2004	70,341 (11.4)	71,392 (10.1)	4%	55,248 (11.0)	55,193 (11.0)	0%
2005	63,839 (10.4)	66,701 (9.5)	3%	50,803 (10.1)	51,007 (10.1)	0%
2006	51,400 (8.3)	59,498 (8.4)	0%	42,229 (8.4)	42,502 (8.4)	0%
2007	46,988 (7.6)	55,608 (7.9)	1%	38,824 (7.7)	38,995 (7.7)	0%
2008	46,180 (7.5)	54,246 (7.7)	1%	37,802 (7.5)	37,898 (7.5)	0%
2009	41,919 (6.8)	53,244 (7.6)	3%	35,205 (7.0)	35,175 (7.0)	0%
2010	42,552 (6.9)	55,593 (7.9)	4%	35,973 (7.1)	35,860 (7.1)	0%
2011	41,502 (6.7)	58,617 (8.3)	6%	36,529 (7.3)	36,470 (7.2)	0%

2012	41,276 (6.7)	60,475 (8.6)	7%	37,075 (7.4)	37,011 (7.3)	0%
2013	9,473 (1.5)	11,827 (1.7)	1%	8,076 (1.6)	8,078 (1.6)	0%
Rural residence[d]	87,490 (14.2)	89,820 (12.7)	4%	68,952 (13.7)	67,861 (13.5)	1%
Long-term care	20,921 (3.4)	37,020 (5.3)	9%	20,538 (4.1)	23,129 (4.6)	3%
LHIN[e]						
1	35,679 (5.8)	36,429 (5.2)	3%	29,201 (5.8)	27,684 (5.5)	1%
2	48,731 (7.9)	56,169 (8.0)	0%	39,542 (7.9)	40,003 (7.9)	0%
3	30,062 (4.9)	32,784 (4.6)	1%	24,531 (4.9)	22,812 (4.5)	2%
4	75,103 (12.2)	95,783 (13.6)	4%	61,236 (12.2)	68,781 (13.7)	4%
5	28,553 (4.6)	36,298 (5.1)	2%	23,584 (4.7)	26,199 (5.2)	2%
6	43,184 (7.0)	52,734 (7.5)	2%	35,609 (7.1)	36,197 (7.2)	0%
7	49,886 (8.1)	61,560 (8.7)	2%	40,894 (8.1)	43,485 (8.6)	2%
8	74,884 (12.1)	88,508 (12.6)	1%	61,529 (12.2)	61,848 (12.3)	0%
9	71,866 (11.7)	88,861 (12.6)	3%	58,702 (11.7)	64,162 (12.7)	3%
10	30,641 (5.0)	32,286 (4.6)	2%	24,907 (4.9)	22,293 (4.4)	2%
11	60,098 (9.8)	58,581 (8.3)	5%	49,208 (9.8)	41,608 (8.3)	5%
12	23,560 (3.8)	24,074 (3.4)	2%	18,914 (3.8)	17,158 (3.4)	2%
13	31,464 (5.1)	30,400 (4.3)	4%	25,408 (5.0)	23,275 (4.6)	2%
14	12,029 (2.0)	9,981 (1.4)	4%	9,847 (2.0)	7,627 (1.5)	3%
Prescribing physician[f]						
General practitioner	474,660 (77.0)	398,920 (56.6)	44%	367,302 (72.9)	368,847 (73.2)	1%
Internist	2,797 (0.5)	2,967 (0.4)	1%	2,461 (0.5)	2,611 (0.5)	0%
Nephrologist	802 (0.1)	788 (0.1)	1%	749 (0.1)	626 (0.1)	1%
Cardiologist	856 (0.1)	1,146 (0.2)	1%	813 (0.2)	909 (0.2)	0%
Other	37,133 (6.0%)	38,396 (5.4)	2%	32,194 (6.4)	34,646 (6.9)	2%

Comorbidities[g]						
Dementia	46,958 (7.6)	68,671 (9.7)	8%	42,887 (8.5)	45,532 (9.0)	2%
Schizophrenia or other psychotic disorders	12,614 (2.0)	17,771 (2.5)	3%	11,363 (2.3)	11,985 (2.4)	1%
Bipolar disorder	9,964 (1.6)	12,986 (1.8)	2%	8,645 (1.7)	8,764 (1.7)	0%
Unipolar depression and/or anxiety disorder	46,254 (7.5)	53,089 (7.5)	0%	38,397 (7.6)	38,481 (7.6)	0%
Haemorrhagic stroke	1,056 (0.2)	1,556 (0.2)	1%	957 (0.2)	990 (0.2)	0%
Ischemic stroke	6,544 (1.1)	9,804 (1.4)	3%	6,005 (1.2)	6,366 (1.3)	1%
TIA	2,545 (0.4)	3,475 (0.5)	1%	2,263 (0.4)	2,363 (0.5)	0%
Chronic liver disease	19,210 (3.1)	23,094 (3.3)	1%	16,167 (3.2)	16,299 (3.2)	0%
Chronic kidney disease[h]	27,800 (4.5)	36,539 (5.2)	3%	25,543 (5.1)	25,543 (5.1)	0%
Congestive heart failure	61,351 (10.0)	77,802 (11.0)	4%	56,214 (11.2)	56,214 (11.2)	0%
Coronary artery disease[i]	158,521 (25.7)	190,688 (27.0)	3%	138,038 (27.4)	138,038 (27.4)	0%
Angina	117,261 (19.0)	135,415 (19.2)	0%	99,400 (19.7)	99,463 (19.7)	0%
Peripheral vascular disease	8,365 (1.4)	10,267 (1.5)	1%	7,422 (1.5)	7,537 (1.5)	0%
Parkinson's disease	8,858 (1.4)	13,096 (1.9)	3%	7,995 (1.6)	8,289 (1.6)	0%
Chronic lung disease	177,653 (28.8)	167,962 (23.8)	11%	138,346 (27.5)	136,245 (27.1)	1%
Atrial fibrillation/flutter	25,513 (4.1)	39,678 (5.6)	7%	23,970 (4.8)	25,574 (5.1)	1%
Cancer[j]	76,143 (12.4)	86,596 (12.3)	0%	62,477 (12.4)	62,302 (12.4)	0%
Alcoholism	3,578 (0.6)	4,757 (0.7)	1%	3,187 (0.6)	3,263 (0.6)	0%
Seizure	3,058 (0.5)	4,290 (0.6)	2%	2,772 (0.6)	2,936 (0.6)	0%
Acute kidney injury	6,238 (1.0)	9,090 (1.3)	3%	5,849 (1.2)	6,079 (1.2)	0%
Acute myocardial infarction	18,673 (3.0)	23,811 (3.4)	2%	16,863 (3.3)	16,947 (3.4)	0%
Pacemaker	23,606 (3.8)	31,405 (4.5)	3%	21,185 (4.2)	21,497 (4.3)	0%

Hospitalization with hyperkalemia	2,607 (0.4)	3,358 (0.5)	1%	2,374 (0.5)	2,422 (0.5)	0%
Hypotension	6,289 (1.0)	8,542 (1.2)	2%	5,661 (1.1)	5,838 (1.2)	0%
Prostatic hyperplasia	72,621 (11.8)	90,528 (12.8)	3%	61,284 (12.2)	61,487 (12.2)	0%
Prostatitis	28,193 (4.6)	33,028 (4.7)	1%	23,411 (4.6)	23,426 (4.7)	0%
Acute urinary retention	7,970 (1.3)	10,869 (1.5)	2%	7,068 (1.4)	7,248 (1.4)	0%
DVT/PE	942 (0.2)	1,611 (0.2)	2%	892 (0.2)	1,005 (0.2)	1%
Charlson comorbidity index[k]						
0	394,182 (64.0)	441,541 (62.6)	3%	396,258 (78.7)	394,517 (78.3)	1%
1	151,182 (24.5)	173,421 (24.6)	0%	44,718 (8.9)	45,227 (9.0)	0%
2	36,695 (6.0)	44,093 (6.3)	1%	31,456 (6.2)	31,689 (6.3)	0%
≥ 3	34,300 (5.6)	46,077 (6.5)	4%	31,180 (6.2)	32,179 (6.4)	1%
Johns Hopkins Aggregated Diagnosis Groups						
0	14,708 (2.4)	18,706 (2.7)	2%	12,004 (2.4)	11,646 (2.3)	0%
1-2	107,191 (17.4)	129,336 (18.3)	2%	87,530 (17.4)	87,189 (17.3)	0%
3-5	256,541 (41.6)	289,615 (41.1)	1%	207,832 (41.3)	207,381 (41.2)	0%
≥ 6	237,919 (38.6)	267,475 (37.9)	1%	196,246 (39.0)	197,396 (39.2)	0%
Medication use[l]						
Antiarrhythmic	8,265 (1.3)	13,318 (1.9)	4%	7,897 (1.6)	8,306 (1.6)	1%
Antipsychotic	15,803 (2.6)	24,798 (3.5)	6%	14,803 (2.9)	15,909 (3.2)	1%
Proton pump inhibitor	113,986 (18.5)	127,557 (18.1)	1%	94,018 (18.7)	94,081 (18.7)	0%
Antiemetic	3,353 (0.5)	4,417 (0.6)	1%	2,971 (0.6)	3,137 (0.6)	0%
Lithium	1,230 (0.2)	1,737 (0.2)	1%	1,071 (0.2)	1,079 (0.2)	0%
Antilipemic	221,688 (36.0)	272,129 (38.6)	5%	188,554 (37.4)	189,507 (37.6)	0%
Antihypertensive	378,579 (61.4)	441,513 (62.6)	2%	315,012 (62.6)	316,392 (62.8)	1%

