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Cardiovascular Adverse Events in Patients Receiveing QT Interval Prolonging Medications

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CARDIOVASCULAR ADVERSE EVENTS IN PATIENTS RECEIVING QT INTERVAL PROLONGING MEDICATIONS

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ABSTRACT

Background

Drug-induced QT interval prolongation is associated with rare but life-threatening ventricular arrhythmia and sudden death. To study ventricular arrhythmia and sudden cardiac death associated with QT prolongation in large databases, an accurate operational definition of this outcome is needed. Frequently prescribed macrolide and fluoroquinolone antibiotics are associated with torsades de pointes arrhythmia and sudden death. Due to the dose-dependent nature of the risk, concomitant use of multiple QT-prolonging drugs may pose a greater threat than singular use. Several observational epidemiologic studies suggest that azithromycin may have an increased risk of ventricular arrhythmia and sudden cardiac death. Meanwhile, other observational studies observed a relatively similar cardiac toxicity profile with azithromycin, as compared with no antibiotic use or other antibiotics.

Objectives

The purpose of the first manuscript in this dissertation is to identify operational definitions of arrhythmias and sudden death associated with QT prolongation used in retrospective database studies and to compare validation results between algorithms. The second manuscript focuses on quantifying the risk of cardiac adverse events related to concurrent concomitant use of QT-prolonging antibiotics and other drugs with similar pro-arrhythmic potential, and the risk factors associated with such events in a national, privately insured population in the United States. The third manuscript

seeks to assess the risk of ventricular arrhythmia and sudden death for macrolide and fluoroquinolone antibiotics in a national, commercially insured population in the United States and to compare these results with previously published observational studies.

Methods

In the first manuscript, we conducted a systematic literature review using PubMed to identify retrospective studies published between January 1, 2000 and August 31, 2016. We identified and reviewed studies of ventricular arrhythmia or sudden death associated with QT prolongation in large administrative databases. Validation methods and results were also extracted where validation was conducted.

In the second manuscript, we performed a retrospective case-control study using an administrative health claims database from a large national insurer from 2011 to 2013. Cases of ventricular arrhythmia or sudden death due to QT prolongation were selected using a validated algorithm identified from the first manuscript. Four controls were matched to each case on age, sex, and region. Concomitant drug use was defined as overlapping durations of prescriptions of a QT-prolonging antibiotic and one other QT drug of interest. Odds ratios of risk factors and concomitant QT-prolonging medication use were calculated using conditional logistic regression.

In the third manuscript, a retrospective cohort study was conducted in the same administrative health claims database from a large national insurer from 2011 to 2013. The study cohort consisted of patients who filled an outpatient prescription for

macrolide and fluoroquinolone antibiotics, or amoxicillin. Amoxicillin episodes were 1-to-1 matched to macrolide and fluoroquinolone episodes on propensity scores. Inpatient admissions or emergency department visits with a primary diagnosis of ventricular arrhythmia were assessed within 10 days and 30 days of the prescription dispensing. Cox proportional hazard models were used to estimate the hazard ratio.

Findings

In the first manuscript, several algorithms for identifying QT prolongation in large databases have been developed and validated. We found a common algorithm for QT prolongation that was validated in Medicaid, Medicare, and the Italian National Health Service data. We also found a validated operational definition for sudden death in Medicaid data.

In the second manuscript, we found that concomitant and proximal use of QT-prolonging antibiotics with other QT medications predicted ventricular arrhythmia or sudden death.

In the third manuscript, azithromycin use and fluoroquinolone use was not associated with an increased cardiac risk compared with amoxicillin. Macrolide antibiotics, as a class, increased the risk of ventricular arrhythmia and sudden death in the 10 days following the prescription dispensing.

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PREFACE

Drug-induced QT interval prolongation is associated with rare but life-threatening ventricular arrhythmia and sudden death. Macrolide and fluoroquinolone antibiotics are considered to have a risk of QT prolongation despite conflicting results observed in retrospective studies. Meanwhile, the risk of concomitant use of multiple QT-prolonging medications remains largely unknown. The purpose of this dissertation is to quantify the risk of ventricular arrhythmia and sudden death associated with macrolide and fluoroquinolone antibiotics, when exposed alone and in combination with other risk factors.

Following the manuscript format, this dissertation consists of three manuscripts:

Manuscript I. Algorithms used to identify arrhythmias and sudden cardiac death associated with QT prolongation in retrospective studies: a systematic literature review

Manuscript II. Concomitant use of QT-prolonging medications and the risk of ventricular arrhythmia or sudden death

Manuscript III. Risk of drug-induced ventricular arrhythmia and sudden death with QT-prolonging antibiotics

TABLE OF CONTENTS

ABSTRACT ..... **ii**

ACKNOWLEDGEMENTS ..... **v**

PREFACE ..... **vi**

TABLE OF CONTENTS ..... **vii**

LIST OF FIGURES ..... **x**

LIST OF TABLES ..... **xi**

INTRODUCTION **1**

DRUG-INDUCED QT PROLONGATION 1

RESEARCH OBJECTIVES 4

REFERENCES 6

Manuscript I. Algorithms used to identify arrhythmias and sudden cardiac death associated with QT prolongation in retrospective studies: a systematic literature review **9**

ABSTRACT 10

BACKGROUND 11

METHODS 13

RESULTS 14

DISCUSSION 18

CONCLUSION 19

REFERENCES 20

Manuscript II. Concomitant use of QT-prolonging medications and the risk of ventricular arrhythmia and sudden death 33

ABSTRACT 34

BACKGROUND 36

METHODS 38

RESULTS 42

DISCUSSION 44

CONCLUSION 47

REFERENCES 48

Manuscript III. Risk of drug-induced ventricular arrhythmia and sudden death with QT-prolonging antibiotics 56

ABSTRACT 57

BACKGROUND 59

METHODS 61

RESULTS 66

DISCUSSION 70

CONCLUSION 76

REFERENCES 77

APPENDICES 88

Appendix A. Risk factors for ventricular arrhythmia or sudden death 88

Appendix B. Exclusion criteria for manuscript III 90

Appendix C. List of covariates for propensity score model 92

Appendix D. Distributions of propensity scores in matched study cohorts 94

Appendix E. Demographics and clinical characteristics of the matched cohorts..... 95

Appendix F. Sensitivity analysis 104

BIBLIOGRAPHY 106

LIST OF FIGURES

Figure Page

Figure 1.1 Flow chart of literature search and selection process 32

Figure 3.1 Study cohort selection process..... 83

Figure 3.2 Cumulative incidence of ventricular arrhythmia and sudden death with azithromycin and amoxicillin 84

Figure 3.3 Cumulative incidence of ventricular arrhythmia and sudden death with macrolides and amoxicillin..... 85

Figure 3.4 Cumulative incidence of ventricular arrhythmia and sudden death with fluoroquinolones and amoxicillin..... 86

Figure 3.5 Cumulative incidences of ventricular arrhythmia and sudden death with fluoroquinolones and amoxicillin in all diagnoses 87

LIST OF TABLES

Table Page

Table 1.1 Literature search strategy and number of searched studies..... 23

Table 1.2 Characteristics of Reviewed retrospective large database studies..... 25

Table 1.3 The most common ICD-9 diagnosis codes for ventricular arrhythmias related to QT prolongation 30

Table 1.4 The most common ICD-9 codes for sudden death related to QT prolongation 31

Table 2.1 Demographics and clinical characteristics of cases and controls 51

Table 2.2 Concomitant QT drug use and predictors of ventricular arrhythmia or sudden death 53

Table 2.3 Proximal QT drug use (±15 days) and predictors of ventricular arrhythmia or sudden death..... 54

Table 2.4 Number of QT-prolonging medications and predictors of ventricular arrhythmia or sudden death 55

Table 3.1 Demographics and clinical characteristics of the study population..... 81

INTRODUCTION

DRUG-INDUCED QT PROLONGATION

Drug-induced QT interval prolongation is associated with rare but life-threatening ventricular arrhythmia and sudden death. Retrospective pharmacoepidemiologic studies are often conducted to assess risks of adverse events of medications.[1,2] Based on such studies, QT prolongation has informed black box warnings and drug withdrawals.[3] In 2013, azithromycin received a black box warning for potential risk of QT prolongation and fatal cardiac arrhythmias based on the findings of a large retrospective pharmacoepidemiologic study.[4,5] In this era of big data, particularly for studies of rare outcomes, such as acute ventricular arrhythmia and sudden cardiac death associated with QT prolongation, an accurate operational definition of the outcome is needed. Physician review of an electrocardiogram is the gold standard for identifying QT prolongation, however it has limited use in retrospective database studies.[6] First, it is often not available in large claims-based databases. Secondly, studies which rely on medical charts are often under-powered to study a rare outcome within a small study population.[7] Lastly, electrocardiogram results are not able to capture arrhythmia and sudden death which occurred outside of the hospital setting.

Macrolide and fluoroquinolone antibiotics are among the most frequently prescribed drugs that are associated QT prolongation, which can lead to torsades de pointes arrhythmia and sudden death.[4,5,8-11] As dose-dependent risks have been identified from pharmacokinetic and pharmacodynamic research with QT-prolonging

medications, greater risk may exist with concomitant use of multiple QT-prolonging drugs.[12,13] Torsades de pointes is also associated with other risk factors such as older age, female sex, hypokalemia, history of heart diseases, and renal impairment.[14,15] Numerous QT-prolonging drugs are metabolized by the same group of cytochrome isoenzymes (mostly CYP3A4).[13,16] When exposed together, one drug will serve as the other's metabolic enzyme inhibitors and cause drug accumulation which further increases the risk of drug-induced QT prolongation, a concentration-related event. In addition, another mechanism for increased risk would be the medications serving as each other's synergist or antagonist.[13,17] Some macrolides and fluoroquinolones are also known to have pharmacokinetic drug-drug interactions.[18] Clarithromycin, erythromycin, and ciprofloxacin are all strong inhibitors of cytochrome P450 isoenzymes.[13]

All macrolide antibiotics are considered to have QT-prolonging potential. Azithromycin is not a CYP3A4 inhibitor, and was therefore considered to be safer than the rest of its class. However, several recent observational epidemiologic studies suggest that azithromycin may have an increased risk of ventricular arrhythmia and sudden cardiac death afterall.[4,19,20] One retrospective cohort study published in 2012 reported a higher risk of cardiovascular death associated with azithromycin compared with no antibiotic use in a Medicaid population.[4] One year later, the United States Food and Drug Administration (FDA) issued a warning to urge healthcare professionals to consider potential cardiovascular risks when prescribing azithromycin.[5] Subsequent observational studies among Veterans Affairs patients and

in the general population of Taiwan reported similar increased risks of serious arrhythmia, cardiovascular death, and all-cause mortality with azithromycin.[19,20]

Alternatively, several observational studies reported a safer cardiac toxicity profile with azithromycin, as compared with no antibiotic use or other antibiotics [21-23] In the Danish adult population, azithromycin use was not associated with an increased risk of cardiovascular death compared to either no antibiotic use or penicillin-V.[22] Another study among the general population of Ontario, Canada found that macrolide antibiotic use was not associated with a higher risk of ventricular arrhythmia compared with non-macrolide antibiotics.[21]

RESEARCH OBJECTIVES

A number of pharmacoepidemiologic drug safety studies have sought to quantify the risk of drug-induced ventricular arrhythmia and sudden death. The algorithms identifying ventricular arrhythmia and sudden cardiac death associated with QT prolongation have varied between studies.[19,20,24-26] Identifying a validated algorithm is needed in order to have an accurate definition of this outcome and for comparability between studies. Interactions among QT-prolonging agents are well-studied in the field of pharmacokinetics and pharmacodynamics but are less well-studied in the field of pharmacoepidemiology. Concomitant use of multiple QT-prolonging drugs may pose a greater threat than singular use. Conflicting cardiac safety profiles for QT-prolonging antibiotics, including azithromycin, have been observed in different populations worldwide. These populations varied in age, social economic status, and disease burden.

Based on these unanswered questions, this dissertation has three objectives related to drug-induced QT interval prolongation, namely:

1. To identify the operational definitions of arrhythmias and sudden death associated with QT prolongation used in retrospective database studies and compare validation results between algorithms.

2. To quantify the risk of cardiac adverse events related to concomitant use of QT-prolonging antibiotics and other drugs with similar pro-arrhythmic potential, and other risk factors associated with such events in a national, privately-insured population in the United States.

3. To assess the risk of ventricular arrhythmia and sudden death associated with macrolide and fluoroquinolone antibiotics in a national, commercially insured population in the United States and compare these results with previously published observational studies.

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Manuscript I. Algorithms used to identify arrhythmias and sudden cardiac death associated with QT prolongation in retrospective studies: a systematic literature review

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ABSTRACT

Drug-induced QT prolongation can lead to ventricular arrhythmia and sudden cardiac death. As ventricular arrhythmia and sudden cardiac death are rare events, large administrative databases can be used to inform pharmacoepidemiologic drug safety studies. In order to compare event rates between studies, validated operational definitions of these events are needed. We conducted a systematic literature review in PubMed to identify diagnosis code algorithms for arrhythmias and sudden cardiac death. Twenty-two studies were included in the review. For arrhythmias, a common operational definition was identified in 23% of the reviewed studies (n=5), with an average positive predictive value (PPV) of 85% from hospital stays and emergency visits. For sudden cardiac death, codes for cause of death was used in 14% of studies (n=3), with an average PPV of 88%. Further validation of a common International Classification of Diseases, 10th Edition (ICD-10) algorithm is needed for each event. In conclusion, researchers should utilize a common, validated algorithm, such as the one identified in our review to operationally define these events to ensure comparability between new research and the existing literature.