Potassium sparing diuretic	7,394 (1.2)	7,828 (1.1)	1%	5,943 (1.2)	5,882 (1.2)	0%
H2RA	45,412 (7.4)	49,780 (7.1)	1%	37,562 (7.5)	38,034 (7.6)	0%
Prokinetic	12,338 (2.0)	14,799 (2.1)	1%	10,793 (2.1)	10,792 (2.1)	0%
QT-prolonging	79,216 (12.9)	96,628 (13.7)	3%	68,376 (13.6)	68,376 (13.6)	0%
Antidiabetic	86,160 (14.0)	107,168 (15.2)	3%	74,116 (14.7)	75,326 (15.0)	1%
Acetylsalicylic acid	45,102 (7.3)	50,932 (7.2)	0%	38,140 (7.6)	38,469 (7.6)	0%
Anticoagulant[m]	1,097 (0.2)	1,913 (0.3)	2%	1,053 (0.2)	1,116 (0.2)	0%
Antiplatelet	21,137 (3.4)	26,750 (3.8)	2%	18,705 (3.7)	18,835 (3.7)	0%
Tricyclic antidepressant	16,779 (2.7)	18,043 (2.6)	1%	13,898 (2.8)	13,639 (2.7)	0%
Opioid	144 (0.0)	152 (0.0)	0%	115 (0.0)	121 (0.0)	0%
Antimalarian	4,165 (0.7)	3,976 (0.6)	1%	3,218 (0.6)	3,126 (0.6)	0%
Antiviral	70 (0.0)	78 (0.0)	0%	59 (0.0)	57 (0.0)	0%
Antineoplastic	18,251 (3.0)	19,862 (2.8)	1%	14,617 (2.9)	14,760 (2.9)	0%
Benzodiazepine	95,661 (15.5)	106,325 (15.1)	1%	78,922 (15.7)	79,561 (15.8)	0%
NSAID[n]	96,993 (15.7)	102,468 (14.5)	3%	77,699 (15.4)	77,092 (15.3)	0%
Cholinesterase inhibitor	0 (0.0)	0 (0.0)	0%	-	-	-
Anticonvulsant	12,039 (2.0)	17,052 (2.4)	3%	10,861 (2.2)	11,419 (2.3)	1%
ACE/ARB	244,089 (39.6)	286,273 (40.6)	2%	203,598 (40.4)	204,220 (40.6)	0%
Beta-adrenergic antagonist	143,479 (23.3)	175,820 (24.9)	4%	122,840 (24.4)	123,696 (24.6)	0%
Calcium channel blocker	137,188 (22.3)	162,728 (23.1)	2%	115,643 (23.0)	116,434 (23.1)	0%
Non-potassium sparing diuretic	140,191 (22.7)	164,702 (23.4)	1%	117,731 (23.4)	118,689 (23.6)	0%

Statin	206,154 (33.4)	253,885 (36.0)	5%	175,534 (34.9)	176,476 (35.0)	0%
Antiparkinson drug	7,655 (1.2)	11,610 (1.6)	3%	6,976 (1.4)	7,263 (1.4)	0%
Digoxin	16,465 (2.7)	27,748 (3.9)	7%	15,850 (3.1)	17,362 (3.4)	2%
Overactive bladder medication	11,989 (1.9)	15,337 (2.2)	2%	10,306 (2.0)	10,385 (2.1)	0%
Warfarin	28,511 (4.6)	52,322 (7.4)	12%	27,911 (5.5)	31,117 (6.2)	3%
Inhaler - acetylcholine	26,454 (4.3)	26,784 (3.8)	3%	21,534 (4.3)	21,606 (4.3)	0%
Inhaler - corticosteroid	38,465 (6.2)	32,138 (4.6)	7%	28,792 (5.7)	27,560 (5.5)	1%
Inhaler - beta-agonist	71,383 (11.6)	61,638 (8.7)	9%	54,089 (10.7)	52,530 (10.4)	1%
Smoking cessation aid	213 (0.0)	220 (0.0)	0%	162 (0.0)	164 (0.0)	0%
Health care use[o]						
GP/FP visits	588,000 (95.4)	671,789 (95.3)	1%	480,748 (95.5)	481,050 (95.5)	0%
Specialist consultations						
Nephrologist consults	23,354 (3.8)	31,104 (4.4)	3%	20,866 (4.1)	21,237 (4.2)	0%
Cardiologist consults	192,925 (31.3)	233,623 (33.1)	4%	163,132 (32.4)	164,185 (32.6)	0%
Prior investigations and treatments						
Carotid ultrasound	23,718 (3.8)	27,395 (3.9)	0%	19,805 (3.9)	19,657 (3.9)	0%
Cardiac catheterization	7,618 (1.2)	10,102 (1.4)	2%	6,875 (1.4)	7,053 (1.4)	0%
Coronary angiogram	8,845 (1.4)	11,493 (1.6)	2%	7,944 (1.6)	8,096 (1.6)	0%
Echocardiography	76,276 (12.4)	95,002 (13.5)	3%	65,733 (13.1)	66,452 (13.2)	0%
EEG	2,452 (0.4)	3,074 (0.4)	1%	2,098 (0.4)	2,099 (0.4)	0%
Holter monitoring	27,888 (4.5)	35,025 (5.0)	2%	23,889 (4.7)	24,311 (4.8)	0%
Cardiac stress test	59,803 (9.7)	68,956 (9.8)	0%	49,842 (9.9)	49,678 (9.9)	0%
Coronary revascularization	4,282 (0.7)	5,866 (0.8)	2%	3,917 (0.8)	4,044 (0.8)	0%
ECG	270,574 (43.9)	319,725 (45.3)	3%	225,533 (44.8)	226,738 (45.0)	0%

Colorectal cancer screening	120,943 (19.6)	135,540 (19.2)	1%	96,970 (19.3)	96,028 (19.1)	0%
Cervical cancer screening	50,974 (8.3)	52,085 (7.4)	3%	39,122 (7.8)	38,535 (7.7)	0%
PSA test	11,272 (1.8)	16,987 (2.4)	4%	10,216 (2.0)	10,024 (2.0)	0%
Mammography	62,602 (10.2)	62,137 (8.8)	5%	48,148 (9.6)	47,222 (9.4)	1%
Influenza vaccination	330,636 (53.6)	372,220 (52.8)	2%	269,517 (53.5)	269,306 (53.5)	0%
Bone mineral density test	78,822 (12.8)	82,424 (11.7)	3%	61,728 (12.3)	60,823 (12.1)	1%
Hearing test	28,892 (4.7)	32,190 (4.6)	1%	23,566 (4.7)	23,393 (4.6)	0%
Cystoscopy	16,682 (2.7)	21,408 (3.0)	2%	14,405 (2.9)	14,577 (2.9)	0%
Transurethral resection of the prostate	1,314 (0.2)	1,869 (0.3)	1%	1,169 (0.2)	1,211 (0.2)	0%
CT of the head	36,303 (5.9)	47,676 (6.8)	4%	31,556 (6.3)	32,637 (6.5)	1%
CT of other areas	53,665 (8.7)	63,780 (9.0)	1%	45,195 (9.0)	45,595 (9.1)	0%
Chest x-ray	25,312 (4.1)	22,786 (3.2)	5%	19,484 (3.9)	19,263 (3.8)	0%
Pulmonary function test	50,909 (8.3)	51,816 (7.3)	3%	40,495 (8.0)	40,142 (8.0)	0%
At-home physician service	16,262 (2.6)	19,799 (2.8)	1%	14,109 (2.8)	14,329 (2.8)	0%
Urinalysis	9,521 (1.5)	34,249 (4.9)	19%	9,520 (1.9)	9,786 (1.9)	0%
Sputum	483 (0.1)	399 (0.1)	1%	367 (0.1)	356 (0.1)	0%

Kidney function[p]						
Baseline SCr concentration, median (IQR), μmol/L	78 (66-93)	79 (67-94)	4%	79 (67-93)	78 (66-93)	1%
eGFR, median (IQR), mL/min/1.73 m^{2q}	74 (61-86)	74 (61-86)	2%	74 (61-86)	74 (61-86)	1%
eGFR						
≥ 60 mL/min/1.73 m^2	81,332 (13.2)	95,913 (13.6)	1%	66,755 (13.3)	66,942 (13.3)	0%
45-59 mL/min/1.73 m^2	16,125 (2.6)	19,597 (2.8)	1%	13,793 (2.7)	13,534 (2.7)	0%
30-44 mL/min/1.73 m^2	6,352 (1.0)	8,217 (1.2)	1%	5,630 (1.1)	5,637 (1.1)	0%
15-29 mL/min/1.73 m^2	1,735 (0.3)	2,478 (0.4)	1%	1,581 (0.3)	1,661 (0.3)	0%
< 15 mL/min/1.73 m^2	226 (0.0)	310 (0.0)	0%	217 (0.0)	202 (0.0)	0%
Urine dipstick protein[r]						
Negative (≤ 0.3 g/L)	612 (0.1)	803 (0.1)	0%	533 (0.1)	508 (0.1)	0%
0.3 g/L - 1.0 g/L	8,734 (1.4)	10,935 (1.6)	1%	7,362 (1.5)	7,372 (1.5)	0%
1.0 g/L - 3.0 g/L	6,985 (1.1)	8,933 (1.3)	1%	5,926 (1.2)	6,148 (1.2)	0%
≥ 3.0 g/L	6,250 (1.0)	8,444 (1.2)	2%	5,517 (1.1)	5,711 (1.1)	0%

Abbreviations: ACE = angiotensin-converting enzyme, ARB = angiotensin II receptor blocker, CKD = chronic kidney disease, CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration, CT = computed tomography, DVT/PE = deep vein thrombosis/pulmonary embolism, ECG = electrocardiography, EEG = electroencephalography, eGFR = estimated glomerular filtration rate, GP/FP = general practitioner/family practitioner, H2RA = histamine H2-receptor antagonist, IQR = interquartile range, LHIN = Local Health Integration Network, NSAID = non-steroidal anti-inflammatory drug, PSA = prostate-specific antigen, SCr = serum creatinine, SD = standard deviation, TIA = transient ischemic attack

[a]Data are presented as the number (percentage) of patients, unless otherwise reported.

[b]Standardized differences are less sensitive to sample size than traditional hypothesis tests. They provide a measure of the difference between groups divided by the pooled standard deviation; a value greater than 10% (0.1) is interpreted as a meaningful difference between the groups (71).

[c]Income was categorized into fifths of average neighborhood income on the index date. Income was not available for 2,160 (0.4%) macrolide antibiotic users and 2,468 (0.4%) non-macrolide antibiotic users in the unmatched cohort. Missing values in the unmatched cohort were

re-classified into income quintile 3 during matching.
[d]Rural residence was defined as a population < 10,000 people. Residential information was not available for 647 (0.1%) macrolide antibiotic users and 708 (0.1%) non-macrolide antibiotic users in the unmatched cohort. Missing values in the unmatched cohort were re-classified into the "No" category during matching.
[e]LHIN refers to health authorities responsible for regional administration of public healthcare services in Ontario. LHIN was not available for 619 (0.1%) macrolide antibiotic users and 684 (0.1%) non-macrolide antibiotic users in the unmatched cohort and 500 (0.1%) macrolide users and 480 (0.1%) non-macrolide antibiotic users in the matched cohort.
[f]Prescriber information was not available for 100,111 (16.2%) macrolide antibiotic users and 262,915 (37.3%) non-macrolide antibiotic users in the unmatched cohort and 100,093 (19.9%) macrolide antibiotic users and 95,973 (19.1%) non-macrolide antibiotic users in the matched cohort.
[g]Comorbid conditions in the five years preceding the index date were considered.
[h]We identified CKD using an algorithm of hospital diagnostic diagnosis codes validated for older adults in our region (83). The presence of codes in this algorithm is associated with a median eGFR of 38 mL/min/1.73 m^2 (IQR 27 to 52 mL/min/1.73 m^2), whereas an absence of codes is associated with a median eGFR of 69 mL/min/1.73 m^2 (IQR 56 to 82 mL/min/1.73 m^2).
[i]Coronary artery disease included receipt of coronary artery bypass graft surgery and percutaneous coronary intervention.
[j]Major cancers included esophagus, lung, bowel, liver, pancreas, breast, male/female reproductive organs, as well as leukemias and lymphomas.
[k]Charlson comorbidity index (84,85) was calculated using five years of hospitalization data. "No hospitalizations" received a score of 0.
[l]Baseline medication use in the 120 days preceding the index date was considered.
[m]Excludes warfarin.
[n]Excludes acetylsalicylic acid.
[o]Chest x-ray, urinalysis and sputum were assessed in the seven days preceding the index date. All other health care use was assessed in the one year preceding the index date.
[p]Baseline SCr measurements were taken in routine care a median of 131 days (IQR 59 to 227 days) and 126 days (IQR 57 to 224 days) prior to the index date for macrolide antibiotic users and non-macrolide antibiotic users, respectively, in the unmatched cohort and 129 days (IQR 59 to 225 days) and 127 days (IQR 58 to 224 days) prior to the index date for macrolide antibiotic users and non-macrolide antibiotic users, respectively, in the matched cohort.
[q]eGFR was calculated using the CKD-EPI equation (86): $141 \times \min([\text{serum creatinine concentration in } \mu\text{mol/L}/88.4]/\kappa, 1)^{\alpha} \times \max([\text{serum creatinine concentration in } \mu\text{mol/L}/88.4]/\kappa, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018$ [if female] × 1.159 [if African-American]; $\kappa = 0.7$ if female and 0.9 if male; $\alpha = -0.329$ if female and -0.411 if male; min = the minimum of serum creatinine concentration/κ or 1; max = the maximum of serum creatinine concentration/κ or 1. Information on race was not available in our data sources and all patients were assumed not to be of African-Canadian race; African-Canadians represented less than 5% of the population of Ontario in 2006 (87).
[r]Urine dipstick protein measurements were available for 22,581 (3.7%) macrolide antibiotic users and 29,115 (4.1%) non-macrolide antibiotic users in the unmatched cohort and 19,338 (3.8%) macrolide antibiotic users and 19,739 (3.9%) non-macrolide antibiotic users in the matched cohort.

Table 3. 30-day risk for hospital encounter with ventricular arrhythmia and all-cause mortality in matched cohort of patients prescribed macrolide antibiotics compared to referent non-macrolide antibiotics

Outcome	Events, *n* (%)		Relative Risk (95% CI)	*P* value
	Macrolide (*n* = 503,612)	Non-Macrolide (*n* = 503,612)		
Ventricular arrhythmia[a]	134 (0.03)	126 (0.03)	1.06 (0.83-1.36)	0.62
All-cause mortality	3,144 (0.62)	3,833 (0.76)	0.82 (0.78-0.86)	< 0.0001

Abbreviations: CI = confidence interval

[a]Based on hospital presentation (emergency room or hospitalization) assessed by hospital diagnosis codes. This method of assessment underestimated the true number of events as ventricular arrhythmias frequently go undetected in routine healthcare (because they often occur outside hospital settings, in unmonitored patients in hospital or in a setting of multi-organ medical illness where recorded codes describe other illnesses besides the ventricular arrhythmia).

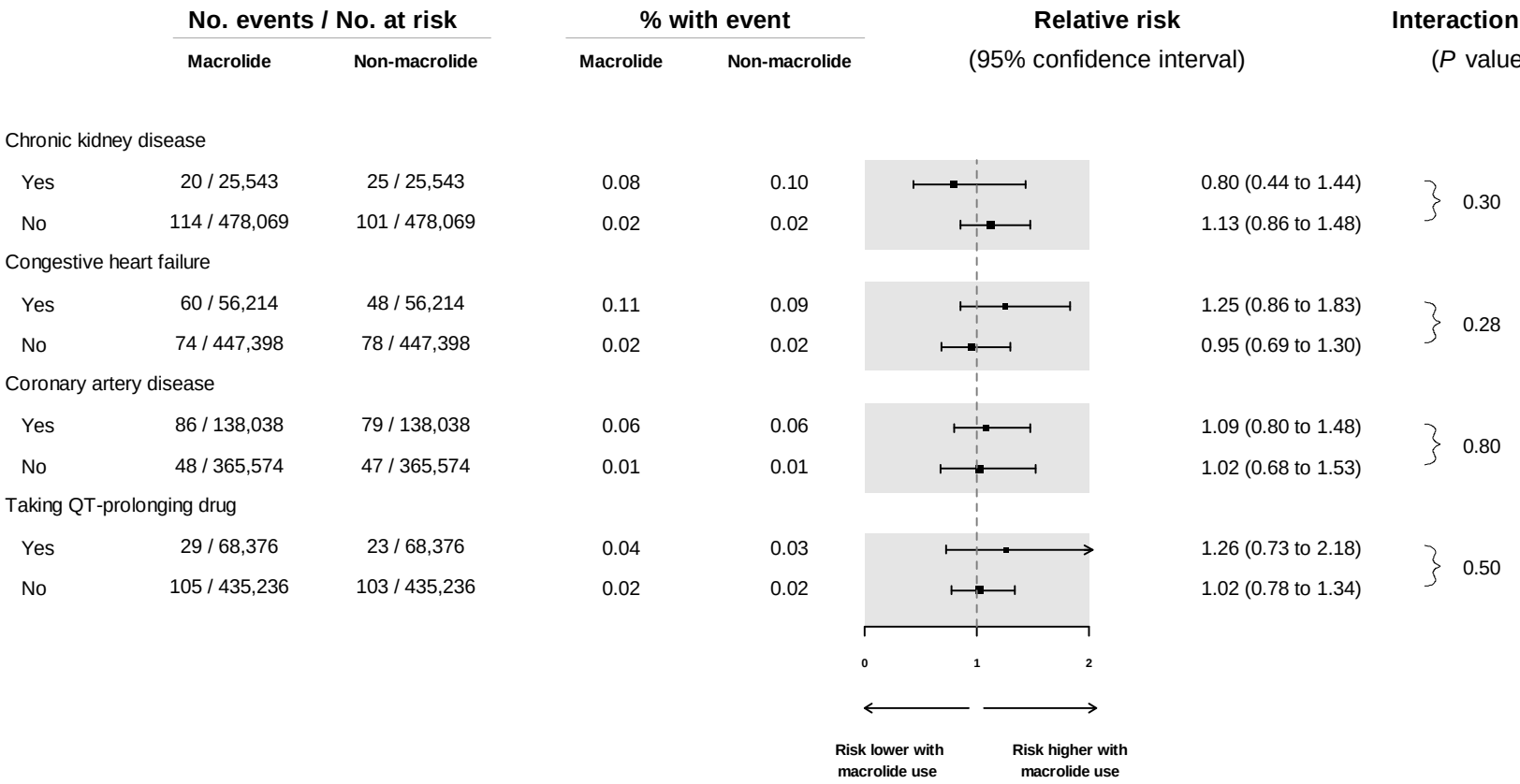

Figure 2. The association between macrolide antibiotic prescription (azithromycin, clarithromycin or erythromycin) and 30-day hospital encounter with ventricular arrhythmia[a] examined in subgroups defined by CKD, CHF, CAD and QT-prolonging drug use

Abbreviations: CAD = coronary artery disease, CHF = congestive heart failure, CKD = chronic kidney disease
Data marker size is proportional to the inverse of the source variance.
[a]Based on hospital presentation (emergency room or hospitalization) assessed by hospital diagnosis codes. This method of assessment underestimated the true number of events as ventricular arrhythmias frequently go undetected in routine healthcare (because they often occur outside hospital settings, in unmonitored patients in hospital or in a setting of multi-organ medical illness where recorded codes describe other illnesses besides the ventricular arrhythmia).