BACKGROUND

Unexpected sudden death is rare, with an estimated incidence ranging from 50 to 100 per 100,000 individuals per year in Europe and North America.[1,2] Acute ventricular arrhythmia may account for over 80% of sudden cardiac deaths.[3] Retrospective pharmacoepidemiologic studies are used to assess risks attributed to drug exposures.[4,5] Based on such studies, QT prolongation has informed black box warnings and drug withdrawals.[6] Terfenadine and cisapride were withdrawn in the United States (US) in 1998 and 2000 respectively, due to their association with QT prolongation and ventricular arrhythmia.[7,8] More recently, in 2013, azithromycin received a black box warning for potential risk of QT prolongation and fatal cardiac arrhythmias based on the findings of a large retrospective pharmacoepidemiologic study.[9,10]

In this era of big data, particularly for studies of rare outcomes, such as acute ventricular arrhythmia and sudden death associated with QT prolongation, an accurate operational definition of the outcome is needed. Physician review of an electrocardiogram (ECG) is the gold standard for identifying QT prolongation, however it has limited use in retrospective database studies.[11] First, ECG results are often not available in large databases. Further, a study identifying events by manual medical record review of ECGs and physician notes would likely be under-powered to quantify the exposure-outcome relationship. Lastly, ECG results for acute ventricular arrhythmia and sudden death which occurred outside of the hospital will not be available, and would result in underestimation of these events.

A number of retrospective pharmacoepidemiologic drug safety studies have sought to quantify the association between these rare outcomes and different medication exposures, however the algorithms identifying ventricular arrhythmia and sudden death associated with QT prolongation have varied between studies.[12-16] Further the performance of these varying algorithms has not been compared. The objective of this systematic literature review was to identify the operational definitions of arrhythmias and sudden death associated with QT prolongation used in retrospective database studies and compare validation results between algorithms.

METHODS

A systematic literature review in the PubMed electronic databases was conducted to identify retrospective studies from peer-reviewed journals. A pre-determined search strategy developed by Mini-Sentinel researchers (Table 1.1) was used to select qualifying studies published between January 1, 2000 and August 31, 2016.[17] This literature review was limited to studies in humans and published in English. Other inclusion criteria were: retrospective studies in large administrative databases; studies that identified ventricular arrhythmia and sudden death associated with QT prolongation; studies that only defined QT prolongation with ECG. Titles and abstracts of studies identified by the search were screened against the inclusion criteria. Qualifying or uncertain studies from title and abstract review underwent further full-text review for selection. References of selected studies were also examined for inclusion. Data extracted included operational definitions and administrative codes used for identifying ventricular arrhythmia and sudden death associated with QT prolongation. Other aspects of study design including publication year, study setting and population, and sample size, were also collected. Validation methods and results were also extracted where validation was conducted.

RESULTS

The search strategy identified 1,237 studies. After title and abstract review, 57 studies were selected for full-text review, after which, 22 (38.6%) studies were selected for inclusion. The literature search, review, and selection process was demonstrated in Figure 1.1 with results of each step in Table 1.1.

The characteristic of included studies is showed in Table 1.2. Half of the included studies were published after 2012, which was the year a previous literature review of validated methods for identifying ventricular arrhythmia was published.[17] Approximately half of the studies (n=12, 55%) were conducted in US populations, using Medicare or Medicaid data (n=9, 41%),[8,9,12,13,18-22] commercial health plan data (n=2, 9%),[7,16] or Veterans Health Administration data (n=1, 4.5%).[15] The remaining studies (n=10, 45%) were conducted in: European databases (n=5, 23%) from the Netherlands,[23] France,[24] Italy,[25] Denmark,[26,27] and Sweden[27]; the Taiwanese National Health Insurance Research Database (n=3, 14%)[14,28,29]; and Canadian provincial databases (n=2, 9%).[30,31] International Classification of Diseases, Ninth Revision (ICD-9) codes were used to identify cardiac arrhythmias and/or sudden cardiac deaths in 17 studies (77%),[7-9,12,13,15,16,18-23,25,28,29,31] while 4 studies (18%) used International Classification of Diseases, Tenth Revision (ICD-10) codes,[24,26,27,30] and 1 study (4.5%) used both ICD-9 and ICD-10 codes. All studies used diagnosis codes for event definitions and no procedure codes were used. [14]

ICD-9 diagnosis codes for arrhythmias were used in 15 out of 22 studies (68%). Shared by 5 studies,[8,13,19,20,25] the most common algorithm (Table 1.3) used

hospital stays and ED visits for ventricular arrhythmia to identify QT prolongation. Validation was conducted in three of these studies by review of the medical record. When limited to principle diagnosis, this algorithm had a positive predictive value (PPV) of 80% and 94% for hospitalization diagnosis and ED diagnosis respectively in Medicaid and Medicare data and the overall PPV was 85%.[13] Other validation studies in a Medicaid and Medicare combined population and in an Italian population showed a PPV of 85% and 73%, respectively.[13,25] One variation of the algorithm (excluded ICD-9 code 798) was used by one of the Taiwanese studies and a Medicaid/HealthCore study but neither study evaluated the validation of the algorithm.[22,28] Another variation (only included ICD-9 codes 427.1, 427.4, and 427.5) of this algorithm in a study using Medicare data demonstrated a PPV of 93%, as validated by medical record review.[18]

The next most common algorithm for arrhythmias was utilized in two studies, one from the Netherlands and the other from Canada.[23,31] The algorithm identified QT prolongation from hospital stays with primary diagnoses of arrhythmias. Only the Dutch study validated the algorithm, where a review of medical records was used to verify the ICD-9 codes used for ventricular arrhythmia and cardiac arrest (PPV 82%) and ICD-9 codes for unspecified cardiac arrhythmias (PPV 10%).[23] The five other studies each used a different algorithm to identify potential QT prolongation. The Harvard community health plan study used select ICD-9 subcodes under 426, 427, 429, 780, and 785 from hospital stays and ED visits, with a low PPV of 4%.[16] The United Healthcare study included office visits and inpatient stays with diagnoses of arrhythmic events (ICD-9 codes 426.x, 427.x) but this approach also had low a PPV of

10% based on a review of medical records.[7] Three other algorithms were used in two of the Taiwanese studies and the Veterans Health Administration study and none of these studies validated their operational definition.[14,15,29]

ICD-10 diagnosis codes for acute ventricular arrhythmia were used in 3 studies (13.6%). A French study,[24] a Denmark-Sweden bi-national study,[27] and one of the Canadian studies[30] each used a different algorithm for identifying QT prolongation in hospital stays or ED visits. The Canadian study used ICD-10 codes I47.2 and I49.0 and a manual chart review was conducted in 202 charts resulting in a PPV of 92%.[30] The French study used ICD-10 codes I46.1, I47.2, and I49.0 from hospital discharge summaries. In comparison with ECG records, this algorithm had a PPV of 60%.[24] The bi-national study used ICD-10 codes I47.2, I49.0, I49.3, I46.0, I46.1, I46.9, R96.0, and R96.1 and no validation was conducted.[27]

Besides arrhythmias, sudden death has also been used to identify QT prolongation in large retrospective databases, with both ICD-9 and ICD-10 codes. ICD-9 codes for sudden death were used in 4 of the 22 (18.2%) reviewed studies. An algorithm used in the Tennessee Medicaid study to identify sudden death associated QT prolongation was also used in 2 other studies (Table 1.4).[12] This algorithm excluded deaths with terminal institutional stays or terminal procedures inconsistent with unresuscitated cardiac arrest. A series of ICD-9 codes for causes of death were used to define plausible sudden cardiac death. This algorithm was validated by medical record review in a general Medicaid population and in opioid users, and the PPV of this algorithm was 87% and 88%, respectively.[12,21] Another algorithm used by

one of the Taiwanese studies defined the study outcome as unspecific cardiovascular death (ICD-9 codes 401-449) and this algorithm was not validated.[14]

The Danish study and one of the Taiwanese studies identified death from cardiovascular causes using ICD-10 codes (n=2, 9.1%).[14,26] Codes used in the Danish study were I00-I99 (diseases of the circulatory system) and R96.x (other sudden death, cause unknown).[26] Codes used in the Taiwanese study were I10-I79 (hypertensive diseases, ischemic heart diseases, pulmonary heart disease and diseases of pulmonary circulation, other forms of heart disease, and cerebrovascular diseases).[14] Neither study performed validation of their algorithms.

DISCUSSION

We identified common, validated operational definitions for identifying arrhythmias and sudden death associated with QT prolongation in large retrospective database studies. The most common algorithm for ventricular arrhythmia (Table 1.3) and sudden death (Table 1.4) had an average PPV of 85% and 88%, respectively. These two algorithms were validated in various patient populations, including Medicaid and Medicare, administrative claims databases, and several European and Canadian databases. For ICD-9 arrhythmias algorithms, the PPV was highest when the limited to principle diagnoses and addition less specific subcodes decreases the PPV.[7,8] Though one ICD-10 algorithm for arrhythmias was found to have a high PPV, this algorithm has not been used or validated in another database.[30] The sole ICD-9 sudden death algorithms had a high PPV for identifying QT prolongation among patients with a low risk of sudden cardiac death.[12]

Our study has a few limitations. Firstly, the literature search terms might miss some other studies that also identified QT prolongation in retrospective databases. We attempted to address this limitation by examining the references of reviewed studies for additional studies and found no additional eligible studies in the references. Secondly, the true incidence of QT prolongation is unknown as QT prolongations can occur without noticeable symptoms.[32,33] As such, validation studies could only calculate the PPV but not sensitivity or specificity. However, as a PPV is the proportion of true positive in tested positive, validated algorithms with high PPV may accurately identify cases captured in large retrospective databases.

CONCLUSION

A common, validated algorithm for QT prolongation related arrhythmias was identified and validated in Medicaid, Medicare, and the Italian National Health Service data, as was a validated operational definition for sudden death in Medicaid data. Consistency between studies is necessary for establishing causal relationships between medications and rare adverse events, such as prolonged QT associated arrhythmias and sudden cardiac death. As such, to ensure comparability between new research and the existing literature, researchers should utilize a common, validated algorithm, such as the one identified in our review, to operationally define these events.

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Table 1.1 Literature search strategy and number of searched studies

	Search terms Limits: Humans; English; publication date between 2000/01/01 to 2016/08/31	Number of results
#1	"Pharmaceutical preparations/adverse effects"[Mesh] OR "Pharmaceutical preparations/contraindications"[Mesh] OR "Pharmaceutical preparations/poisoning"[Mesh] OR "Pharmaceutical preparations/therapeutic use"[Mesh] OR "Pharmaceutical preparations/toxicity"[Mesh] OR "Pharmaceutical preparations/therapy"[Mesh] OR "Pharmaceutical preparations/analysis"[Mesh] OR "Chemical actions and uses/adverse effects"[Mesh] OR "Chemical actions and uses/contraindications"[Mesh] OR "Chemical actions and uses/poisoning"[Mesh] OR "Chemical actions and uses/therapeutic use"[Mesh] OR "Chemical actions and uses/toxicity"[Mesh] OR "Chemical actions and uses/therapy"[Mesh] OR "Chemical actions and uses/analysis"[Mesh] OR "Chemical actions and uses/epidemiology"[Mesh] OR "Drug toxicity"[Mesh] OR "Diseases Category/chemically induced"[Mesh] OR "Diseases Category/drug therapy"[Mesh] OR "Diseases Category/epidemiology"[Mesh] OR "Validation Studies"[pt] OR "Validation Studies as Topic"[Mesh] OR "Sensitivity and Specificity"[Mesh] OR "Predictive Value of Tests"[Mesh] OR "Reproducibility of Results"[Mesh] OR “Predictive Value”[tw]	2,359,927
#2	"Premier"[All] OR "Solucient"[All] OR "Cerner"[All] OR "Ingenix"[All] OR "LabRx"[All] OR "IHCIS"[All] OR "marketscan"[All] OR "market scan"[All] OR "Medstat"[All] OR "Thomson"[All] OR "pharmetrics"[All] OR "healthcore"[All] OR "united healthcare"[All] OR "UnitedHealthcare"[All] OR "UHC"[All] OR "GPRD"[All] OR "general practice research database"[All] OR "Research Database"[All] OR "Group Health"[All] OR "HCUP"[All] OR ("Healthcare Cost"[All] AND "Utilization Project"[All]) OR ("Health Care Cost"[All] AND "Utilization Project"[All]) OR "MEPS"[All] OR "Medical Expenditure Panel Survey"[All] OR "NAMCS"[All] OR "National Hospital Ambulatory Medical Care Survey"[All] OR "National Ambulatory Medical Care Survey"[All] OR "NHIS"[All] OR "National Health Interview Survey"[All] OR "Kaiser"[All] OR "HMO Research"[All] OR "Health Maintenance Organization"[All] OR "HMO"[All] OR "Cleveland Clinic"[All] OR "Lovelace"[All] OR "Department of Defense"[All] OR "Henry Ford"[All] OR ("Denmark"[All] AND "Epidemiology"[All]) OR "i3 Drug Safety"[All] OR "i3"[All] OR "Aetna"[All] OR "Humana"[All] OR "Wellpoint"[All] OR "IMS"[All] OR "Intercontinental Marketing Services"[All] OR "IMS Health"[All] OR "Geisinger"[All] OR "GE Healthcare"[All] OR "MQIC"[All] OR "PHARMO"[All] OR "Institute for Drug Outcome Research"[All] OR "Pilgrim"[All] OR "Puget Sound"[All] OR "Regenstrief"[All] OR "Saskatchewan"[All] OR "Tayside"[All] OR "MEMO"[All] OR "Medicines Monitoring Unit"[All] OR "Veterans Affairs"[All] OR "Partners Healthcare"[All] OR "Mayo Clinic"[All] OR "Rochester Epidemiology"[All] OR "Indiana	521,010

	Health Information Exchange"[All] OR "Indiana Health"[All] OR "Intermountain"[All] OR "THIN"[All] OR “The health improvement network"[All] OR "blue cross"[All] OR "health partners"[All] OR "health plan"[All] OR "health services"[All] OR "Nationwide Inpatient Sample"[All] OR "National Inpatient Sample"[All] OR "medicaid"[All] OR "medicare"[All] OR "MediPlus"[All] OR "Outcome Assessment"[All] OR "insurance database"[All] OR "insurance databases"[All] OR "Data Warehouse"[All] OR "ICD-9"[All] OR “international statistical classification"[All] OR “international classification of diseases"[All] OR "ICD-10"[All] OR "Database Management Systems"[Mesh] OR "Medical Records Systems, Computerized"[Mesh] OR "CPT"[All] OR "Current procedural terminology"[All] OR "drug surveillance"[All] OR (“claims”[tw] AND “administrative”[tw]) OR (“data”[tw] AND “administrative”[tw]) OR "Databases, Factual"[Mesh] OR "Databases as topic"[Mesh] OR "Medical Record Linkage"[Mesh] OR "ICD-9-CM"[All Fields] OR "ICD-10-CM"[All Fields]	
#3	"Clinical Trial"[pt] OR "Editorial"[pt] OR "Letter"[pt] OR "Meta-Analysis"[pt] OR "Randomized Controlled Trial"[pt] OR "Clinical Trial, Phase I"[pt] OR "Clinical Trial, Phase II"[pt] OR "Clinical Trial, Phase III"[pt] OR "Clinical Trial, Phase IV"[pt] OR "Comment"[pt] OR "Controlled Clinical Trial"[pt] OR "case reports"[pt] OR "Clinical Trials as Topic"[Mesh] OR "double-blind"[All] OR "placebo-controlled"[All] OR "pilot study"[All] OR "pilot projects"[Mesh] OR "Review"[pt] OR "Prospective Studies"[Mesh]	2,995,791
#4	"Arrhythmias, Cardiac"[Mesh:NoExp] OR "Brugada Syndrome"[Mesh:NoExp] OR "Cardiac Complexes, Premature"[Mesh] OR "CommotioCordis"[Mesh:NoExp] OR "Heart Block"[Mesh] OR "Long QT Syndrome"[Mesh] OR "Parasystole"[Mesh] OR "Pre-Excitation Syndromes"[Mesh] OR "Tachycardia"[Mesh] OR "Ventricular Fibrillation"[Mesh] OR "Ventricular Flutter"[Mesh] OR "Death, Sudden, Cardiac"[Mesh] OR "Torsades de Pointes"[Mesh] OR "Heart Arrest"[Mesh] OR "Tachycardia, Supraventricular"[Mesh]	55,302
#5	Search #1 AND #2	182,942
#6	Search #5NOT OTHERWISE SPECIFIED #3	120,606
#7	Search #6 AND #4	1,237

Table 1.2 Characteristics of reviewed retrospective large database studies

	First author	Publish year	Population and setting	Design and sample size	Administrative codes for outcome definition	Code version	Validation method and result
1	Hanrahan	1995	US, Harvard Community Health Plan, 1988-1990	Cohort study, n=26,320	Hospitalization and ED visit with the following diagnosis: ICD-9 codes 426.0-426.5 (except 426.2), 427.1, 427.4-427.6, 427.9, 429.2, 429.9, 780.2-780.4, 785.0, 785.1, 785.5	ICD-9	Diagnosis codes identified 1,749 events in 1,290 patients. Medical records review confirmed 70 events in 61 patients, PPV=4% (70/1749)
2	Enger	2002	US, United Healthcare, 1993-1998	Case-control study, n=28,078	Office visit and inpatient stay with diagnosis of arrhythmias: ICD-9 codes 426.x, 427.x	ICD-9	Medical records reviewed for patients identified in both claims and NDI data. Claims PPV=10% (14/146)
3	McDonald	2002	US, Medicare, 1985-1995	Descriptive study, n=4,073	Hospitalization with primary discharge diagnosis of ventricular tachycardia and cardiac arrest: ICD-9 codes 427.1, 427.4, 427.5	ICD-9	Linked to Seattle-area Myocardial Infarction and Triage Intervention registry for validation, PPV=77%, NPV=94%; Chart review in 30 Kaiser Permanente hospitals, PPV=93%
4	De Bruin	2005	The Netherlands, PHARMO database, 1999-2000	Validation study, n=111	Hospitalization with primary discharge diagnosis of ventricular arrhythmias and cardiac arrest: ICD-9 codes 427.1, 472.4, 427.41, 427.42, 427.5, 427.69 or unspecified cardiac arrhythmias: ICD-9 codes 427.2, 427.60, 427.8, 427.89, 427.9	ICD-9	Medical records review. Ventricular arrhythmias and cardiac arrest codes, PPV=82% (50/61). Unspecified cardiac arrhythmias codes, PPV=10% (5/50). Overall PPV=50% (55/111)

5	Hennessy	2008	US, Medicaid, 1999-2000	Nested case–control study, n=145	Hospitalization with principle or non-principal discharge diagnosis of: ICD-9 codes 427.1, 427.4, 427.41, 427.42, 427.5, 798, 798.1, 798.2	ICD-9	Hospital medical records review of a random sample of 126 events identified with codes, PPV = 94% (118/126). If limited to principle diagnoses, then PPV=100% (7/7).
6	Molokhia	2008	France, Midi-Pyrenees hospital record, 1999-2004	Descriptive study, n=861	Hospital discharge summaries with diagnosis of ventricular fibrillation, and sudden cardiac death: ICD-10 codes I47.2, I49.0, I46.1	ICD-10	ECG records used to identify non-fatal drug-induced QT prolongation, confirmed 24 events in 40 diagnoses, PPV=60%
7	Zambon	2009	Italy, National Health Service Database, 1998-2003	Case-control study, n=1,275	Hospitalization with the primary diagnoses of selected cardiovascular conditions: ICD-9 codes 427.1, 427.4, 427.41, 427.42, 427.5, 798, 798.1, 798.2	ICD-9	Previous validated with medical record review in a different study, PPV=73% (8/11)
8	Chung	2010	US, Medicaid, 1990-1993	Validation study, n=926	Sudden cardiac while having no evidence of a terminal institutional stay or no terminal procedures inconsistent with unresuscitated cardiac arrest, ICD-9 codes 401.9, 402.9, 410, 411, 414.0, 414.8, 414.9, 425.4, 427.1, 427.4, 427.5, 427.9, 429.2, 429.9, 440.9, 798.9	ICD-9	A validation sample was collected for 1994-2005, within a 100-mile radius of Nashville and the same criteria mentioned before applied too. PPV=87% (151/174)
9	Hennessy	2010	US, Medicaid and Medicare, 1999–2002	Validation study, n=5,239	Hospitalization or ED visit with a principal diagnosis of sudden cardiac death or ventricular arrhythmia: ICD-9 codes 427.1, 427.4, 427.41,	ICD-9	Medical record review. Hospitalization diagnosis, PPV=79.7%; ED diagnosis, PPV=93.6%; overall,

					427.42, 427.5, 798, 798.1, 798.2		PPV=85.3%
10	Johannes	2010	Canada, Saskatchewan Health, 1990-2005	Nested Case-control study, n=83,212	Hospitalization with primary discharge diagnosis of ventricular arrhythmias and cardiac arrest: ICD-9 codes 427.1, 472.4, 427.41, 427.42, 427.5, 427.69 or unspecified cardiac arrhythmias: ICD-9 codes 427.2, 427.60, 427.8, 427.89, 427.9	ICD-9	No validation study conducted
11	Leonard	2011	US, Medicaid, 1999–2003	Cohort study, n=4,222	Inpatient stay and ED visit with primary discharge diagnosis of: ICD-9: 427.1, 427.4, 427.41, 427.42, 427.5, 798, 798.1, 798.2	ICD-9	No validation study conducted
12	Kawai	2012	US, Medicaid, 1992-2007	Validation study, n=453,836	Sudden cardiac death in a community setting while having no evidence of a terminal institutional stay or no terminal procedures inconsistent with unresuscitated cardiac arrest, ICD-10 codes 401.9, 402.9, 410, 411, 414.0, 414.8, 414.9, 425.4, 427.1, 427.4, 427.5, 427.9, 429.2, 429.9, 440.9, 798.9	ICD-9	Medical records review. The computerized case definition was validated in a group of opioid users, PPV =88% (71/81)
13	Ray	2012	US, Medicaid, 1992-2006	Cohort study, n=347,795	Sudden cardiac while having no evidence of a terminal institutional stay or no terminal procedures inconsistent with unresuscitated cardiac arrest, ICD-10 codes 401.9, 402.9, 410, 411, 414.0, 414.8, 414.9, 425.4, 427.1, 427.4, 427.5, 427.9, 429.2, 429.9,	ICD-9	No validation study conducted

					440.9, 798.9		
14	Schelleman	2012	US, Medicaid, 1999-2003; HealthCore Database, 2001-2006	Cohort study, n=219,954	Hospitalization or ED visit with a principal diagnosis of sudden cardiac death or ventricular arrhythmia: ICD-9 codes 427.1, 427.4, 427.41, 427.42, 427.5, 798.1, 798.2	ICD-9	No validation study conducted
15	Leonard	2013	US, Medicaid, 1999–2003	Cohort study, n=747	Hospitalization or ED visit with a principal diagnosis of sudden cardiac death or ventricular arrhythmia: ICD-9 codes 427.1, 427.4, 427.41, 427.42, 427.5, 798, 798.1, 798.2	ICD-9	No validation study conducted
16	Svanstrom	2013	Denmark and Danish, Civil Registration System, 1997-2010	Cohort study, n=1,102,419	Death from cardiovascular causes: ICD-10 codes I00-99, R96.0, R96.1	ICD-10	No validation study conducted.
17	Rao	2014	US, VHA Database, 1999-2012	Cohort study, n=594,792	Inpatient and ED encounter for serious cardiac arrhythmias: ICD-9 codes 426.82, 427.0, 427.1, 427.2, 427.41, 427.42, 427.5	ICD-9	No validation study conducted
18	Chen	2015	Taiwan, NHIRD, 2000-2011	Case-crossover study, n= 25,356	Hospitalization or ED visit with a principal diagnosis of cardiac arrhythmias: ICD-9 codes 427.x, 798.x	ICD-9	No validation study conducted
19	Chou	2015	Taiwan, NHIRD,	Cohort study, n=10,684,100	Inpatient or outpatient (including ED visit) diagnosis of severe	ICD-9 and	No validation study conducted

			2001-2011		ventricular arrhythmia (primary outcome): ICD-9 codes 427.1, 427.4, 427.5, 798.1, 798.2, 798.9, V12.53 Cardiovascular death (secondary outcome) ICD-9 codes 401–449 ICD-10 codes I10–I79	ICD-10	
20	Wu	2015	Taiwan, NHIRD, 2000-2009	Case-crossover study, n= 17,718	Hospitalization or ED visit with a principal diagnosis of sudden cardiac death or ventricular arrhythmia: ICD-9 codes 427.1, 427.4, 427.41, 427.42, 427.5, 798.1, 798.2	ICD-9	No validation study conducted
21	Inghammar	2016	Denmark and Sweden, National healthcare registry, Denmark: 1997-2011; Sweden: 2006-2013	Cohort study, n=2,124,632	Hospital inpatient admission or ED visit with a diagnosis of serious arrhythmias: ICD-10 codes I47.2, I49.0, I49.3, I46.0, I46.1, I46.9, R96.0, R96.1	ICD-10	No validation study conducted
22	Trac	2016	Canada, Ontario Health Insurance Plan, 2002-2013	Cohort study, n= 1,321,671	Hospital admission or ED visit a diagnosis of ventricular arrhythmias: ICD-10 codes I47.2, I49.0	ICD-10	Manual review of 202 medical records identified with the codes, PPV=92%

ED = Emergency Department; ICD = International Classification of Diseases; NDI = National Death Index; NHIRD = National Health Insurance Research Database; NPV = Negative Predictive Value; PPV = Positive Predictive Value; US = United States; VHA = Veterans Health Administration

Table 1.3 The most common ICD-9 diagnosis codes for ventricular arrhythmias related to QT prolongation

ICD-9 code*	Code description
427.1	Paroxysmal ventricular tachycardia
427.4	Ventricular fibrillation and flutter
427.41	Ventricular fibrillation
427.42	Ventricular flutter
427.5	Cardiac arrest
427.9	Cardiac dysrhythmia, not otherwise specified
798+	Sudden death, cause unknown
798.1	Instantaneous death
798.2	Death occurring in less than 24 hours from onset of symptoms, not otherwise explained

ED = Emergency Department; ICD = International Classification of Diseases

* Algorithm used by 5 reviewed studies[8,13,19,20,25]
+ A more specific algorithm (without the general code 798) was used in 2 other studies[22,28]