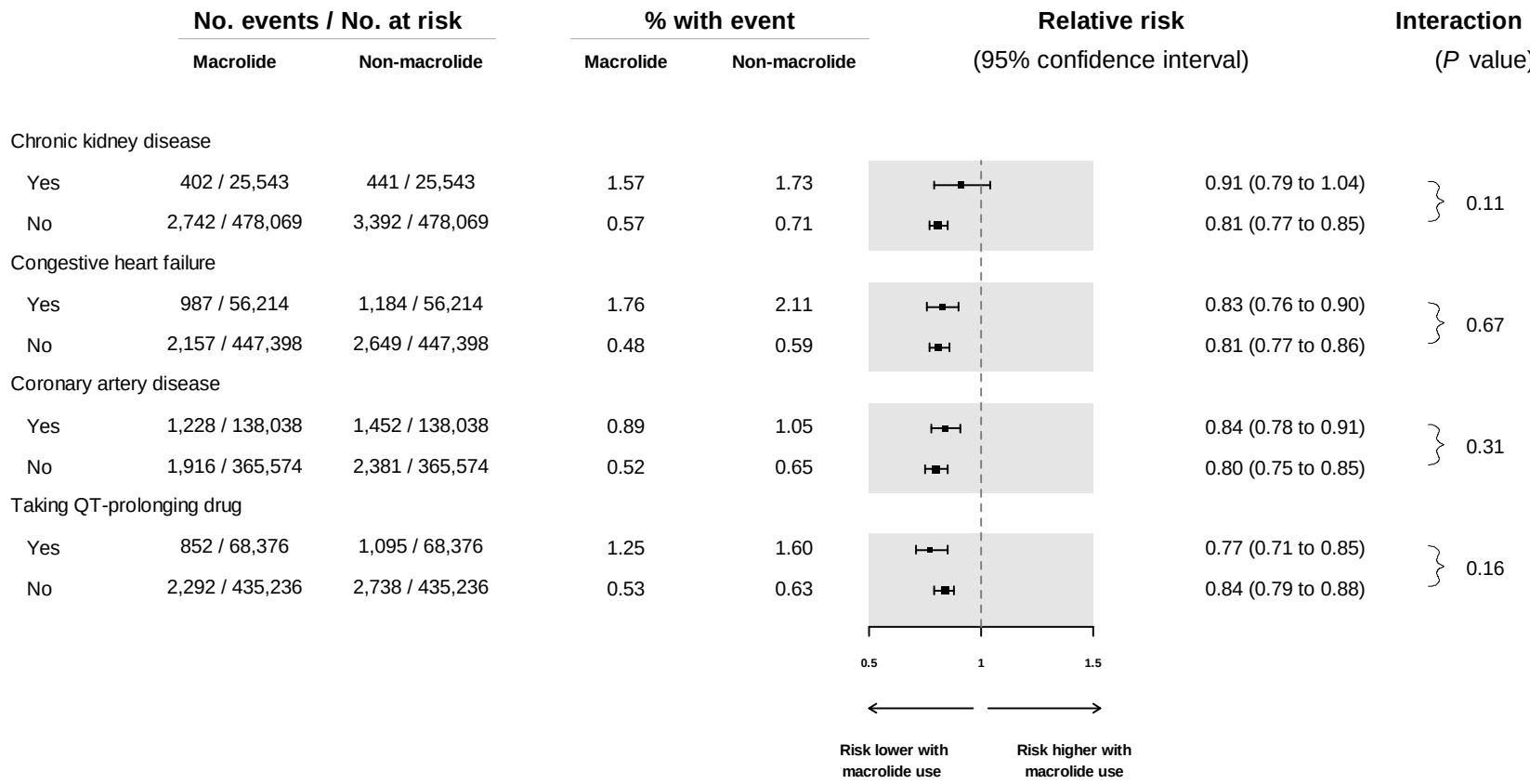

Figure 3. The association between macrolide antibiotic prescription (azithromycin, clarithromycin or erythromycin) and 30-day all-cause mortality examined in subgroups defined by CKD, CHF, CAD and QT-prolonging drug use

Abbreviations: CAD = coronary artery disease, CHF = congestive heart failure, CKD = chronic kidney disease
Data marker size is proportional to the inverse of the source variance.

Chapter 6

6 Discussion

In this population-based cohort study, we observed that new use of a macrolide antibiotic compared to non-macrolide antibiotics was associated with a similar 30-day risk of ventricular arrhythmia (0.03% vs. 0.03%) and a slightly lower risk of all-cause mortality (0.62% vs. 0.76%).

6.1 Summary and interpretation of study results

The studies included in our literature review show inconsistent findings. Although a plausible explanation for these observed differences may be variation in the average age, sex and baseline comorbidity of the studied populations, some publications warrant further attention.

Of particular interest is the comparison of our findings with those of Ray *et al.* who observed a higher 5-day risk of cardiovascular death (HR 2.49, 95% CI 1.38-4.50) and death from any cause (HR 2.02, 95% CI 1.24-3.30) among patients taking azithromycin compared with those taking amoxicillin (8). Although the authors matched azithromycin use to antibiotic non-use, no matching was done for those prescribed amoxicillin. Compared with the azithromycin group, patients receiving amoxicillin seemed healthier overall, with lower percentages of baseline medication use (with the exception of digoxin and insulin), lower prevalence of comorbidities and fewer hospitalizations and emergency department visits. Accordingly, fewer deaths could have occurred among those receiving amoxicillin if they were less prone to events than the macrolide antibiotic group.

In this same study, the authors reported the greatest risk of cardiovascular death in patients with the highest baseline risk of cardiovascular disease. Additionally, Schembri *et al.* reported an increased risk of cardiovascular events with prolonged courses of clarithromycin (> 7 days), especially in patients with pre-existing coronary artery disease

(18). For these reasons, we explored congestive heart failure and coronary artery disease as subgroups in our study. We found that these variables did not significantly alter the association between macrolide antibiotic use and our outcomes. Nonetheless, these findings should be interpreted with caution and physicians should always consider a patient's baseline risk for adverse events before prescribing macrolides or other antibiotics. Patients at particular risk include those with existing QT interval prolongation, a history of torsades de pointes, hypokalemia, hypomagnesemia, significant bradycardia, bradyarrhythmias or use of certain antiarrhythmic drugs (88–90). To minimize risk, others advocate for ECG to monitor the QT interval before and after initiating therapy (91).

A plausible explanation for the observed reduction in 30-day all-cause mortality with macrolide antibiotic use may be their immunomodulatory effects (92). These effects are believed to be mediated by several properties of macrolide antibiotics that have been observed including decreases in pro-inflammatory cytokines (TNF-α, IL-1, IL-6, IL-8 and IFN-γ), increases in anti-inflammatory cytokines and decreases in neutrophil chemotaxis, leukocyte adhesion, and oxidative metabolism (93). However, because the absolute magnitude of this effect was small, this finding should be interpreted with caution.

6.2 Study strengths and limitations

Our study has several strengths. The use of Ontario's healthcare databases with data on universal prescription drug coverage in older adults provided us with a large representative sample of patients who received the study antibiotics in routine care. This allowed us to estimate the risks of uncommon but serious adverse events with good precision and external validity. We assessed clinically important adverse events (hospital encounter with ventricular arrhythmia and death), rather than relying on surrogate outcomes such as a prolonged QT interval on an ECG, making these findings of particular interest to clinicians and regulatory agencies. We used the non-macrolide

antibiotics amoxicillin, cefuroxime and levofloxacin as a referent group to reduce the influence of confounding by indication.

Experimental studies provide the strongest evidence for whether or not an exposure has an effect on the risk of a disease (94). However, clinical trials are costly and the relatively small number of patients enrolled in the trials makes the estimation of risk for relatively rare adverse drug events difficult (95). Large observational studies can complement the findings of clinical trials by enabling the investigation of uncommon but important adverse drug events with adequate statistical power. Moreover, such observational studies can include vulnerable groups of patients who may be excluded from clinical trials and better reflect what occurs in routine clinical settings where treatments and monitoring are less regulated than in clinical trials (96,97)

Our study has some limitations. Prospective data collection with independent outcome adjudication would be a preferred methodology to assess risk. In this study, we analyzed retrospective data using administrative diagnosis codes assigned from physician records, and cardiac rhythm tracings were not available in our data sources. The diagnosis codes we used for a hospital encounter with ventricular arrhythmia have a good PPV but limited sensitivity. However, we have no reason to suspect any systematic difference in diagnostic recording by antibiotic type, suggesting that our relative measures of risk are robust. As with all observational studies, residual confounding can never be eliminated; however, we used a statistical technique to ensure our comparison groups were similar on 106 measured baseline characteristics. Our findings might not generalize well to other regions if Ontario physicians deliberately avoided prescribing macrolide antibiotics to patients at highest risk of ventricular arrhythmia (such as those with baseline QT prolongation), or discontinued macrolide antibiotics when the QT interval was prolonged in a follow-up ECG. However, our impression is that Ontario physicians rarely take ventricular arrhythmia risk into account when deciding to prescribe a macrolide. Although shorter follow-up periods were used in prior studies (8–10,12,17,18,37), we consider the 30-day follow-up used in our study to be clinically relevant. We did, however, repeat our analyses within 14 days of macrolide antibiotic prescription and found similar results.

6.3 Study implications

This study was prompted by Health Canada and U.S. FDA warnings about a higher risk of QT interval prolongation and subsequent ventricular arrhythmia among patients taking azithromycin (5,6). Though caution should be exercised when prescribing macrolide antibiotics to high-risk patients where drug clearance or electrical activity of the heart is impaired and outcomes less predictable, our study findings and examination of the current literature suggest that the risk of ventricular arrhythmia and death from macrolide antibiotic use may be overstated. A careful re-examination and updating of drug prescribing references (44,57–59) and warnings from regulatory agencies appears warranted. The findings from this study are reassuring for health care providers who prescribe macrolide antibiotics to a wide range of patients in routine care.

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Appendices

Appendix A. Modified Downs and Black checklist for the assessment of the methodological quality of both randomized and non-randomized studies (36)

Item	Criteria	Possible Answers
Reporting		
1	*Is the hypothesis/aim/objective of the study clearly described?*	Yes = 1 No = 0
2	*Are the main outcomes to be measured clearly described in the Introduction or Methods section?* If the main outcomes are first mentioned in the Results section, the question should be answered no.	Yes = 1 No = 0
3	*Are the characteristics of the patients included in the study clearly described?* In cohort studies and trials, inclusion and/or exclusion criteria should be given. In case-control studies, a case-definition and the source for controls should be given.	Yes = 1 No = 0
4	*Are the interventions of interest clearly described?* Treatments and placebo (where relevant) that are to be compared should be clearly described.	Yes = 1 No = 0
5	*Are the distributions of principal confounders in each group of subjects to be compared clearly described?* A list of principal confounders is provided.	Yes = 2 Partially = 1 No = 0
6	*Are the main findings of the study clearly described?* Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions. (This question does not cover statistical tests which are considered below).	Yes = 1 No = 0
7	*Does the study provide estimates of the random variability in the data for the main outcomes?* In non-normally distributed data the interquartile range of results should be reported. In normally distributed data the standard error, standard deviation or confidence intervals should be reported. If the distribution of the data is not described, it must be assumed that the estimates used were appropriate and the question should be answered yes.	Yes = 1 No = 0
8	*Have all important adverse events that may be a consequence of the intervention been reported?* This should be answered yes if the study demonstrates that there was a comprehensive attempt to measure adverse events. (A list of possible adverse events is provided).	Yes = 1 No = 0

9	*Have the characteristics of patients lost to follow-up been described?* This should be answered yes where there were no losses to follow-up or where losses to follow-up were so small that findings would be unaffected by their inclusion. This should be answered no where a study does not report the number of patients lost to follow-up.	Yes = 1 No = 0
10	*Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?*	Yes = 1 No = 0
External validity		
11	*Were the subjects asked to participate in the study representative of the entire population from which they were recruited?* The study must identify the source population for patients and describe how the patients were selected. Patients would be representative if they comprised the entire source population, an unselected sample of consecutive patients, or a random sample. Random sampling is only feasible where a list of all members of the relevant population exists. Where a study does not report the proportion of the source population from which the patients are derived, the question should be answered as unable to determine.	Yes = 1 No = 0 Unable to determine = 0
12	*Were those subjects who were prepared to participate representative of the entire population from which they were recruited?* The proportion of those asked who agreed should be stated. Validation that the sample was representative would include demonstrating that the distribution of the main confounding factors was the same in the study sample and the source population.	Yes = 1 No = 0 Unable to determine = 0
13	*Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?* For the question to be answered yes the study should demonstrate that the intervention was representative of that in use in the source population. The question should be answered no if, for example, the intervention was undertaken in a specialist centre unrepresentative of the hospitals most of the source population would attend.	Yes = 1 No = 0 Unable to determine = 0
Internal validity - bias		
14	*Was an attempt made to blind study subjects to the intervention they have received?* For studies where the patients would have no way of knowing which intervention they received, this should be answered yes.	Yes = 1 No = 0 Unable to determine = 0