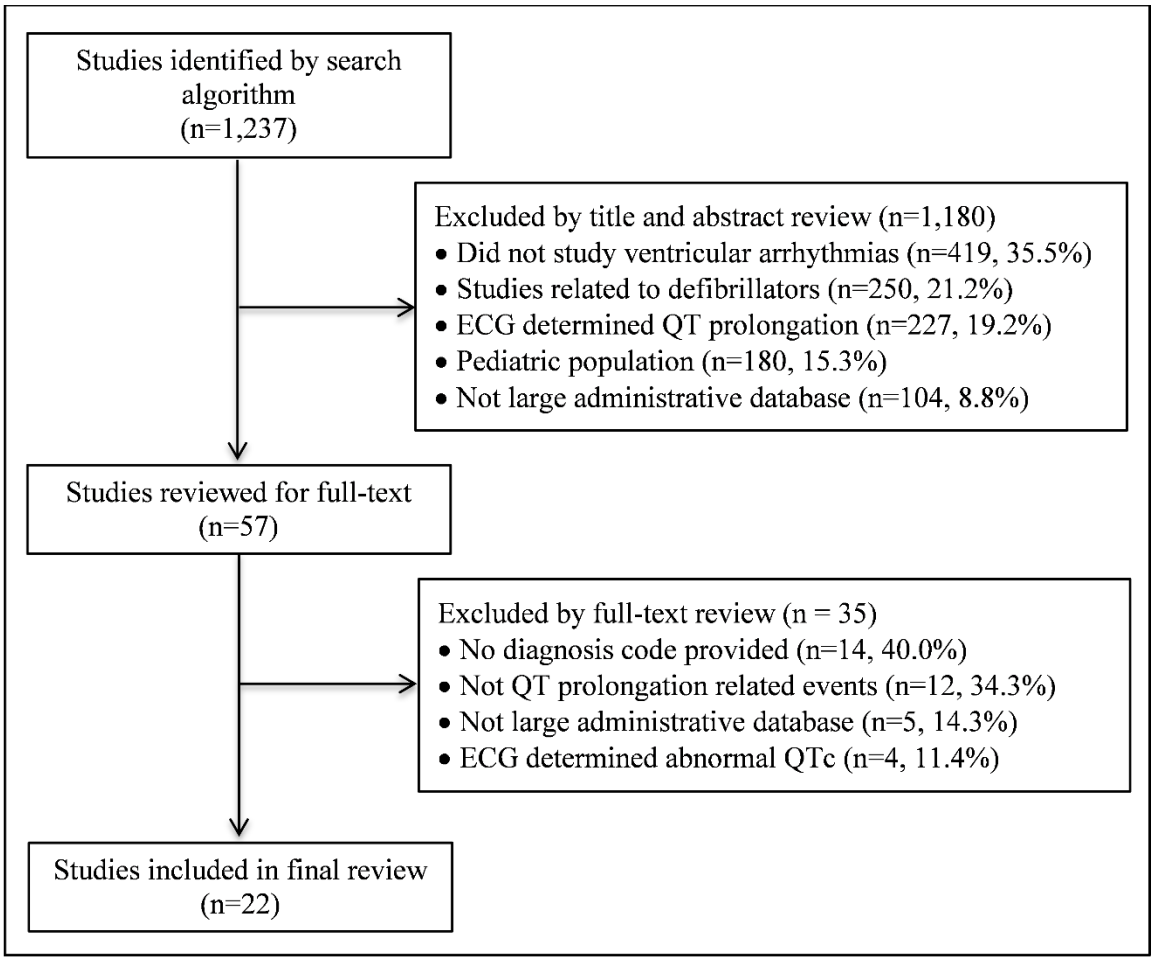
Table 1.4 The most common ICD-9 codes for sudden death related to QT prolongation

ICD-9 code*	Code description
401.9	Essential hypertension, not otherwise specified
402.9	Hypertensive heart disease, not otherwise specified
410	Myocardial infarction
411	Other acute/subacute ischemic heart disease
414.0	Coronary atherosclerosis
414.8	Chronic ischemic heart disease, other
414.9	Chronic ischemic heart disease, unspecified
425.4	Primary cardiomyopathy, not otherwise specified
427.1	Paroxysmal ventricular tachycardia
427.4	Ventricular fibrillation and flutter
427.5	Cardiac arrest
427.9	Cardiac dysrhythmia, not otherwise specified
429.2	Cardiovascular arteriosclerosis
429.9	Cardiovascular disease, not otherwise specified
440.9	Atherosclerosis, generalized and unspecified
798.9	Unattended death

ICD = International Classification of Diseases

* Algorithm used by 3 reviewed studies[9,12,21]

Figure1.1 Flow chart of literature search and selection process



Manuscript II. Concomitant use of QT-prolonging medications and the risk of ventricular arrhythmia and sudden death

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ABSTRACT

Background: A major drug safety concern associated with hundreds of medication is the potential for QT interval prolongation. However, the real-world impact of taking multiple medications with QT prolongation potential has not been widely studied since events related to this adverse event are rare.

Objective: To investigate the risk for ventricular arrhythmia or sudden death associated with concomitant prescriptions of QT-prolonging drugs.

Methods: A retrospective case-control study was conducted using an administrative health claims database from a large national insurer. Cases of ventricular arrhythmia or sudden death between 2011 and 2013 were matched with four controls of the same age, sex, and geographic region. Concomitant drug use was defined as exposure to an antibiotic with QT-prolonging potential and one other medication carrying the same risk with overlapping durations of prescriptions. Proximal drug use was defined as a gap no larger than 15 days between durations of a QT-prolonging antibiotic and one other QT-prolonging drug. Adjusted odds ratios were estimated for concomitant and proximal QT-prolonging medication use and other risk factors using conditional logistic regression.

Results: We identified 4,612 cases of ventricular arrhythmia and sudden death and 18,448 controls. Concomitant QT medication use was a strong predictor of ventricular arrhythmia and sudden death (adjusted odds ratio [aOR] 2.91; 95% confidence interval [CI] 1.19-7.08). Proximal QT medication use was also predictive of ventricular arrhythmia and sudden death (aOR 2.20; 95% CI 1.23-3.40). Our study confirmed

several known predictors, such as hypokalemia and cardiac arrhythmia, and also identified several new predictors, including higher Charlson Comorbidity Index. Risk of ventricular arrhythmia or sudden death increased as the number of exposures to QT medications increased in the 10 days prior to the event.

Conclusion: In this privately-insured adult population, concomitant and proximal use of QT-prolonging antibiotics with other QT medications was predictive of ventricular arrhythmia or sudden death. In clinical practice, exposure to multiple QT-prolonging medications should be avoided or closely monitored when necessary.

BACKGROUND

Macrolide and fluoroquinolone antibiotics are among the most frequently prescribed drugs that are associated QT prolongation, which can lead to torsades de pointes (TdP) arrhythmia and sudden death.[1-6] The risk is dose-dependent, therefore concomitant use of multiple QT-prolonging medications (QT medication) may pose a greater threat than singular use. TdP is also associated with other risk factors such as older age, female sex, hypokalemia, history of heart diseases, and renal impairment.[7,8]

Pharmacokinetic interactions among QT-prolonging agents are well-studied. Numerous QT drugs are metabolized by the same group of cytochrome isoenzymes (mostly CYP3A4).[9,10] When exposed together, one drug will serve as the other's metabolic enzyme inhibitor and cause drug accumulation which further increases the risk of drug-induced QT prolongation, a concentration-related event. In addition, pharmacodynamics is another mechanism for increased risk as the medications can serve as each other's synergist or antagonist.[9,11] Some macrolides and fluoroquinolones are also well known for pharmacokinetic drug-drug interactions.[12] Clarithromycin, erythromycin, and ciprofloxacin are all strong inhibitors of cytochrome P450 isoenzymes (CYPs).[9] Thus, their safety profile may outweigh any potential benefits when used concomitantly, especially if one of the drugs is prescribed in high doses. When such interactions are suspected, available therapeutic alternatives should be considered in order to reduce the risk of ventricular arrhythmia and sudden death.[13]

This study sought to quantify predictors of ventricular arrhythmia and sudden death associated with drug-induced QT prolongation, including concomitant exposure to one QT-prolonging antibiotic (QT antibiotic) and one other QT-prolonging medication (other QT medication) with similar pro-arrhythmic potential, in a national, privately-insured population.

METHODS

To achieve the study objective, a retrospective matched case-control study was conducted to assess risk factors of ventricular arrhythmia and sudden death, including concomitant QT medication exposures.

Data source

We utilized the de-identified Optum Clinformatics™ DataMart database (OptumInsight, Eden Prairie, MN) for this study, which is an administrative health claims database from a large national insurer. We utilized member eligibility files, medical claims, confinement claims, and pharmacy claims to conduct this study.

Study population

From the data source, we identified cases of severe ventricular arrhythmias and/or sudden death from January 1, 2011 to December 31, 2013. The cases were defined as having a primary hospitalization diagnosis or first-listed emergency department (ED) visit for ventricular arrhythmia, cardiac arrest, sudden death, or instantaneous death (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes: 427.1, 427.4, 427.41, 427.42, 427.5, 798, 798.1, and 798.2). This outcome definition was validated in previous studies with positive predictive values (PPVs) of over 80%.[14,15] Four controls were matched to each case by exact age in years, sex, and geographic region of the patient.

The diagnosis date was defined as the case index date (t_0) and each matched control was assigned their case's index date. Included patients were at least 18 years of

age on index date and had at least 365 days of continuous enrollment prior to the index date to identify relevant predictors, including medical history and previous medication exposures. We excluded patients that had congenital cardiovascular anomalies since these patients had a higher baseline risk for sudden death compared to the rest of the population. Patients with unknown age or sex were also excluded from the study.

Independent Predictors

Medications with risk of QT prolongation were identified from pharmacy claims, and categorized by class: QT antibiotics (macrolides or fluoroquinolones), antidepressants, antipsychotics, antihistamines, and antiarrhythmics.[16-18] The list of medications assessed can be found in Appendix A. Prescription duration was calculated from the fill date and days of supply. A patient was considered having concomitant drug exposure if the patient: 1) received any QT antibiotic 30 days prior to index date, 2) also received other QT medications (antidepressants, antipsychotics, antihistamines, or antiarrhythmics), and 3) the prescriptions of the QT antibiotic and the other QT medication overlapped by at least one day.[19] In a sensitivity analysis, rather than concomitant use, a proximal use definition of within $\pm$ 15 days was applied. We also identified the number of QT medications used by each patient 10 days prior to the index date. The value was categorized as 0, 1, 2, and $\geqslant$3 to assess the risk of multiple QT medications in that time frame, regardless of overlap.

Other potential predictors included the Charlson Comorbidity Index, calculated from medical and confinement claims 365 days prior to the index date.[20,21] We also assessed other known risk factors for ventricular arrhythmia or sudden death in the

365 days prior to the index date.[7,12,22,23] Due to potential cardiac risks, clarithromycin, erythromycin, ciprofloxacin, and levofloxacin dose adjustment is recommended for patients with hypokalemia and renal impairment.[24] Therefore, the effect of hypokalemia and chronic kidney disease were assessed as risk factors in our study. Furthermore, relevant cardiac comorbidities were identified from diagnosis (Appendix A).[7,23,25]

Statistical Analysis

For direct comparisons between cases and controls, the Pearson Chi-square ($\chi 2$) test was utilized for categorical variables. For categorical variables that did not meet assumptions for $\chi 2$ ($n < 5$), the Fisher's exact test was used. T-test was used for comparing continuous normally distributed demographic variables. Conditional logistic regression was used to identify independent predictors associated being a case using an iterative, manual backward elimination approach.[26] We used univariable analyses to select potential significant independent predictors that had a p-value < 0.05. Selected variables were tested for collinearity and correlated variables were selected based on clinical significance. Then a multivariable conditional logistic regression model containing all covariates identified in the univarible analyses was fit to assess the importance of each covariate and non-significant variables (p-value > 0.05) were removed one-by-one until only significant predictors remained in the model. Adjusted odds ratios (AORs) and associated 95% confidence intervals (CI) were reported from the final conditional logistic regression model.

All statistical analyses were performed using SAS Enterprise Guide, version 7.1 (SAS Institute Inc., Cary, NC, USA). This study was reviewed and approved as exempt by the University of Rhode Island's Institutional Review Board.

RESULTS

We identified 4,612 patients who had ventricular arrhythmia or sudden death from January 1, 2011 through December 31, 2013 and 18,448 controls matched on age, sex, and geographic region. The matched cases and controls had identical distributions for the matching variables (Table 2.1). The comorbidity burden in the cases was higher than the controls. The mean Charlson comorbidity index was 2.8 (standard deviation [SD] 3.1) among cases and 0.5 (SD 1.3) among controls. Cases were significantly ($p<0.0001$) more likely to have a history of cardiovascular diseases than controls as well as myocardial infarction (10.3% cases, 1.1% controls), congestive heart failure (31.6% cases, 2.5% controls), cardiac arrhythmia (40.0% cases, 5.3% controls), and heart valve disease (21.7% cases, 3.3% controls), diabetes with complications (11.6% cases, 2.0% controls) and hypokalemia (7.4% cases, 0.9% controls).

In the study population, 1,862 patients had exposure to QT-prolonging antibiotics 30 days prior to the event date. Among these patients, 404 were exposed to macrolide antibiotics and 1,458 were exposed to fluoroquinolone antibiotics, while none were exposed to both classes of medications in that 30 day period. Only 37 patients in our study population had concomitant exposures (Table 2.1). Proximal QT-prolonging medication use, where medication durations occurred within 15 days of each other, was observed in 81 patients. Among the 23,060 patients included in this study, 20,461 (88.7%) did not use any QT-prolonging medications in the 10 days prior

to index date, while 1,807 (7.8%) patients used one QT-prolonging medication, 619 (2.7%) used two, and 173 (0.8%) used three or more.

Predictors

Patients with concomitant QT-prolonging medication use (QT antibiotic + other QT medication) had a 3-fold increase in the odds of ventricular arrhythmia or sudden death (adjusted odds ratio [aOR] 2.91; 95% CI 1.19-7.08, Table 2.2). Proximal QT-prolonging medication use within 15 days was also a strong predictor of ventricular arrhythmia or sudden death (aOR 2.2, 95% CI 1.23-3.99, Table 2.3). The strongest predictors of ventricular arrhythmia or sudden death for both concomitant (Table 2.2) and proximal (Table 2.3) use were the Charlson Comorbidity Index and a history of cardiac arrhythmias. Similar predictors of comorbidity burden and specific cardiac conditions were identified when evaluating concomitant or proximal QT-prolonging medication exposures. History of palpitation, congestive heart failure, chronic pulmonary disease, cardiomyopathy, and hypokalemia were also identified as independent predictors in the multivariable models. Patients who had diabetes without complications, myocardial infarction, mild liver disease, chronic pulmonary disease, heart murmurs, and heart valve disease all had an increased odds of being a case.

The use of any number of QT-prolonging medications in the 10 days prior to the event was predictive of ventricular arrhythmia or sudden death. Compared with patients who did not used any QT-prolonging medication, those who were exposed to 1, 2, or more than 2 (≥3) QT drugs had 162%, 157%, and 211% higher odds of developing ventricular arrhythmia or sudden death (Table 2.4).