15	*Was an attempt made to blind those measuring the main outcomes of the intervention?*	Yes = 1 No = 0 Unable to determine = 0
16	*If any of the results of the study were based on "data dredging", was this made clear?* Any analyses that had not been planned at the outset of the study should be clearly indicated. If no retrospective unplanned subgroup analyses were reported, then answer yes.	Yes = 1 No = 0 Unable to determine = 0
17	*In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?* Where follow-up was the same for all study patients the answer should be yes. If different lengths of follow-up were adjusted for by, for example, survival analysis the answer should be yes. Studies where differences in follow-up are ignored should be answered no.	Yes = 1 No = 0 Unable to determine = 0
18	*Were the statistical tests used to assess the main outcomes appropriate?* The statistical techniques used must be appropriate to the data. For example nonparametric methods should be used for small sample sizes. Where little statistical analysis has been undertaken but where there is no evidence of bias, the question should be answered yes. If the distribution of the data (normal or not) is not described it must be assumed that the estimates used were appropriate and the question should be answered yes.	Yes = 1 No = 0 Unable to determine = 0
19	*Was compliance with the intervention/s reliable?* Where there was non-compliance with the allocated treatment or where there was contamination of one group, the question should be answered no. For studies where the effect of any misclassification was likely to bias any association to the null, the question should be answered yes.	Yes = 1 No = 0 Unable to determine = 0
20	*Were the main outcome measures used accurate (valid and reliable)?* For studies where the outcome measures are clearly described, the question should be answered yes. For studies which refer to other work or that demonstrates the outcome measures are accurate, the question should be answered as yes.	Yes = 1 No = 0 Unable to determine = 0
Internal validity - confounding (selection bias)		
21	*Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?* For example, patients for all comparison groups should be selected from the same hospital. The question should be answered unable to determine for cohort and case-control	Yes = 1 No = 0 Unable to determine = 0

	studies where there is no information concerning the source of patients included in the study.	
22	*Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?* For a study which does not specify the time period over which patients were recruited, the question should be answered as unable to determine.	Yes = 1 No = 0 Unable to determine = 0
23	*Were study subjects randomized to intervention groups?* Studies which state that subjects were randomized should be answered yes except where method of randomization would not ensure random allocation. For example alternate allocation would score no because it is predictable.	Yes = 1 No = 0 Unable to determine = 0
24	*Was the randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?* All non-randomized studies should be answered no. If assignment was concealed from patients but not from staff, it should be answered no.	Yes = 1 No = 0 Unable to determine = 0
25	*Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?* This question should be answered no for trials if: the main conclusions of the study were based on analyses of treatment rather than intention to treat; the distribution of known confounders in the different treatment groups was not described; or the distribution of known confounders differed between the treatment groups but was not taken into account in the analyses. In non-randomized studies if the effect of the main confounders was not investigated or confounding was demonstrated but no adjustment was made in the final analyses the question should be answered as no.	Yes = 1 No = 0 Unable to determine = 0
26	*Were losses of patients to follow-up taken into account?* If the numbers of patients lost to follow-up are not reported, the question should be answered as unable to determine. If the proportion lost to follow-up was too small to affect the main findings, the question should be answered yes.	Yes = 1 No = 0 Unable to determine = 0
Power		
27[a]	*Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?* Sample sizes have been calculated to detect a difference of x% and y%.	Yes = 1 No = 0 Unable to determine = 0

[a]Item has been modified.

Appendix B. Checklist of recommendations for reporting of observational studies using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (40)

	Item No	Recommendation	Reported
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	Abstract
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract
Introduction			
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported	Chapters 1, 2 & 3
Objectives	3	State specific objectives, including any prespecified hypotheses	Chapter 3
Methods			
Study design	4	Present key elements of study design early in the paper	Chapter 4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Chapter 4
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Chapter 4, Figure 1
		(b) For matched studies, give matching criteria and number of exposed and unexposed	Chapter 4, Figure 1
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Chapter 4, Appendices C, D, E, F & G
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment	Chapter 4, Appendices C & D

		methods if there is more than one group	
Bias	9	Describe any efforts to address potential sources of bias	Chapters 4 & 6
Study size	10	Explain how the study size was arrived at	Chapter 4; based on availability of the data
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Chapter 4
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	Chapter 4
		(b) Describe any methods used to examine subgroups and interactions	Chapter 4
		(c) Explain how missing data were addressed	Chapter 4
		(d) If applicable, explain how loss to follow-up was addressed	Not applicable
		(e) Describe any sensitivity analyses	Chapter 4
Results			
Participants	13	(a) Report numbers of individuals at each stage of study-e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed	Chapter 5, Figure 1
		(b) Give reasons for non-participation at each stage	Chapter 5, Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14	(a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders	Chapter 5, Table 2, Appendix G
		(b) Indicate number of participants with missing data for each variable of interest	Chapter 5, Table 2, Appendix I
		(c) Summarize follow-up time (e.g. average and total amount)	Chapter 5

Outcome data	15	Report numbers of outcome events or summary measures over time	Chapter 5, Table 3
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g. 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Chapter 5, Table 2, Appendix G
		(b) Report category boundaries when continuous variables were categorized	Not applicable
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done-e.g. analyses of subgroups and interactions, and sensitivity analyses	Chapter 5, Figures 1 and 2, Appendices I & J
Discussion			
Key results	18	Summarize key results with reference to study objectives	Chapter 6
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Chapter 6
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Chapter 6
Generalizability	21	Discuss the generalizability (external validity) of the study results	Chapter 6
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Acknowledgements

Appendix C. Coding definitions for demographics and comorbid conditions

Variable	Database	Codes
Demographics		
Age	RPDB	
Sex	RPDB	
Socioeconomic status (neighbourhood income quintiles)	Statistics Canada	
Location of residence - Rural status	Statistics Canada	
Long-term care	ODB	LTC
Prescribing physician / LHIN[a]	RPDB	LHIN
Comorbidities		
Dementia	CIHI-DAD OHIP OMHRS	ICD-9: 2900, 2901, 2903, 2904, 2908, 2909, 2948, 2949, 3310-3312, 2941, 797 ICD-10: F00-F03, F051, F065, F066, F068, F069, F09, G30, G31, R54 OHIP dx: 290, 331, 797 DSM-IV: 29040-29043, 29120, 29282, 29410, 29411, 29480, 78090
Schizophrenia or other psychotic disorders	CIHI-DAD OHIP OMHRS	ICD-9: 2950-2959, 2970-2973, 2978-2981, 2983, 2984, 2988, 2989 ICD-10: F060, F062, F105, F107, F115, F117, F125, F127, F135, F137, F145, F147, F155, F157, F165, F167, F175, F177, F185, F187, F195, F197, F200-F206, F208, F209, F220, F228-F233, F238, F239, F24, F250-F252, F258, F259, F28, F29 OHIP dx: 291, 292, 295, 297, 298 OHIP fee: Q021 DSM-IV: 29130, 29150, 29211, 29212, 29381, 29382, 29510, 29520, 29530, 29540, 29560, 29570, 29590, 29710, 29730, 29880, 29890
Bipolar disorder	CIHI-DAD OHIP OMHRS	ICD-9: 2960, 2961, 2964-2968 ICD-10: F300-F302, F308-F319 OHIP dx: 296 OHIP fee: Q020 DSM-IV: 29600-29606, 29640-29646, 29650-29656, 29660-29666, 29670, 29680, 29689

Unipolar depression and/or anxiety disorder	CIHI-DAD OHIP OMHRS	ICD-9: 2962, 2963, 3000, 3002-3004, 3091, 311 ICD-10: F063, F064, F320-F323, F328-F334, F338, F339, F341, F400-F402, F408-F413, F418-F422, F428-F431 OHIP dx: 311 DSM-IV: 29189, 29284, 29289, 29383, 29384, 29620-29626, 29630-29636, 30000-30002, 30021-30023, 30029, 30030, 30040, 30113
Haemorrhagic stroke	CIHI-DAD	ICD-9: 430, 431 ICD-10: I600-I607, I609, I61
Ischemic stroke	CIHI-DAD	ICD-9: 434, 436 ICD-10: H341, I630-I635, I638, I639
Transient ischemic attack	CIHI-DAD	ICD-9: 4358, 4359 ICD-10: G45
Chronic kidney disease	 CORR CIHI-DAD OHIP CIHI-DAD OHIP CIHI-DAD OHIP CIHI-DAD OHIP	<u>Transplant</u> Treatment code: 171, 181 Transplanted organ: 10-12, 18, 19 ICD-9: V420, 99681 ICD-10: N165, T861, Z940 CCP: 6743, 675 CCI: 1PC85 OHIP fee: E762, E769, E771, G347, G348, G408, G409, G412, S434, S435, Z631 <u>Peritoneal dialysis</u> CCP: 6698 CCI: 1PZ21HPD4 OHIP fee: G330-G333, G861, G864, H540, H740 <u>Hemodialysis</u> CCP: 5195 CCI: 1PZ21HQBR, 1PZ21HQBS OHIP fee: G082, G083, G085, G090-G096, G294, G295, G323, G325, G326, G333, G860, G862, G863, G865, G866, H540, H740, R849 <u>Chronic kidney disease</u> ICD-9: 2504, 4030, 4031, 4039-4041, 4049, 585, 586, 5888, 5889 ICD-10: E102, E112, E132, E142, I12, I13, N08, N18, N19 OHIP dx: 403, 585

Chronic liver disease	CIHI-DAD OHIP	ICD-9: 070, 2750, 2751, 4561, 4562, 571, 5722-5724, 5728, 573, 7824, 7891, 7895, V026 ICD-10: B16-B19, B942, E830, E831, I85, K70, K713-K715, K717, K721, K729, K73, K74, K753, K754, K758, K759, K76, K77, R160, R162, R17, R18, Z225 OHIP dx: 070, 571, 573 OHIP fee: Z551, Z554
Congestive heart failure	CIHI-DAD OHIP	ICD-9: 425, 428, 514, 5184 ICD-10: I255, I500, I501, I509, J81 CCP: 4961-4964 CCI: 1HP53, 1HP55, 1HZ53GRFR, 1HZ53LAFR, 1HZ53SYFR OHIP dx: 428 OHIP fee: R701, R702, Z429
Coronary artery disease (minus angina)	CIHI-DAD OHIP	ICD-9: 410, 412, 414, 4292, 4295-4297 ICD-10: I21-I25, R931, T822, Z955, Z958, Z959 CCP: 4801-4805, 481-483 CCI: 1IJ26, 1IJ27, 1IJ50, 1IJ54, 1IJ57, 1IJ76 OHIP dx: 410, 412 OHIP fee: E646, E651, E652, E654, E655, G262, G298, R741-R743, Z434, Z448
Angina	CIHI-DAD OHIP	ICD-9: 413 ICD-10: I20 OHIP dx: 413
Peripheral vascular disease	CIHI-DAD OHIP	ICD-9: 4402, 4408, 4409, 4439, 444, 5571 ICD-10: I700, I702, I708, I709, I731, I738, I739, K551 CCP: 5014, 5016, 5018, 5028, 5038, 5125, 5129 CCI: 1KA50, 1KA76, 1KE76, 1KG26, 1KG50, 1KG57, 1KG76MI, 1KG87 OHIP fee: E626, E649, E672, R780, R783-R787, R791, R794, R797, R804, R809, R813-R815, R855, R856, R867, R875, R936, R937, R860, R861, R933, R934
Parkinson's disease	CIHI-DAD OHIP	ICD-9: 332 ICD-10: F023, G20 OHIP dx: 332
Chronic lung disease	CIHI-DAD	ICD-9: 4168, 4169, 491-496, 500-505, 5064, 5069, 5081, 515-517, 5185, 5188, 5198, 5199 ICD-10: I272, I278, I279, J40-J45, J47,

	OHIP	J60-J68, J701, J703, J704, J708, J709, J82, J84, J92, J941, J949, J953, J961, J969, J984, J988, J989, J99 OHIP dx: 491-494, 496, 501, 502, 515, 518, 519 OHIP fee: J889, J689
Atrial fibrillation/flutter	CIHI-DAD	ICD-9: 4273 ICD-10: I48
Cancer	CIHI-DAD OHIP	ICD-9: 150, 154, 155, 157, 162, 174, 175, 185, 203-208, 2303, 2304, 2307, 2312, 2330, 2334 ICD-10: C15, C18-C20, C22, C25, C34, C50, C56, C61, C82, C83, C85, C91-C95, D00, D010-D012, D022, D05, D075, 971, 980, 982, 984-991, 993 OHIP dx: 203-208, 150, 154, 155, 157, 162, 174, 175, 183, 185
Alcoholism	CIHI-DAD	ICD-9: 303, 3050 ICD-10: E244, E512, F10, G312, G621, G721, I426, K292, K70, K860, T510, X45, X65, Y15, Y573, Z502, Z714, Z721
Seizure	CIHI-DAD	ICD-9: 345, 7803 ICD-10: G40, G41, R560, R568
Acute kidney injury	CIHI-DAD	ICD-9: 584 ICD-10: N17
Acute myocardial infarction	CIHI-DAD	ICD-9: 410 ICD-10: I21, I22
Pacemaker	CIHI-DAD OHIP	CCP: 0345-0349, 4971-4973, 4987 CCI: 1HD53GRJA, 1HD54GRJA, 1HD55, 1HZ09, 1HZ37, 1HZ53GRFR, 1HZ53GRNK, 1HZ53GRNL, 1HZ53GRNM, 1HZ53GRNN, 1HZ53LAFR, 1HZ53SYFR, 1HZ54LANJ, 1HZ55, 2HZ07NK, 2HZ07NL, 2HZ07NM, 2HZ24 OHIP fee: E628, G115, G176, G177, G303, R752, Z412, Z428, Z433-Z435, Z444-Z446
Hyperkalemia	CIHI-DAD	ICD-9: 2767 ICD-10: E875
Hypotension	CIHI-DAD	ICD-9: 458 ICD-10: I95
Prostatic hyperplasia	CIHI-DAD OHIP	ICD-9: 600 ICD-10: N40 OHIP dx: 600

Prostatitis	CIHI-DAD OHIP	ICD-9: 6010-6012 ICD-10: N410-N412 OHIP dx: 601
Acute urinary retention	CIHI-DAD	ICD-9: 7882 ICD-10: R33
Deep vein thrombosis/Pulmonary embolism	CIHI-DAD	ICD-9: 4151, 4511, 4512, 514 ICD-10: I26, I743, I801-I803
Health care use		
GP/FP visits	IPDB, OHIP	Mainspecialty = GP/FP
<u>Specialist consultations</u>		
Nephrologist consults	IPDB OHIP	Mainspecialty = NEPHROLOGY OHIP fee: A135, A161, A163-A166, A168, C101, C132, C135, C137, C138, E083, G323, G860
Dialysis[b]	OHIP	OHIP fee: G323, G325, G326, G330-G332, G860-G866, R849
Cardiologist consults	IPDB, OHIP	Mainspecialty = CARDIOLOGY
<u>Prior investigations and treatments</u>		
Carotid ultrasound	CIHI-DAD OHIP	CCP: 0281 CCI: 3JE30 OHIP fee: J190, J191, J201, J501, J189, J489-J492
Cardiac catheterization	CIHI-DAD OHIP	CCP: 4995-4997 CCI: 2HZ24GPKJ, 2HZ24GPKL, 2HZ24GPKM, 2HZ24GPXJ, 2HZ28GPPL, 2HZ71GP, 3HZ30GP, 3IJ30GP OHIP fee: G296, G297, G299-G301, G304-G306
Coronary angiogram	CIHI-DAD OHIP	CCP: 4892-4898, 4996, 4997 CCI: 3IP10 OHIP fee: G297, Z442
Echocardiography	CIHI-DAD OHIP	CCP: 0282 CCI: 3IP30 OHIP fee: G560-G562, G566-G568, G570-G572, G574-G581
Electroencephalography	OHIP	OHIP fee: G414-G418, G540, G542, G544-G546, G554, G555
Holter monitoring	CIHI-DAD OHIP	CCI: 2HZ24JAKH OHIP fee: G650-G661, G682-G690, G692, G693

Cardiac stress test	CIHI-DAD OHIP	CCP: 0341-0344 CCI: 2HZ08, 3IP70 OHIP fee: G111, G112, G174, G315, G319, J604, J606-J609, J611-J613, J667, J804, J807-J809, J811-J813, J666, J866, J867
Coronary revascularization	CIHI-DAD OHIP	CCP: 480-483 CCI: 1IJ26, IIJ27, 1IJ50, 1IJ57, 1IJ76, 1IJ54GQAZ, 1IJ57GQ OHIP fee: E646, E651, E652, E654, G262, G298, R741-R743, Z434
Electrocardiography	CIHI-DAD OHIP	CCI: 2HZ24JAKE OHIP fee: G310, G313
Colorectal cancer screening	OHIP	OHIP fee: G004, L179, L181, Q043, Q152, X112, X113, Z535, Z536, Z555, Z580
Cervical cancer screening	OHIP	OHIP fee: E430, G365, G394, L713, L812
Prostate-specific antigen test	OHIP	OHIP fee: L354, L358
Mammography	OHIP	OHIP fee: X172, X178, X184, X185, X201
Influenza vaccination	OHIP	OHIP fee: G590, G591
Bone mineral density test	OHIP	OHIP fee: J654, J688, J854, J888, X149, X152, X153, X155, Y654, Y688, Y854, Y888
Hearing test	OHIP	OHIP fee: G153, G154, G440-G443, G448, G450-G452, G525, G526, G529, G530, G533, G815, G816
Cystoscopy	OHIP	OHIP fee: Z606, Z607, Z628, Z632-Z634
Transurethral resection of the prostate	CIHI-DAD OHIP	CCP: 721 CCI: 1QT59BAAD, 1QT59BAAG, 1QT59BAAW, 1QT59BAAZ, 1QT59BACG, 1QT59BAGX, 1QT87BA, 1QT87BAAG, 1QT87BAAK OHIP fee: S655
Computed tomography of head	OHIP	OHIP fee: X188, X400-X402, X405, X408
Computed tomography of other areas	OHIP	OHIP fee: X124-X128, X231-X233, X403, X404, X406, X407, X409, X410, X412, X413, X415, X416
Chest x-ray	OHIP	OHIP fee: X090-X092, X195
Pulmonary function test	OHIP	OHIP fee: E450, E451, J301, J303-J311, J313, J315-J320, J322-J324, J327, J328, J330-J335, J340, J341

At-home physician services	OHIP	OHIP fee: A901, B960-B964, B966, B990, B992-B994, B996-B998
Urinalysis	OHIP	OHIP fee: L253-L255, L633, L634, L641, G009, G010
Sputum	OHIP	OHIP fee: L629, L716, L815

Abbreviations: CCI = Canadian Classification of Health Interventions (available after 2002), CCP = Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures (before 2002), CIHI-DAD = Canadian Institute for Health Information Discharge Abstract Database, CORR = Canadian Organ Replacement Register, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th edition, GP/FP = general practitioner/family practitioner, ICD-9 = International Classification of Diseases, Ninth Revision, ICD-10 = International Classification of Diseases, Tenth Revision, IPDB = Institute for Clinical Evaluative Sciences (ICES) Physician Database, LHIN = Local Health Integration Network, ODB = Ontario Drug Benefit, OHIP = Ontario Health Insurance Plan, OMHRS = Ontario Mental Health Reporting System, RPDB = Registered Persons Database of Ontario

[a]LHIN refers to health authorities responsible for regional administration of public healthcare services in Ontario.

[b]Only includes dialysis visits with nephrologist present.

Appendix D. Coding definitions for hospital encounter with ventricular arrhythmia and all-cause mortality

Outcome	Database	Codes
Ventricular arrhythmia	CIHI-DAD, NACRS	ICD-10: I472, I4900
All-cause mortality[a]	RPDB	Vital status field

Abbreviations: CIHI-DAD = Canadian Institute for Health Information Discharge Abstract Database, ICD-10 = International Classification of Diseases, Tenth Revision, NACRS = National Ambulatory Care Reporting System, RPDB = Registered Persons Database of Ontario

[a]All-cause mortality has a sensitivity of 97.8% and specificity of 100% (70).