DISCUSSION

In our study, we identified that concomitant exposure to one QT antibiotic and another QT-prolonging drug predicted ventricular arrhythmia and sudden death. Recent exposure to any QT-prolonging medication within 10 days was also predictive, and the strength of this relationship increased with increasing number of QT-prolonging medications. To our knowledge, this is the first observational study to assess the association of ventricular arrhythmia or sudden death with concomitant use of QT-prolonging medications in a large, national, commercially insured population.

There have been extensive pharmacokinetic and pharmacodynamic research on interactions between QT medications, and between QT-prolonging medications and other risk factors for ventricular arrhythmia.[8,9,12,27,28] Case reports have also reported QT prolongation among patients exposed to multiple drugs with known risk of QT prolongation and TdP.[29-31] Few studies have assessed the effects of receiving multiple QT-prolonging medications in retrospective studies. Several previous studies assessed the prevalence of concomitant use of antipsychotics that prolong QT interval.[24,32] A study using claims from a pharmacy benefits manager in the United States found that 51% of QT-prolonging antipsychotic users filled prescriptions for another QT medication with an overlap of at least 1 day in the durations of the two prescriptions.[32] Another study in a tertiary care hospital in Switzerland found that 38.7% (1,332/3,444) administered courses of macrolides or fluoroquinolones had concomitant use of additional QT-prolonging drugs.[24]

There have been general warnings regarding concomitant use of QT-prolonging drugs and contraindications noted on many drug labels. These warnings may have contributed to the low prevalence of concomitant QT medication use in our cases and controls. During the study period, only 37 patients (0.2%) had concomitant use (QT antibiotic and other QT medication) within the 30-day window prior to ventricular arrhythmia or sudden death. Our sensitivity analysis also only identified 81 patients (0.4%) with proximal use (QT antibiotic and other QT medication). Despite this infrequent use, concomitant (aOR 2.91) and proximal (aOR 2.20) use of QT medications was a strong predictor of ventricular arrhythmia and sudden death. These results suggest co-administration of medications with pro-arrhythmic potential should be avoided in clinical practice as the subsequent risk of ventricular arrhythmia and sudden death was high.

Several risk factors for QT prolongation and outcomes of this have been identified in previous studies.[7,8,12,17,22] Our study confirms several risk factors for QT prolongation, including hypokalemia, cardiac arrhythmia, cardiomyopathy, coronary artery disease, heart murmurs, heart valve disease, and palpitation. Our study provided the magnitude of these risk factors in a large national retrospective population. We also identified several new predictors in our population, such as myocardial infarction, diabetes without complications, metastatic solid tumor, congestive heart failure, chronic pulmonary disease, and mild liver disease.

This study, however, is not without limitations. In lieu of actual drug administration information, we relied on dispensed prescriptions records from an administrative claims database as our measure of exposure. Therefore, inpatient

exposure to injected or intravenously administered QT-prolonging medications could not be assessed. In addition, several risk factors for ventricular arrhythmia and sudden death, such as smoking status and body mass index, were also not available from our data source. Other over-the-counter medications with QT-prolonging potential, such as diphenhydramine,[33] are not captured by administrative data. Therefore, patients categorized as unexposed to QT-prolonging medications may have been misclassified. Finally, due to the nature of an administrative claims database, we relied on diagnosis codes for ventricular arrhythmia and sudden death. Therefore, had these events occurred but not resulted in claims with these specific diagnoses, misclassification of case-control status could have also occurred. We did utilize an outcome definition that has been validated in several populations.[14,15]

Closer monitoring should be implemented when concomitant exposure of QT-prolonging medications is necessary. Further research is still required for class specific combinations, dose-related effects, and interactions between medications and medical conditions. In our retrospective analysis, we only looked at antibiotics, antiarrhythmics, antihistamines, antidepressants, and antipsychotics while there are many other drugs with pro-arrhythmic potential (known, possible, and conditional according to CredibleMeds), which could be expanded in future studies.[33] Additionally, the interaction between QT medications and medical conditions is important area of future study as the physiologic and pathologic changes in patients might alter the metabolism and excretion of QT medications and disturb the balance of ions for normal ventricular myocyte function.[34,35]

CONCLUSION

We confirmed several known predictors of QT prolongation in this privately-insured adult population, including hypokalemia, cardiac arrhythmia, cardiomyopathy, coronary artery disease, heart murmurs, heart valve disease, palpitation, myocardial infarction, diabetes without chronic complication, metastatic solid tumor, congestive heart failure, chronic pulmonary disease, and mild liver disease. The concomitant exposure to a QT-prolonging antibiotic and other QT medication was predictive of ventricular arrhythmia or sudden death. Risk of ventricular arrhythmia or sudden death increased as the number of exposures to QT medications increased in the 10 days prior to the event. In clinical practice, exposure to multiple QT-prolonging medications should be avoided or closely monitored when necessary.

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Table 2.1 Demographics and clinical characteristics of cases and controls

Characteristics	**Cases (n=4,612)**		**Controls (n= 18,448)**	
	Mean	SD	Mean	SD
Age, y	59.5	13.7	59.5	13.7
Charlson comorbidity index	2.8	3.1	0.5	1.3
Charlson comorbidity index	**No.**	**%**	**No.**	**%**
0	1259	27.3	14537	78.8
1	876	19.0	1769	9.6
2	591	12.8	939	5.1
≥3	1886	40.9	1203	6.5
Comorbidities	**No.**	**%**	**No.**	**%**
AIDS/HIV	27	0.6	19	0.1
Angina pectoris	207	4.5	161	0.9
Any malignancy	745	16.2	782	4.2
Cardiac arrhythmia	1846	40.0	974	5.3
Cardiomyopathy	835	18.1	185	1.0
Cerebrovascular disease	647	14.0	571	3.1
Chronic kidney disease	849	18.4	449	2.4
Chronic pulmonary disease	1349	29.3	1244	6.7
Congestive heart failure	1456	31.6	464	2.5
Coronary artery disease	1450	31.4	1063	5.8
Dementia	64	1.4	90	0.5
Diabetes with chronic complication	537	11.6	371	2.0
Diabetes without chronic complication	1508	32.7	1554	8.4
Heart murmurs	133	2.9	118	0.6
Heart valve disease	1001	21.7	605	3.3
Hemiplegia or paraplegia	80	1.7	39	0.2
Hypokalemia	343	7.4	157	0.9
Metastatic solid tumor	240	5.2	81	0.4
Mild liver disease	361	7.8	267	1.4
Moderate or severe liver disease	47	1.0	22	0.1
Myocardial infarction	475	10.3	197	1.1
Palpitation	438	9.5	320	1.7
Peptic ulcer disease	85	1.8	70	0.4
Peripheral vascular disease	688	14.9	540	2.9
Renal disease	799	17.3	399	2.2
Rheumatic disease	181	3.9	205	1.1
Ventricular septal defect	0	0.0	1	0.0

Concomitant QT medication exposure	**No.**	**%**	**No.**	**%**
Concomitant QT antibiotic and other QT medication 30 days prior to index date	20	0.4	17	0.1
Proximal QT antibiotic and other QT medication 30 days prior to index date	46	1.0	35	0.2
Number of QT medication use 10 days prior to index date				
0	3310	71.8	17151	93.0
1	879	19.1	928	5.0
2	316	6.8	306	1.6
≥3	107	2.3	66	0.4

Table 2.2 Concomitant QT drug use and predictors of ventricular arrhythmia or sudden death

Study variable	**Adjusted odds ratio**	**95% confidence interval**
Concomitant QT-prolonging medication use (QT antibiotic + other QT medication)	2.91	1.19-7.08
Charlson comorbidity index		
0	1.00	N/A
1	3.40	2.95-3.92
2	3.81	3.20-4.52
≥3	4.67	3.82-5.72
Comorbidities		
Cardiac arrhythmia	3.58	3.11-4.11
Cardiomyopathy	2.01	1.54-2.62
Chronic pulmonary disease	1.40	1.22-1.60
Congestive heart failure	1.83	1.50-2.24
Coronary artery disease	1.86	1.61-2.15
Diabetes without chronic complication	1.26	1.10-1.44
Heart murmurs	1.48	1.03-2.12
Heart valve disease	1.48	1.26-1.74
Hypokalemia	2.11	1.62-2.74
Metastatic solid tumor	3.25	2.31-4.58
Mild liver disease	1.39	1.11-1.74
Myocardial infarction	1.36	1.08-1.76
Palpitation	1.74	1.40-2.15

Table 2.3 Proximal QT drug use (±15 days) and predictors of ventricular arrhythmia or sudden death

Study variable	**Adjusted odds ratio**	**95% confidence interval**
Proximal QT-prolonging medication use (QT antibiotic + other QT medication)*	2.2	1.23-3.40
Charlson comorbidity index		
0	1.00	N/A
1	3.40	2.95-3.92
2	3.50	3.20-4.52
≥3	4.70	3.84-5.74
Comorbidities		
Cardiac arrhythmia	3.56	3.10-4.09
Cardiomyopathy	2.00	1.53-2.61
Chronic kidney disease	1.66	1.37-2.00
Chronic pulmonary disease	1.40	1.23-1.60
Congestive heart failure	1.83	1.50-2.24
Coronary Artery Disease	1.86	1.61-2.15
Diabetes without chronic complication	1.25	1.09-1.43
Heart murmurs	1.50	1.04-2.15
Heart valve disease (cortic stenosis)	1.47	1.25-1.73
Hypokalemia	2.11	1.63-2.75
Metastatic solid tumor	3.23	2.30-4.54
Mild liver disease	1.40	1.12-1.75
Myocardial infarction	1.39	1.09-1.78
Palpitation	1.74	1.41-2.16

* ±15 days allowed between durations of prescriptions

Table 2.4 Number of QT-prolonging medications and predictors of ventricular arrhythmia or sudden death

Study variable	**Adjusted odds ratio**	**95% confidence interval**
Number of QT-prolonging drug used		
0	1.00	N/A
1	2.62	2.28-3.01
2	2.57	2.05-3.22
≥3	3.11	2.05-4.71
Charlson comorbidity index		
0	1.00	N/A
1	3.11	2.69-3.60
2	3.47	2.91-4.14
≥3	4.11	3.35-5.06
Comorbidities		
Cardiac arrhythmia	3.58	3.11-4.11
Cardiomyopathy	2.01	1.54-2.62
Chronic pulmonary disease	1.40	1.22-1.60
Congestive heart failure	1.83	1.50-2.24
Coronary artery disease	1.86	1.61-2.15
Diabetes without chronic complication	1.26	1.10-1.44
Heart murmurs	1.48	1.03-2.12
Heart valve disease	1.48	1.26-1.74
Hypokalemia	2.11	1.62-2.74
Metastatic solid tumor	3.25	2.31-4.58
Mild liver disease	1.39	1.11-1.74
Myocardial infarction	1.36	1.08-1.76
Palpitation	1.74	1.40-2.15

Manuscript III. Risk of drug-induced ventricular arrhythmia and sudden death with QT-prolonging antibiotics

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ABSTRACT

Background: Warnings regarding the increased risk of ventricular arrhythmia with azithromycin have been issued by regulatory agencies. However, conflicting results have been observed in retrospective studies evaluating this association.

Objectives: To evaluate the 10-day and 30-day risk of ventricular arrhythmia or sudden death associated with azithromycin relative to amoxicillin in a national, commercially insured population.

Methods: A retrospective cohort study was conducted using an administrative health claims database from a large national insurer. The study cohort consisted of patients who filled an outpatient prescription between 2011 and 2013 for macrolide and fluoroquinolone antibiotics, or amoxicillin. Amoxicillin episodes were 1-to-1 matched to macrolide and fluoroquinolone episodes on propensity scores. Inpatient admissions or emergency department visits with a primary diagnosis of ventricular arrhythmia were assessed within 10 days and 30 days of prescription dispensing using Cox proportional hazards models.

Results: The use of azithromycin was not associated with an elevated 10-day (hazard ratio [HR]: 1.44, 95% confidence interval [CI]: 0.79-2.64, p=0.23) or 30-day (HR: 1.17, 95% CI: 0.81-1.68, p=0.41) risk of ventricular arrhythmia or sudden death compared with amoxicillin. A class risk for macrolides or fluoroquinolones was also not observed. In a sensitivity analysis which expanded the outcome definition to include primary and secondary diagnoses, macrolides, as a class, had a 68% higher 10-

day (HR: 1.68, 95% CI: 1.16-2.44, p=0.03) risk of ventricular arrhythmia or sudden death.

Conclusions: Among a commercially insured population, azithromycin use was not associated with an increased risk of ventricular arrhythmia or sudden death compared with amoxicillin. Our findings suggest that the cardiac risk associated with azithromycin may be population specific.

BACKGROUND

Macrolide and fluoroquinolone antibiotics are known to increase the risk of cardiac arrhythmia, including QT prolongation and torsades de pointes (TdP).[1,2] Several observational epidemiologic studies suggest that azithromycin may also have an increased risk of ventricular arrhythmia and sudden death.[3-5] One retrospective cohort study published in 2012 reported a higher risk of cardiovascular death associated with azithromycin compared with no antibiotic use (hazard ratio [HR]: 2.88, 95% confidence interval [CI]: 1.79-4.63) or amoxicillin (HR: 2.49, 95% CI: 1.38-4.50) in a Medicaid population.[4] One year later, the United States Food and Drug Administration (FDA) issued a warning to urge healthcare professionals to consider potential cardiovascular risks when prescribing azithromycin.[6] Subsequent observational studies reported similar increased risks of serious arrhythmia, cardiovascular death, and all-cause mortality among patients taking azithromycin among Veterans Affairs patients and in the general population of Taiwan.[3,5]

Meanwhile, several observational studies observed a relatively similar cardiac toxicity profile with azithromycin, as compared with no antibiotic use or other antibiotics.[7-9] In the Danish adult population, azithromycin use (n = 1,102,050) was not associated with an increased risk of cardiovascular death compared to either no antibiotic use (rate ratio = 0.93, 95% CI 0.56-1.55) or penicillin-V use (adjusted absolute risk different = -1, 95% CI -9 to +11).[8] Another study among the general population of Ontario, Canada found that macrolide antibiotic use was not associated with a higher risk of ventricular arrhythmia (relative risk [RR]: 1.06, 95% CI: 0.83–1.36) compared to non-macrolide antibiotics.[7] The same study also observed a lower

risk of all-cause mortality for azithromycin (RR: 0.82, 95% CI: 0.78–0.86) compared to non-macrolide antibiotics.