Appendix E. Coding definitions for cause of death data in Ontario Registrar General Vital Statistics Database

Cause of Death	ICD-9 Codes
Cardiovascular	
Ischemic heart disease	4019, 4020, 4100, 4110, 4120, 4130, 4140, 4141, 4148, 4149, 4230, 4292, 4298
Heart failure	3989, 4029, 4049, 4254, 4255, 4257-4259, 4280, 4281, 4289, 7798
Cerebrovascular	430, 431, 435, 436, 438, 3448, 3623, 4320, 4321, 4329-4333, 4338-4341, 4349, 4370, 4372-4376, 4378, 4379
Arrhythmia	4260, 4261, 4267, 4269-4276, 4278, 4279, 4299, 7850, 7853, 9960, v450, v533
Valvular heart disease	393, 3940-3942, 3949-3952, 3959, 3960, 3970, 3979, 3980, 3989, 4010, 4011, 4039, 4240-4243, 4249
Other	4151, 4400-4402, 4408-4415, 4419-4423, 4428-4431, 4438-4442, 4448, 4449, 4470-4472, 4474-4476, 4478-4481, 4489, 7982, 7989, 9960
Infection	
Abdominal	0020-0023, 0029-0032, 0038-0043, 0048, 0049, 0060-0066, 0068-0072, 0078-0080, 0084-0086, 0088, 0093, 541-543, 0700-0703, 0705, 0706, 0709, 5400, 5401, 5409, 5740-5743, 5745, 5750-5756, 5758, 5759
Cardiac	4209, 4229
Kidney/genitourinary	0900-0907, 0909-0913, 0919, 0929, 0939, 0943, 0948-0950, 0960, 0970, 0971, 0979, 5900, 5990
Neurological	064, 0360, 0362-0364, 0368, 0369, 0620-0625, 0628-0630, 0632, 0638, 0639, 3200-3203, 3207-3210, 3218
Respiratory	0130, 0131, 0138-0140, 0159, 0169, 0170, 0172-0174, 0176, 0178, 0180, 0188, 0189, 0330, 0331, 0338, 0339, 483, 4660, 4661, 4787, 4800-4802, 4808-4810, 4820-4824, 4828, 4829, 4847, 4848, 4850, 4860, 4870, 4871, 4878, 5110, 5118-5120, 5140, 5172, 5178, 5180-5182, 5185, 5188, 5190, 5191, 5193, 5194, 5198, 5199, 7991, 9973
Septicemia	0380-0384, 0388, 0389

Other	0010, 0011, 0019, 0050-0052, 0054, 0058, 0059, 0101, 0200-0202, 0205, 0208-0210, 0220-0223, 0228-0233, 0238-0240, 0250, 0260, 0261, 0269-0272, 0278, 0279, 0300-0303, 0308-0311, 0318-0321, 0323, 0328, 0329, 0341, 0350, 0370, 0390-0393, 0398-0400, 0408, 0410-0419, 0429, 0451, 0452, 0459, 0461-0463, 0468, 0469, 0478-0480, 0490, 0491, 0498, 0499, 0509, 0519, 0520, 0530-0532, 0537, 0539-0547, 0549-0552, 0557, 0559, 0560, 0567, 0569, 0570, 0578, 0579, 0600, 0601, 0609, 0610, 0650-0652, 0654, 0658-0663, 0668, 0669, 0710, 0720-0723, 0727, 0729, 0730, 0740, 0741, 0743, 0750, 0760, 0761, 0769, 0771-0774, 0778-0781, 0783, 0785-0788, 0790, 0798-0800, 0810-0812, 0819-0822, 0823, 0829-0832, 0838-0844, 0846, 0849, 0850, 0855, 0859-0865, 0870, 0871, 0879, 0880, 0888, 0980, 0981, 0984-0988, 0990-0992, 0998-1000, 1008, 1009, 1020-1033, 1039, 1040, 1048, 1049, 1100-1105, 1108-1113, 1118-1125, 1128, 1129, 1140, 1150, 1151, 1159-1162, 1170-1172, 1174-1177, 1179, 1180, 1200-1203, 1208-1214, 1218-1221, 1223-1236, 1238-1240, 1250-1253, 1255-1257, 1259, 1261, 1268-1281, 1288-1290, 1300, 1310, 1318-1323, 1329, 1330, 1338, 1340-1342, 1348, 1349, 1362, 1363, 1368-1374, 1380, 1390, 1391, 1398, 3240, 4298, 6829, 7713
Cancer	
Malignant	1400, 1401, 1403-1406, 1408-1414, 1416, 1418-1422, 1428-1431, 1439-1441, 1448-1456, 1458-1464, 1466-1473, 1478-1483, 1488-1491, 1498, 1500-1505, 1508-1516, 1518-1523, 1528-1543, 1548, 1550-1552, 1560-1562, 1568-1574, 1578-1580, 1588-1591, 1598-1605, 1608-1613, 1618-1620, 1622-1625, 1628, 1629, 1639-1643, 1648-1650, 1658, 1659, 1700-1710, 1712-1746, 1748, 1749, 1790, 1800, 1801, 1808-1810, 1820, 1821, 1828, 1830, 1832-1835, 1838-1844, 1848-1850, 1860, 1869, 1871-1894, 1898-1906, 1908-1923, 1928-1930, 1940, 1941, 1943-1946, 1948-1955, 1958, 1960-1963, 1965, 1966, 1968-1978, 1980-1988, 1990, 1991, 2000-2002, 2008, 2011, 2014-2017, 2019-2026, 2028-2031, 2038, 2040, 2041, 2048-2051, 2053, 2058-2060, 2068-2070, 2072, 2078, 2080, 2081, 2088, 2089, 2387, 2733, 2849, 2850, 2898
Non-malignant	2100-2140, 2150, 2152-2157, 2159-2167, 2169, 2170, 2180, 2190, 2191, 2198-2200, 2210-2212, 2218-2224, 2228-2233, 2238-2246, 2249-2254, 2258-2260, 2270, 2271, 2273-2276, 2278-2281, 2290, 2298, 2299

Other	
Chronic lung disease	1173, 4900, 4910-4912, 4918-4920, 4930, 4931, 4939, 4940, 4950-4960, 5000, 5010, 5020, 5030, 5040, 5050, 5163
Diabetes	2500-2502, 2504-2507, 2510
Neurological and dementias	2900, 2901, 2904, 2908, 2909, 2940, 2941, 3030, 3078, 3220, 3222, 3229, 3234, 3235, 3238-3241, 3249, 3250, 3260, 3308, 3310-3314, 3317-3321, 3330-3342, 3344, 3348-3352, 3360-3363, 3368-3371, 3379, 3400, 3410, 3411, 3418-3421, 3429, 3430, 3432, 3434, 3438-3446, 3448-3455, 3457-3462, 3468-3470, 3480-3485, 3488-3490, 3492, 3498, 3499, 3501, 3502, 3508-3511, 3518-3520, 3522-3526, 3529-3536, 3538-3545, 3548-3559, 3561, 3563, 3564, 3568-3582, 3588-3596, 3598, 3599, 3886, 7428, 7805, 7807, 7840, 7860, 9958, 9970
Digestive	2111, 2113, 5200-5236, 5238-5246, 5248-5253, 5258-5265, 5268-5280, 5282-5286, 5288-5296, 5298-5317, 5319-5327, 5329-5337, 5339-5347, 5349-5351, 5353-5356, 5361, 5368, 5370, 5371, 5373, 5374, 5376, 5378, 5379, 5500, 5501, 5509-5513, 5518-5523, 5528-5533, 5538, 5539, 5550-5552, 5559, 5560, 5570, 5571, 5579, 5580, 5600-5603, 5608, 5620, 5621, 5640-5643, 5645-5651, 5660, 5670, 5672, 5678-5680, 5688-5696, 5698-5700, 5710-5716, 5718-5721, 5723, 5724, 5728, 5730, 5732-5734, 5738, 5739, 5759-5765, 5768-5772, 5778-5781, 5789-5794, 5798, 5799, 9974
Suicide and accidents	E000-E030, E800-E807, E810-E838, E840-E858, E860-E876, E878-E888, E890-E999
Other	Every other code

Appendix F. Standard daily drug doses for the treatment of respiratory tract infections

Drug	Standard daily doses (mg)[a]
Macrolide antibiotics	
Azithromycin	250 to 500
Clarithromycin	500 to 1,000
Erythromycin	500 to 2,000
Non-macrolide antibiotics	
Amoxicillin	750 to 1,750
Cefuroxime	500 to 1,000
Levofloxacin	500 to 750

[a]Prescriptions for any daily drug doses that are not standard for the treatment of respiratory tract infections were excluded from our two groups to ensure generalizability to usual prescribing.

Appendix G. Variables included in the propensity score

Variables Included in the Propensity Score	
Demographics	Age Sex Neighbourhood income quintile Index date Rural residence Long-term care Local Health Integration Network
Comorbidities	Dementia Schizophrenia or related psychotic disorder Bipolar disorder Unipolar depression and/or anxiety disorder Haemorrhagic stroke Ischemic stroke Transient ischemic attack Chronic liver disease Chronic kidney disease Congestive heart failure Coronary artery disease Angina Peripheral vascular disease Parkinson's disease Chronic lung disease Atrial fibrillation/flutter Cancer Alcoholism Seizure Acute kidney injury Acute myocardial infarction Pacemaker Hyperkalemia Hypotension Prostatic hyperplasia Prostatitis Acute urinary retention Deep vein thrombosis/Pulmonary embolism Charlson comorbidity index Johns Hopkins Aggregated Diagnosis Groups

Medications	Antiarrhythmic Antipsychotic Proton pump inhibitor Antiemetic Lithium Antilipemic Antihypertensive Potassium sparing diuretic Histamine H2-receptor antagonist Prokinetic QT-prolonging Antidiabetic Acetylsalicylic acid Anticoagulant (excludes warfarin) Antiplatelet Tricyclic antidepressant Opioid Antimalarian Antiviral Antineoplastic Benzodiazepine Non-steroidal anti-inflammatory drug (excludes acetylsalicylic acid) Anticonvulsant Angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker Beta-adrenergic antagonist Calcium channel blocker Non-potassium sparing diuretic Statin Antiparkinson drug Digoxin Overactive bladder medication Warfarin Inhaler - acetylcholine Inhaler - corticosteroid Inhaler - beta-agonist Smoking cessation aid
Health Care Use	Number of any hospitalizations Number of any emergency room visits General practice/Family practice visit Nephrology visit Cardiology visit

Investigations (a surrogate marker of health care access)	Carotid ultrasound Cardiac catheterization Coronary angiogram Echocardiography Electroencephalography Holter monitoring Cardiac stress test Coronary revascularization Electrocardiography Colorectal cancer screening Cervical cancer screening Prostate-specific antigen test Mammography Influenza vaccination Bone mineral density test Hearing test Cystoscopy Transurethral resection of the prostate Computed tomography of the head Computed tomography of other areas Chest x-ray Pulmonary function test At-home physician service Urinalysis Sputum
Other	Prescriber specialty Number of medications (polypharmacy) Baseline serum creatinine measurement

Appendix H. QT-prolonging drugs included in subgroup analysis

Drug Name	Drug Identification Numbers
Amiodarone hydrochloride	00705934, 02036282, 02239835, 02240071, 02240604, 02242472, 02243836, 02245781, 02246194, 02364336
Amitriptyline	00016306
Amitriptyline hydrochloride	00016322, 00016330, 00016349, 00037400, 00037419, 00037427, 00335053, 00335061, 00335088, 00377872, 00377880, 00377899
Amitriptyline hydrochloride & perphenazine	00140651, 00176931, 00176966
Amoxapine	00527084, 00527092, 00527106, 00527114, 02169886, 02169894, 02169908
Amprenavir	02243541, 02243542, 02243543
Aripiprazole	02322374, 02322382, 02322390, 02322404, 02322412, 02322455
Atazanavir	02248610, 02248611
Chloroquine	00021261
Chloroquine diphosphate	00033642, 01912984, 02017539
Chlorpromazine	00025151, 00025186, 01929968
Chlorpromazine hydrochloride	00025178, 00025453, 00025461, 00025488, 00025496, 00025518, 00232157, 00232807, 00232823, 00232831, 00580988, 01929909, 01929917, 01929925, 01929933, 01929941, 01929976, 01929992
Cisapride	00836311, 00836338, 00836354, 02054817
Cisapride monohydrate	09852913
Citalopram hydrobromide	02239607, 02239608, 02246056, 02246057, 02246594, 02246595, 02248010, 02248011, 02248050, 02248051, 02248170, 02248171, 02248944, 02251558, 02251566, 02252112, 02252120, 02275562, 02275570, 02285622, 02285630, 02293218, 02293226, 02301830, 02304686, 02304694, 02306239, 02306247, 02313405, 02313413, 02322781, 02322803, 02331950, 02331977, 02353660, 02353679, 02355256, 02355272, 02355280, 02371898, 02371901, 09852913
Clomipramine	02040751, 02040778, 02040786, 02130165, 02130173
Clomipramine hydrochloride	00324019, 00330566, 00402591, 02139340, 02139359, 02139367, 02230063, 02230064, 02230065, 02230256, 02244816, 02244817, 02244818
Darunavir	02284057, 02324016, 02324024, 02338432, 02393050
Desipramine hydrochloride	00010448, 00353868, 00353876, 00425265, 00776157, 01946242, 01946269, 01946277, 01948776, 01948784, 01948792, 01948806, 02024896, 02024918, 02024926, 02099128, 02099136, 02211947, 02211955, 02211963,

	02216248, 02216256, 02216264, 02216272, 02223325, 02223333, 02223368
Dextropropoxyphene hydrochloride	00151351
Dextropropoxyphene napsylate	00261432
Disopyramide	00382876, 00439363, 01989553, 01989561, 02224801, 02224828
Disopyramide phosphate	00396370, 00396389, 00584231, 00619760, 01989545, 02030799, 02030802, 02030810, 02224836
Dolasetron mesylate	02231378, 02231379
Domperidone	00642851, 00855820, 02157195
Domperidone maleate	01912070, 02103613, 02230473, 02231477, 02236466, 02268078, 02350440, 02369206, 02403870
Doxepin hydrochloride	00024325, 00024333, 00024341, 00326925, 00400750, 00584274, 00842745, 00842753, 00842761, 00842788, 00842796, 00842818, 01913441, 01913468, 01913476, 02049996, 02050005, 02050013, 02050021, 02050048, 02050056, 02140071, 02140098, 02140101, 02140128, 02144123, 02144131, 02144158
Escitalopram oxalate	02263238, 02263254
Flecainide acetate	00628220, 00817147, 01966197, 01966200, 02275538, 02275546
Fosamprenavir calcium	02261545
Hydroxychloroquine	02246691, 02252600
Hydroxychloroquine sulfate	00033669, 01928287, 02017709
Imipramine	00377902, 00377929
Imipramine hydrochloride	00010464, 00010472, 00010480, 00021504, 00021512, 00021520, 00312797, 00326852, 00360201, 00377910
Indinavir sulfate	02229161, 02229196
Lopinavir & ritonavir	02243643, 02243644, 02285533, 02312301
Maprotiline hydrochloride	00360481, 00360503, 00360511, 00641855, 02158604, 02158612, 02158620, 02158639
Mesoridazine besylate	00027448, 00027456, 00027464, 00027448, 00027456, 00027464
Methadone	09850619, 09851771, 09852891
Methadone hydrochloride	09857217, 09857218, 09857219, 09857220, 09857221, 09857223
Mexiletine	00599956, 00599964, 02231690, 02231692
Mexiletine hydrochloride	02230359, 02230360
Moxifloxacin hydrochloride	02242965
Nelfinavir mesylate	02238617, 02238618, 02248761
Ondansetron	02239372, 02239373

Ondansetron hydrochloride	02229639, 02258188, 02258196, 02264056, 02264064, 02274310, 02274329, 02278529, 02278537, 02288184, 02288192, 02291967, 02296349, 02296357, 02297868, 02297876, 02305259, 02305267, 02306212, 02306220, 02312247, 02312255, 02313685, 02313693, 02371731, 02371758, 02376091, 02376105, 02389983, 02389991
Ondansetron hydrochloride dihydrate	02344440, 02344459
Paroxetine	02262754, 02262762
Paroxetine hydrochloride	01940473, 01940481, 02027887, 02240907, 02240908, 02240909, 02247751, 02247752, 02247811, 02247812, 02248012, 02248013, 02248014, 02248451, 02248452, 02248557, 02248558, 02254751, 02254778, 02269430, 02269449, 02282860, 02368870, 02368889, 02383284, 02383292
Pimozide	00313815, 00313823, 00573817, 02245432, 02245433
Probucol	00749044
Procainamide hydrochloride	00029076, 00296031, 00353523, 00638676, 00638684, 00638692, 00639885, 00713325, 00713333, 00713341
Propafenone	02343053, 02343061
Propafenone hydrochloride	00603708, 00603716, 02243324, 02243325, 02243727, 02243728, 02245372, 02245373, 02294559, 02294575
Propoxyphene hydrochloride	00010081
Protriptyline hydrochloride	00322741
Quetiapine fumarate	02236951, 02236952, 02236953, 02240862, 02244107, 02284235, 02284243, 02284278, 02284286, 02296551, 02296578, 02296594, 02296608, 02299062, 02300184, 02300192, 02300206, 02300214, 02307804, 02307812, 02307839, 02307847, 02311704, 02311712, 02311747, 02311755, 02313901, 02313928, 02313936, 02313944, 02313995, 02314002, 02314010, 02314029, 02316080, 02316099, 02316110, 02316129, 02317893, 02317907, 02317931, 02321513, 02330415, 02330423, 02330458, 02330466, 02353164, 02353199, 02387794, 02387808, 02387824, 02390205, 02390213, 02390248, 02390256, 02395444, 02395452, 02395460, 02395479, 02395487, 02397102
Quinidine gluconate	00311731, 00704644
Quinidine polygalacturonate	00026131
Quinidine sulfate	00004782, 00021733, 00023868, 00026883, 00094412, 00249580, 00346837, 00441740, 01913883
Ritonavir	02229137, 02229145, 02241480, 02357593
Saquinavir mesylate	02216965, 02239083, 02279320
Sotalol	02229778, 02229779, 02229780, 02234013, 02257858

Sotalol hydrochloride	00483923, 00897272, 02084228, 02084236, 02163772, 02167794, 02170841, 02210428, 02230650, 02231181, 02231182, 02238326, 02238327, 02238415, 02270625, 02270633, 02368625
Thioridazine hydrochloride	00027359, 00027375, 00027529, 00027537, 00027545, 00027553, 00037478, 00037486, 00037494, 00037508, 00238775, 00360198, 00360228, 00360236, 00360244, 00456063, 00456071, 00456098, 00456101, 00575119, 00575127, 00575135, 00575143, 00775320, 02229553
Trimipramine	01940449, 01940457
Trimipramine maleate	00025828, 00025836, 00025844, 00025852, 00442437, 00740799, 00740802, 00740810, 00740829, 00761605, 00761613, 00761621, 00761648, 00761656, 01926284, 01926322, 01926330, 01926349, 01926357, 01940430, 02020602, 02020610, 02020629, 02070987
Ziprasidone hydrochloride	02298597, 02298600, 02298619, 02298627

Appendix I. 30-day cause of death in matched cohort of patients prescribed macrolide antibiotics (azithromycin, clarithromycin or erythromycin) compared to referent non-macrolide antibiotics (amoxicillin, cefuroxime or levofloxacin)[a]

Cause of death[b]	Macrolide (*n* = 503,612)	Non-Macrolide (*n* = 503,612)	Standardized Difference[c]
Cardiovascular[d]	638 (0.13)	755 (0.15)	1%
Infection[e]	96 (0.02)	100 (0.02)	0%
Cancer[f]	569 (0.11)	785 (0.16)	1%
Other[g]	429 (0.09)	551 (0.11)	1%

[a]Data are presented as the number (percentage) of patients.
[b]Cause of death was not available for 1,412 (0.3%) macrolide antibiotic users and 1,642 (0.3%) non-macrolide antibiotic users in the matched cohort.
[c]Standardized differences are less sensitive to sample size than traditional hypothesis tests. They provide a measure of the difference between groups divided by the pooled standard deviation; a value greater than 10% (0.1) is interpreted as a meaningful difference between the groups (71).
[d]Cardiovascular included death by ischemic heart disease, heart failure, cerebrovascular, arrhythmia and valvular heart disease.
[e]Infection type included abdominal, cardiac, kidney/genitourinary, neurological, respiratory and septicemia.
[f]Both malignant and non-malignant cancers were considered.
[g]Other causes of death included chronic lung disease, diabetes, neurological and dementias, digestive, suicide and accidents.

Appendix J. 14-day risk for hospital encounter with ventricular arrhythmia and all-cause mortality in matched cohort of patients prescribed macrolide antibiotics compared to referent non-macrolide antibiotics

Outcome	Events, *n* (%)		Relative Risk (95% CI)	*P* value
	Macrolide (*n* = 503,612)	Non-Macrolide (*n* = 503,612)		
Ventricular arrhythmia[a]	71 (0.01)	72 (0.01)	0.99 (0.71-1.37)	0.93
All-cause mortality	1,687 (0.34)	2,061 (0.41)	0.82 (0.77-0.87)	< 0.0001

Abbreviations: CI = confidence interval

[a]Based on hospital presentation (emergency room or hospitalization) assessed by hospital diagnosis codes. This method of assessment underestimated the true number of events as ventricular arrhythmias frequently go undetected in routine healthcare (because they often occur outside hospital settings, in unmonitored patients in hospital or in a setting of multi-organ medical illness where recorded codes describe other illnesses besides the ventricular arrhythmia).

Curriculum Vitae

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