Motivated by the FDA warnings and conflicting results observed in different populations worldwide, we sought to assess the risk of ventricular arrhythmia (VA) or sudden death (SD) for macrolide and fluoroquinolone antibiotics in database national commercially insured population in the United States (US) and compare the results with previously published observational studies.

METHODS

Data source

We utilized the de-identified Optum Clinformatics™ DataMart database (OptumInsight, Eden Prairie, MN) for this study, which is an administrative health claims database from a large national insurer. We utilized member eligibility files, medical claims, confinement claims, and pharmacy claims to conduct this study.

Study population

We identified outpatient prescription of oral macrolide antibiotics (azithromycin, clarithromycin, and erythromycin), fluoroquinolone antibiotics (ciprofloxacin, gemifloxacin, levofloxacin, moxifloxacin, and ofloxacin), or amoxicillin (including amoxicillin-calvulanate) from January 1, 2011 to November 30, 2013. The prescription fill date was defined as the index date (t_0) of each antibiotic episode. Subsequent antibiotic episodes for each unique patient were only included when the subsequent index date was more than 30 days after the end date (index date + days of supply) of a previous episode. Eligible antibiotic episodes were selected using the same criteria as previous studies.[4] The inclusion criteria were (1) at least 1 year of continuous enrollment prior to the index date for the assessment of baseline characteristics including medical history; and (2) at least 18 years of age on the index date. We excluded those that were (1) missing age or gender information; (2) hospitalized 30 days prior to the index date; (3) treated with multiple study antibiotics on the index date; (4) nursing home or other long-term care facility resident; and (5) previously diagnosed with cancer, organ transplant, congenital cardiovascular

anomalies, other congenital anomalies/childhood conditions, substance abuse, human immunodeficiency virus (HIV) infection, or life-threatening end-stage illness one year prior to the index date (Appendix B).[4]

Drug exposure

Eligible antibiotic episodes were categorized into three treatment groups and one control group based on filled outpatient oral antibiotics: (1) azithromycin; (2) all macrolide antibiotics, which included azithromycin, clarithromycin, and erythromycin; (3) all fluoroquinolones, which included ciprofloxacin, gemifloxacin, levofloxacin, moxifloxacin, and ofloxacin; and (4) amoxicillin serving as the active comparator group or control group for each of the three aforementioned treatment groups, which included amoxicillin alone and amoxicillin-clavulanate. Previous research has shown that amoxicillin use does not increase the risk of QT prolongation related cardiovascular outcomes.[4,10]

Outcome definitions

The study outcome was ventricular arrhythmia and sudden death (referred to as an "event" for the rest of the manuscript), defined as having a primary diagnosis during a hospitalization or first-listed emergency department (ED) visit for severe ventricular arrhythmia, cardiac arrest, sudden death, or instantaneous death (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes: 427.1, 427.4, 427.41, 427.42, 427.5, 798, 798.1, and 798.2). This outcome definition was validated in previous studies with positive predictive values (PPVs) of over 80%.[11-14] Drug-induced QT prolongation is dose-related and the effect

diminishes quickly as study medications are metabolized and excreted.[15] Therefore, we conducted the analysis on two study endpoints which were day 10 and day 30 after the index date.[3,4,7]

Statistical Analysis

Descriptive analyses were performed for the study cohort. The characteristics of the study population, including age, gender, year, month, and geographical region were assessed at the index date. Diagnoses of conditions related to indications were available in the data source and were controlled for in the propensity score. Medical history, medication use, and healthcare utilization were assessed from inpatient and outpatient diagnoses and procedures in the medical and confinement files, as well as from prescription information in the pharmacy files during the 1-year period before the index date (Appendix C).[4]

In this study, propensity score matching was used to balance the baseline characteristics of the study groups for the purpose of estimating the probability of exposure.[16] Propensity score methods allow one to minimize the effects of observed confounding when using observational data. For each comparison (azithromycin-amoxicillin, macrolides-amoxicillin, fluoroquinolone-amoxicillin), a separate propensity score was calculated using logistic regression. The propensity score model was developed through an iterative, manual backward elimination approach using Wald statistics and likelihood ratio tests (p-value < 0.2 for main effects).[17,18] Parson's greedy matching was used to match within 0.000001 of the propensity score, without replacement, one amoxicillin episode from the control group to a single episode in

each of the three treatment groups. The adequacy of matching was assessed with a visual assessment of the distribution of propensity scores and by calculating the standardized difference between study groups.[17] Differences of less than 10% were considered negligible between exposure groups.[17] If important residual systematic differences were identified, interactions terms between covariates already in the model would be assessed.[19]

In each matched comparison cohort, antibiotic episodes were followed for a minimum of 10 days and up to 30 days after the index date. Date of diagnosis of the outcome was used to define time to event. The Cox proportional hazards (PH) model was used to estimate the relative hazard of ventricular arrhythmia and sudden death by regressing survival on treatment status.[16,20] The PH assumption was evaluated from the statistical significance of the correlation between the Schoenfeld residuals and the ranking of individual failure times.[20] Since antibiotic episodes selected in matched cohorts were more likely to be similar to each other than randomly selected subjects, study outcomes were considered dependent within matched pairs. Therefore, the robust variance estimator was used to account for the matched nature of the study cohort. Estimated HR with 95% confidence intervals (CIs) for each comparison was obtained.

For sensitivity analyses, we expanded the definition of the event from a primary diagnosis to any diagnoses within a hospitalization or ED visit. This definition has lower PPVs than the primary definition, however the PPVs for this definition are still over 70%.[13] We also conducted a subgroup analysis among patients with a history of chronic kidney disease (CKD) because they have a higher risk of

developing QT prolongation. Studies have shown that patients with chronic kidney disease had longer QTc than patient without CKD.[21,22] Furthermore, patients with CKD had impaired renal excretion of azithromycin, thereby leading to higher intravascular concentration of the drug. Because the pro-arrythmic effect of macrolides is dose-dependent, the increased concentration of the drug in patients with CKD may increase their risk of ventricular arrhythmia and sudden death.[15,21,23]

All statistical analyses were performed using SAS Enterprise Guide, version 7.1 (SAS Institute Inc., Cary, NC, USA). This study was reviewed and approved as exempt by the University of Rhode Island's Institutional Review Board.

RESULTS

Characteristic of the study cohorts

The study population included 15,634,507 enrollees who filled a total of 12,774,368 outpatient prescriptions for oral macrolide antibiotics (azithromycin, clarithromycin, and erythromycin), fluoroquinolone antibiotics (ciprofloxacin, gemifloxacin, levofloxacin, moxifloxacin, ofloxacin), and amoxicillin (including amoxicillin-calvulanate) during the study period. After applying the exclusion criteria, we identified 5,105,097 eligible prescriptions episodes: 28% azithromycin, 3% other macrolides (clarithromycin and erythromycin), 25% fluoroquinolones, and 43% amoxicillin (Table 3.1). The mean age of the entire study population was 45 years (range: 18-87) and 61% were female.

Azithromycin, all macrolide and all fluoroquinolone episodes were matched 1:1 to amoxicillin episodes on propensity scores. An equal number of amoxicillin prescription episodes were matched to azithromycin, all macrolides, and all fluoroquinolones. The azithromycin-amoxicillin cohort consisted of 1,329,575 azithromycin prescription episodes with an equal number of amoxicillin prescriptions episodes. The fluoroquinolones-amoxicillin and macrolide-amoxicillin cohorts consisted of 1,096,138 and 1,457,873 prescription episodes of fluoroquinolone and macrolide prescription episodes, each with an equal number of amoxicillin prescriptions episodes (Figure 3.1).

Propensity score matching resulted in similar propensity score distributions between the treatment and control groups (Appendix D). The propensity score also

successfully balanced the study variables that contributed to the propensity score for each model, as measured by standardized differences (Appendix D). Standardized differences suggested insignificant differences between the treatment and control groups. Therefore, interaction terms between covariates were not assessed.

Ventricular arrhythmia or sudden death

Azithromycin-amoxicillin

We identified 1,329,575 azithromycin prescription episodes (mean age: 43 years, females: 61%) and an equal number of propensity matched amoxicillin episodes. Among azithromycin recipients, there were 26 events (20 per 1 million episodes) during the 10-day follow-up period. During the same 10-day follow-up period, 18 events (13 per 1 million episodes) occurred among amoxicillin recipients. During the remaining 11-30 days of follow-up, 37 and 36 additional events occurred among azithromycin and amoxicillin recipients, respectively. The cumulative incidence was 47 and 41 per 1 million episodes for azithromycin and amoxicillin recipients, respectively. In time-to-event analyses, azithromycin was not associated with ventricular arrhythmia or sudden death, compared with amoxicillin (Figure 3.2). In the 10-day analysis, risk of ventricular arrhythmia or sudden death was elevated with azithromycin but not statistically significant (HR: 1.44, 95% CI: 0.79-2.64, p=0.230). In the longer follow-up period of 30 days, the risk remained non-significant for azithromycin with a lower HR of 1.17 (95% CI: 0.81-1.68, p=0.407).

All macrolides-amoxicillin

We identified 1,457,873 macrolide prescription episodes (mean age: 43 years, females: 61%) and an equal number of propensity matched amoxicillin episodes. There were 26 and 23 events during the first 10 days after dispensing macrolides and amoxicillin, respectively, with an incidence of 18 and 16 per 1 million episodes, respectively. During the 30-day follow-up period, 63 and 59 events occurred among all macrolides and amoxicillin recipients, respectively. Macrolide antibiotics were not associated with ventricular arrhythmia or sudden death in the 10-day (HR: 1.13, 95% CI: 0.64-1.98, p=0.669) and 30-day follow-up periods (HR: 1.07, 95% CI 0.75-1.52, p=0.717; Figure 3.3).

All fluoroquinolones-amoxicillin

We identified 1,096,138 fluoroquinolone prescription episodes (mean age: 46 years, females: 63%) and an equal number of propensity matched amoxicillin episodes for this cohort. Among fluoroquinolone recipients, there were 24 events (22 per 1 million episodes) during the 10-day follow-up period. During the same follow-up period, 22 events (20 per 1 million episodes) occurred among amoxicillin recipients. During the 30-day follow-up period, 64 and 59 events occurred among fluoroquinolone and amoxicillin recipients, respectively with a cumulative incidence of 58 and 54 per 1 million episodes for fluoroquinolone and amoxicillin recipients, respectively. Fluoroquinolones were not associated with ventricular arrhythmia or sudden death (Figure 3.4). In the 10-day follow-up period, the HR was 1.09 (95% CI: 0.61-1.94, p=0.768), which decreased to 0.92 at 30-days (95% CI: 0.65-1.31, p=0.922).

Sensitivity Analysis

Sensitivity analyses showed similar results when we expanded the event definition from a primary diagnosis only to any recorded diagnoses during hospital stays or ED visits. Azithromycin and fluoroquinolones were not associated with a higher risk of ventricular arrhythmia or sudden death compared with amoxicillin (Appendix E). The sensitivity analysis for macrolides also showed no increased risk in the 30-day follow-up period (HR: 1.24, 95% CI 0.97-1.58, p=0.950) but did demonstrate a significant increased risk of ventricular arrhythmia or sudden death at 10 days (HR: 1.68, 95% CI 1.16-2.44, p=0.031, Figure 3.5).

In the subgroup analysis among patients with chronic kidney disease, risk of ventricular arrhythmia or sudden death was similar in all comparison groups (10-day HR 1.65, 95% CI 0.39-6.90, p=0.493; 30-day HR 1.16, 95% CI 0.39-3.44, p=0.796; results not presented in tables or figures).

DISCUSSION

In our study, we did not observe a significantly increased risk of ventricular arrhythmia or sudden death associated with azithromycin use alone, however when evaluating all macrolides, a 68% higher risk at 10 days was identified in our analysis of the event as either a primary or secondary diagnosis. To our knowledge, this is the first observational study to assess the association of ventricular arrhythmia and sudden death with azithromycin, all macrolides, and all fluoroquinolones in a large, national, commercially insured population. Our inclusion criteria were similar to those used in previous studies,[3,4] and we evaluated the risk of cardiac adverse events at multiple time points (10 days and 30 days) so our results could be compared with these other studies.[5,7] Furthermore, our study outcome has been validated in several populations.[11,13,14]

It was previously thought that azithromycin did not exhibit a pro-arrhythmic potential as seen with the other macrolides, erythromycin and clarithromycin.[24] Based on in vitro preclinical studies, azithromycin was observed to be weak cardiac human ether-a-go-go-related gene (hERG) potassium channel blocker, and it is widely recognized that pharmacological inhibition hERG potassium channel is correlated with drug-induced QT-prolongation.[24-27] Azithromycin is also a group 3 cytochrome P-450 CYP3A4 inhibitor which binds weakly with CYP3A4, and thus has less potential for adverse effects and drug-drug interactions with other CYP3A4 inhibitors such as erythromycin.[10,28-30] However, we have observed a great discrepancy between in vitro studies and real-world clinical practice that is now largely recognized as the result of genetic factors.[31]

A previous population-based study in senior patients (age > 65 years) from Ontario, Canada reported no association between macrolide use and ventricular arrhythmia compared to non-macrolide antibiotic use in the 14 and 30 days after the index date.[7] As compared with the Canadian study, we also assessed all macrolide antibiotics together and did not observe an increased risk at 30 days. However, our findings differed from the Canadian study at the shorter follow-up time point, where we observed a significant association with macrolides. Both studies assessed macrolides as the exposure of interest but different comparators were used. In our study, we selected amoxicillin as the comparator due to its low cardiovascular risk.[4,10] The comparator used in the Canadian study was defined as non-macrolide antibiotics, which included amoxicillin, cefuroxime, or levofloxacin. Levofloxacin is a fluoroquinolone antibiotic has been associated QT-prolonging effect.[32,33] The inclusion of levofloxacin in the non-macrolide group may have diminished the risk difference between the study groups. Study outcomes were slightly different as well; we included both ventricular arrhythmia and sudden death, while the Canadian study only assessed ventricular arrhythmia.

Our findings related to the risk of azithromycin and cardiac adverse events were in agreement with a population-based study from Denmark. In the Danish general population, there was no association between azithromycin use and the risk of cardiovascular death compared to either penicillin V (5-day rate ratio [RR] 0.93, 95% CI, 0.56-1.55) or no antibiotics (5-day RR 2.85, 95% CI, 1.13-7.24) in 5, 10, and 35 day follow-up periods.[8] Like our study population, the Danish general population was also younger (mean age for azithromycin use: 39.7 years) and healthier.[8] Our study

varied from the Danish study, in that we used different comparators and a different definition of the study outcome.

Alternatively, a study in the Tennessee Medicaid population observed a higher risk of cardiovascular death associated with azithromycin than with either no antibiotic use or amoxicillin use.[4] Factors that may contribute to the conflicting study results between our study and the Tennessee Medicaid study include the different demographic and baseline characteristics of the study populations. Risk factors for drug-induced ventricular arrhythmia and sudden death include female gender,[15,34] older age,[15,34] history of chronic kidney disease,[21,35] hypokalemia,[36,37] existing cardiac conditions,[25] and use of other QT-prolonging medications.[25,38] Unlike the Tennessee Medicaid study, our study was conducted in a younger, privately-insured population. Our propensity score matched cohorts were younger and healthier overall, with fewer comorbidities.[4] In our study, the mean age of the azithromycin-amoxicillin matched cohort was 43 years, whereas that of the Tennessee Medicaid study was 48 years. In our azithromycin-amoxicillin cohort, only 2.0% had complications of diabetes, 0.9% had heart failure, 9.7% used angiotensin-converting-enzyme (ACE) inhibitors, 8.4% used beta-blockers, and 7.4% had inpatient stays. In the Tennessee Medicaid study, 7.5% of their matched cohort had complications of diabetes, 4.3% had heart failure, 28.1% used ACE inhibitors, 21.5% used beta-blockers, and 23.0% had inpatient stays. Our study also differed in the definition of the study outcome and prevalence of that outcome, as they assessed a broader definition of death, as cardiovascular rather than sudden death, and they did not assess rates of ventricular arrhythmia. In our study, the 10-day cumulative incidence of ventricular arrhythmia and sudden death was 20 per

million azithromycin episodes. In contrast, the Tennessee Medicaid study reported the 10-day cumulative incidence of cardiovascular death to be 360 per million azithromycin episodes.

An increased risk of cardiac arrhythmias was also reported with azithromycin among Veterans in the US and in Taiwan. The VA study reported an increased 5-day risk of serious cardiac arrhythmias (HR 2.13, 95% CI 1.44-3.15) associated with azithromycin.[3] Despite the same drug exposure group, there was a considerable age difference between the older VA population and ours (mean age 56 vs. 43 years). The VA study only assessed the outcome of ventricular arrhythmia, with a 10-day cumulative incidence rate of 200 per million azithromycin episodes. As mentioned above, the 10-day cumulative incidence of ventricular arrhythmia and sudden death was only 20 per million azithromycin episodes in our study. Similarly, azithromycin was associated with an increased 7-day risk of ventricular arrhythmia and sudden death (adjusted odds ratio [aOR] 4.32, 95% CI, 2.95–6.33) and cardiovascular death (aOR 2.62, 95% CI, 1.69–4.06) in the general population of Taiwan.[5] Though our study population differed from the Taiwanese study population in many aspects, such as race/ethnicity and healthcare practice, azithromycin users were similar in several baseline characteristics, including age (45 vs. 43 years), and other comorbidities, including congestive heart failure (1.5% vs. 1.0%). Like our study, the Taiwanese study also used amoxicillin as the comparator. Nonetheless, the 7-day cumulative incidence rate was 520 per million azithromycin episodes in the Taiwanese general population since they used a broader definition of ventricular arrhythmia and sudden death from both inpatient and outpatient visits. This outcome definition which

included outpatient visits for ventricular arrhythmia and sudden death has not been validated and resulted in a high observed cumulative incidence in the general population of Taiwan.

Several previous studies also observed diminishing risks during longer follow-up periods. During the shorter follow-up period of 5 days, both the Tennessee Medicaid and VA studies reported an increased risk associated with azithromycin use as compared with amoxicillin use. During days 6 to 10 of follow-up, the risk was no longer significant in either the Tennessee Medicaid study (HR 0.88, 95% CI 0.43-1.80) or the VA study (HR 0.73, 95% CI 0.49-1.10).[3,4] For studies which assessed 30-day risk, none reported an increased risk.[7,8]

Our study has several important limitations. In lieu of actual drug administration information, we relied on dispensed prescriptions records from an administrative claims database as our measure of exposure. Also, utilization of erythromycin and clarithromycin was uncommon in our population, therefore risk could not be assessed for individual macrolide antibiotics other than azithromycin. In addition, though diagnoses of infection were available in the data source and were controlled for in the propensity score, specific indications for each dispensed antibiotic were not available in the pharmacy claims data. In order to minimize the potential influence of confounding by the indication, we used amoxicillin, another antibiotic that has similar indications and minimal cardiac toxicity.[4] Several risk factors for ventricular arrhythmia and sudden death, such as smoking status and body mass index were not available in our data source.[15] Therefore, despite propensity score matching using predicted probabilities from a model which included many baseline covariates,

there was still potential for unmeasured confounding in our study.[39] Another limitation was that our study could not assess a more proximal time frame to the prescription dispensing. Azithromycin is commonly prescribed for 5 days but we could only assess the study outcome at 10 days due to the low cumulative incidence observed in our study population. Finally, due to the nature of using an administrative claims database, we relied on diagnosis codes of ventricular arrhythmia and sudden death. Therefore, had these events occurred but not resulted in claims with these specific diagnoses, misclassification could have occurred. It is difficult to measure the true prevalence of QT prolongation as there is no method to quantify undetected events.[40,41] Without the true denominator, validated algorithms for QT prolongation identification report only PPV but not sensitivity/specificity for the same reason.[11,42] We did attempt to use the most accurate definition possible, by using two methods with high PPVs for identifying the study outcome. Nevertheless, bias towards the null for all studies utilizing these definitions for identifying events related to QT prolongation is a possibility as we would not expect this misclassification to differ by exposure status.

CONCLUSION

Among this privately-insured adult population, azithromycin and fluoroquinolones were not associated with a higher risk of ventricular arrhythmia and sudden death compared with amoxicillin. Macrolide antibiotics demonstrated a higher 10-day risk of ventricular arrhythmia and sudden death compared with amoxicillin, suggesting a class effect, with differing quantitative risk between azithromycin and the other macrolides, clarithromycin and erythromycin.

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Table 3.1 Demographics and clinical characteristics of the study population

Characteristics	**AMO**	**AZI**	**MAC**	**FLQ**
Prescriptions (no.)	2,220,068	1,454,889	1,608,020	1,277,009
Prescriptions / patient (no.)	1.7	1.7	1.8	1.8
Mean age ± SD (year)	43.7±14.2	43.5±14.0	43.6±13.5	47.2±14.1
Female (%)	59.2	61.8	61.7	64.6
Year (%)				
2011	32.6	31.5	31.9	33.5
2012	34.8	34.9	34.7	35.0
2013	32.6	33.6	33.4	31.5
Month (%)				
January	10.7	10.9	10.9	10.5
February	9.7	10.0	10.0	9.5
March	9.5	9.6	9.6	9.3
April	8.1	8.1	8.1	8.0
May	7.9	7.8	7.8	7.9
June	7.1	6.7	6.7	7.2
July	6.7	6.2	6.2	6.8
August	7.1	6.7	6.7	7.3
September	7.4	7.4	7.4	7.6
October	8.4	8.3	8.3	8.5
November	8.8	9.1	9.1	8.8
December	8.8	9.3	9.2	8.7
Region (%)				
Northeastern	10.3	13.1	12.9	10.2
Midwest	26.7	22.8	22.6	22.6
South	47.7	52.6	52.7	53.5
West	15.3	11.5	11.7	13.7
Comorbidities (%)				
Angina	0.6	0.7	0.7	0.9
Acute myocardial infarction	0.6	0.5	0.5	0.8
Other coronary heart disease	3.4	3.3	3.3	4.8
Heart valve disease	2.9	2.6	2.6	3.5
Conduction disorder	0.9	0.8	0.8	1.2
Atrial fibrillation	1.2	1.0	1.0	1.5
Cardiac arrhythmia	4.1	4.0	4.0	5.5
Congestive heart failure	1.1	1.0	1.0	1.7
Hypertension	23.1	23.7	23.8	30.1
Other cardiovascular disease	4.2	3.9	3.9	5.4
Hyperlipidemia	24.9	25.7	25.8	31.7
Hyperkalemia	0.2	0.2	0.2	0.4
Chronic kidney disease	1.2	1.1	1.1	2.0
Rheumatic disease	31.6	32.5	32.7	37.4
Chronic liver disease	2.4	2.5	2.5	3.7
Chronic lung disease	8.8	11.2	11.5	13.0
Medication use history (%)				
Angiotensin-converting-enzyme inhibitor	10.4	10.1	10.2	12.9

Angiotensin receptor blocker	5.9	6.2	6.2	8.2
Aspirin	0.4	0.4	0.4	0.5
Sodium-channel blocker	0.2	0.1	0.1	0.2
Beta-blocker	9.1	8.9	8.9	11.7
Potassium-channel blocker	0.3	0.2	0.2	0.4
Calcium-channel blocker	6.0	6.0	6.0	8.0
Digoxin	0.3	0.2	0.2	0.3
Loop diuretic	1.9	1.9	1.9	3.2
Other diuretic	11.2	11.5	11.5	14.5
Insulin	1.9	1.8	1.8	2.7
Oral anti-diabetic	6.2	6.2	6.2	8.2
Beta-agonist	9.4	12.7	13.0	13.2
Statins	15.4	15.1	15.1	20.0
Fibrate lipid-lowering agent	1.9	1.9	1.9	2.6
Nitrate antianginal	0.8	0.8	0.8	1.2
Other antihypertensive	2.2	2.0	2.0	4.0
Peripheral vasodilator	0.2	0.2	0.2	0.3
Platelet inhibitor, none aspirin	1.1	1.1	1.1	1.6
Tricyclic/tetracyclic antidepressant	2.3	2.3	2.3	3.2
SSRI/SNRI antidepressant	11.5	12.1	12.2	14.2
Trazodone antidepressant	1.8	1.8	1.8	2.4
Other antidepressant	3.1	3.1	3.1	3.8
Lithium	0.2	0.2	0.2	0.2
Atypical antipsychotic	1.2	1.1	1.1	1.5
Other antipsychotic	0.3	0.4	0.4	0.5
Benzodiazepine anticonvulsant	6.4	7.0	7.0	8.4
GABA agonist anticonvulsant	3.1	3.1	3.1	4.6
Hydroxyzine	0.8	1.0	1.0	1.1
Other bronchodilator	1.0	1.4	1.4	2.0
Healthcare utilization (%)				
Any none study drug prescription past 30 days	60.7	62.6	62.9	69.5
Any antibiotic use past 30 days	7.6	7.2	7.4	9.2
Any outpatient visit past 30 days	42.0	42.7	42.9	48.0
Any outpatient visits 30-365 days	86.6	88.7	88.9	91.2
Any ED visit past 7 days	1.0	1.0	1.0	1.1
Any hospitalization past 30 days	0.4	0.3	0.3	0.5
Any hospitalization past 30-365 days	7.9	7.4	7.4	10.6

AMO = Amoxicillin, AZI = Azithromycin, ED = Emergency Department, FLQ = Fluoroquinolone Antibiotics, GABA = Gamma-Amino Butyric Acid, oMAC = Other Macrolide Antibiotics; SD = Standard Deviation, SNRI = Serotonin–Norepinephrine Reuptake Inhibitor, SSRI = Selective Serotonin Reuptake Inhibitors

Figure 3.1 Study cohort selection process

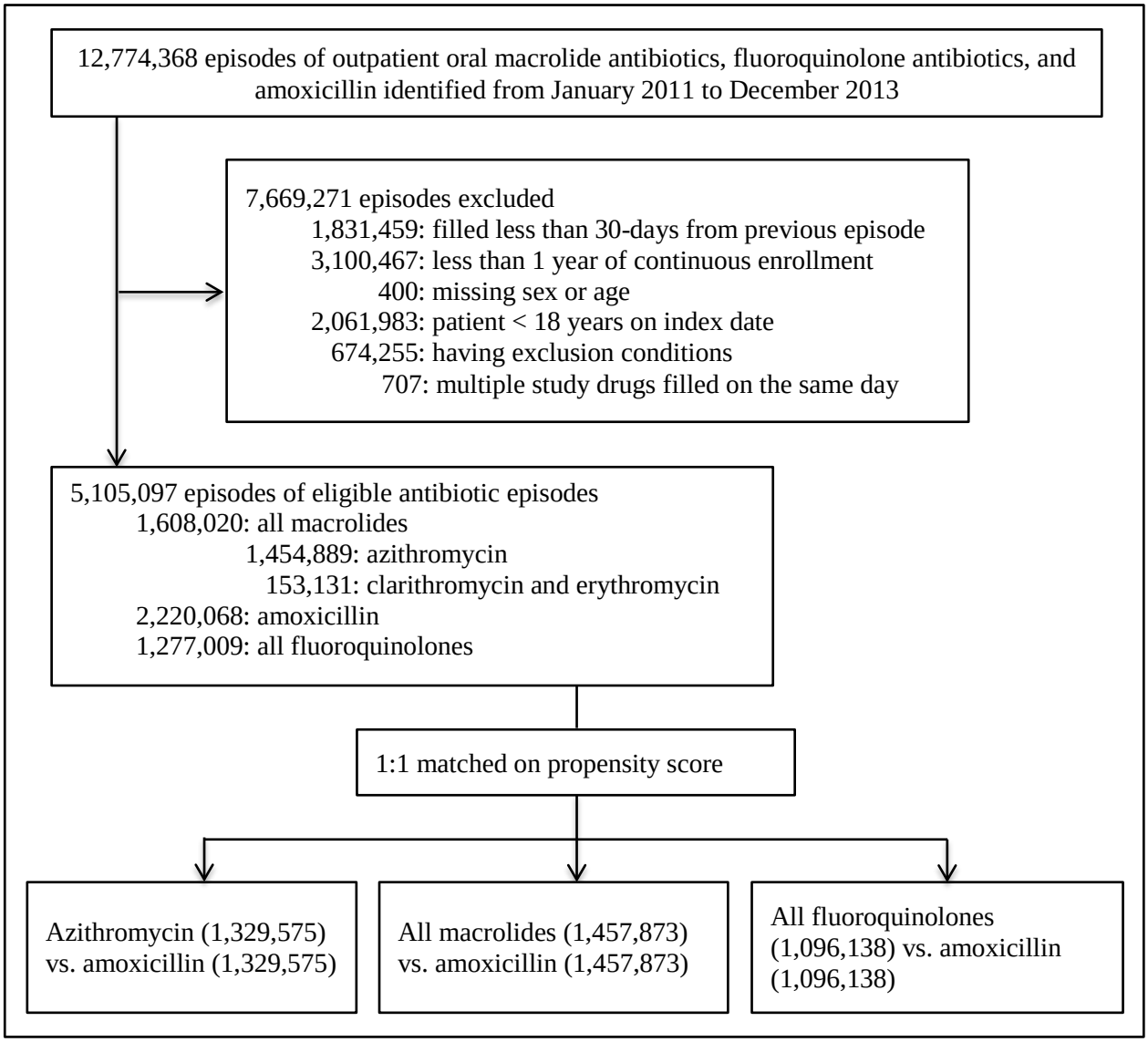


Figure 3.2 Cumulative incidence of ventricular arrhythmia and sudden death with azithromycin and amoxicillin

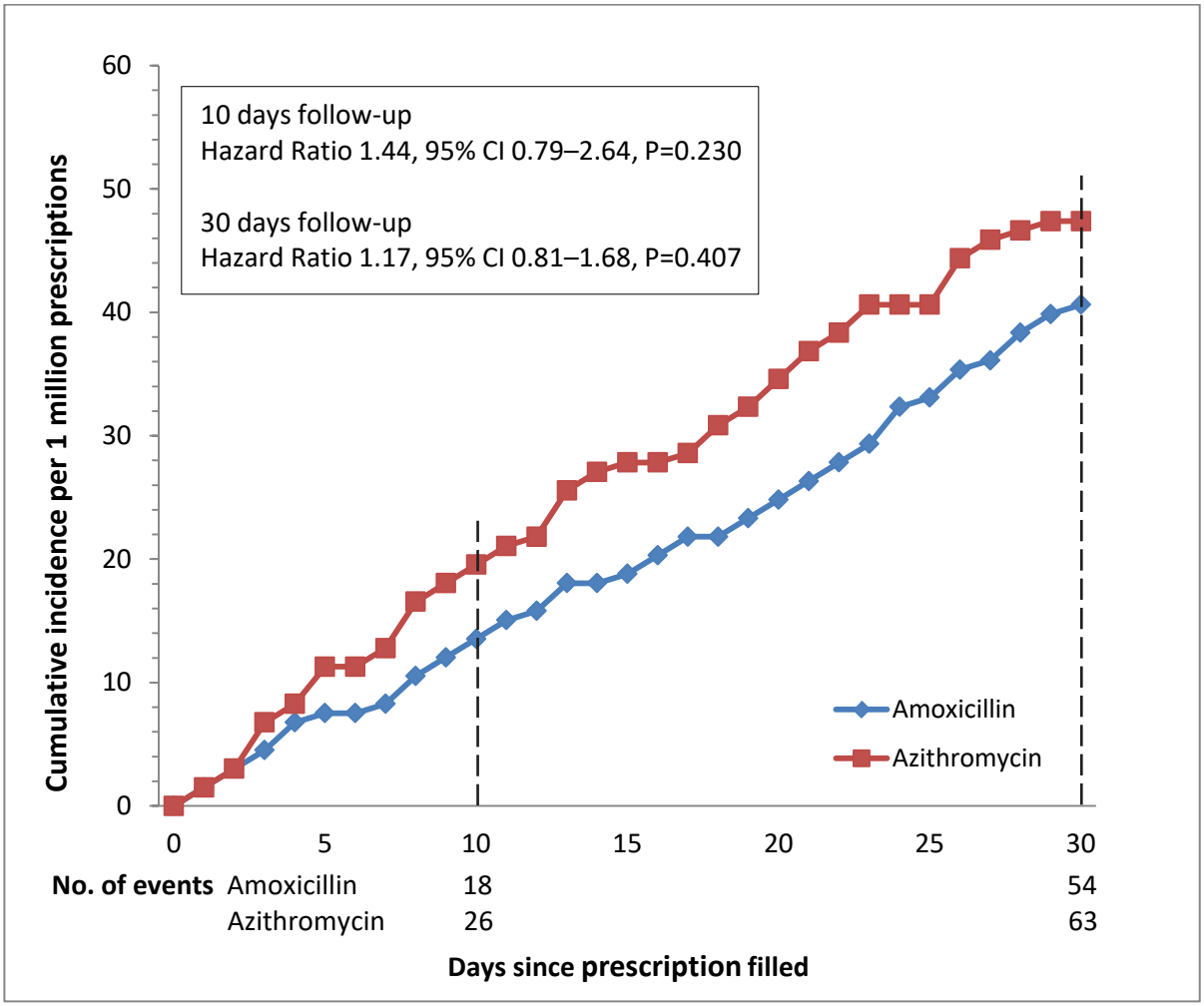


Figure 3.3 Cumulative incidence of ventricular arrhythmia and sudden death with macrolides and amoxicillin

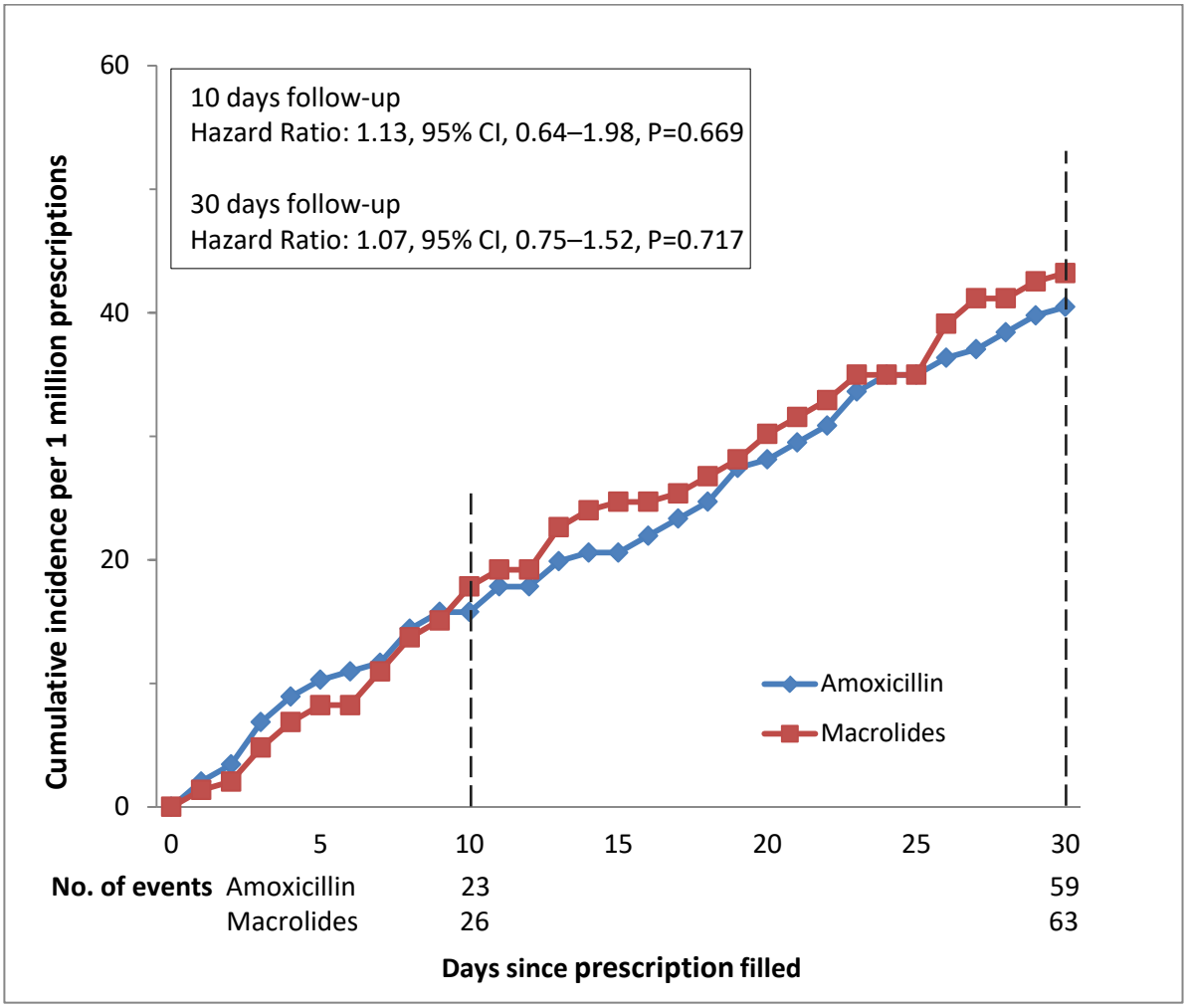


Figure 3.4 Cumulative incidence of ventricular arrhythmia and sudden death with fluoroquinolones and amoxicillin

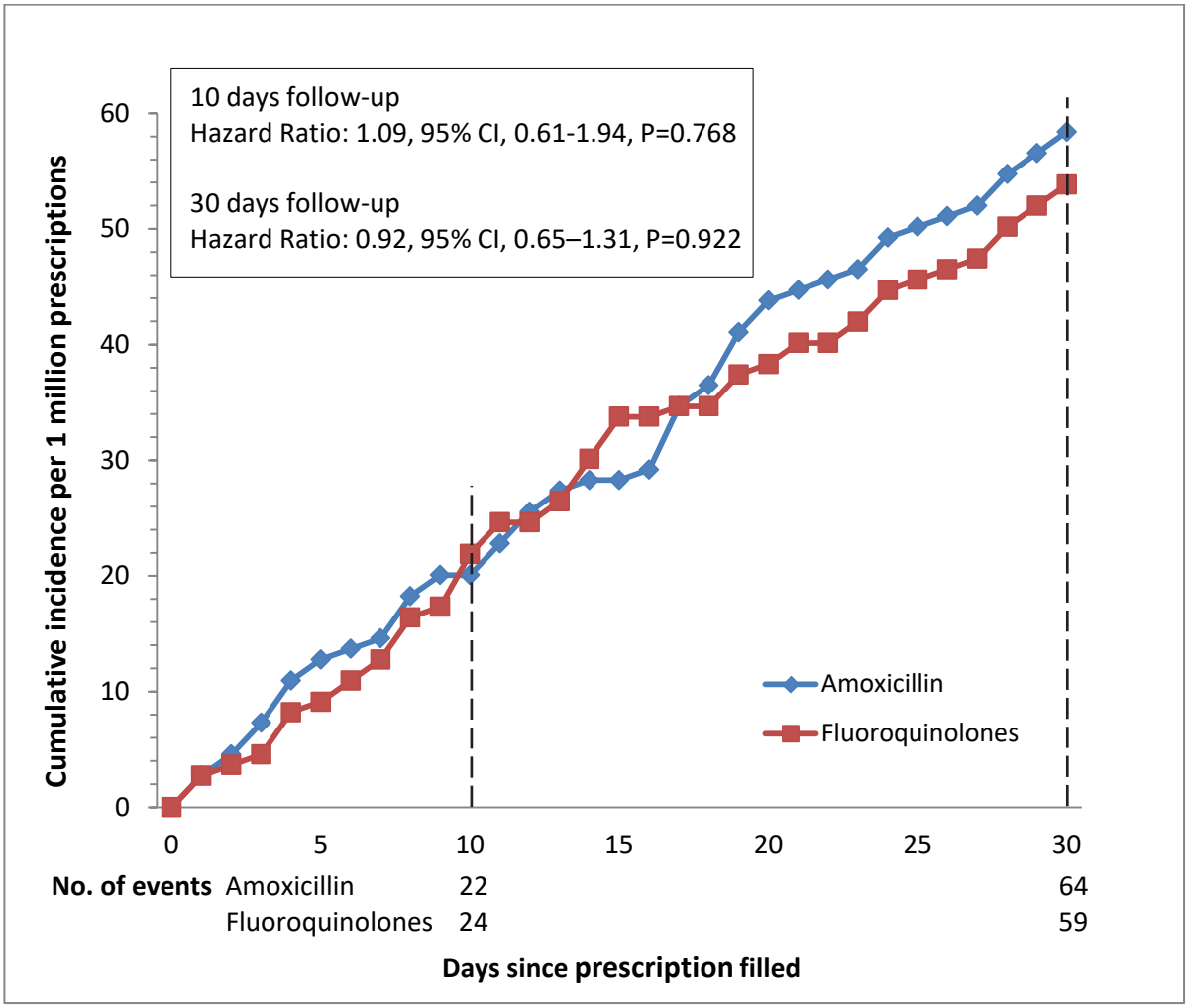
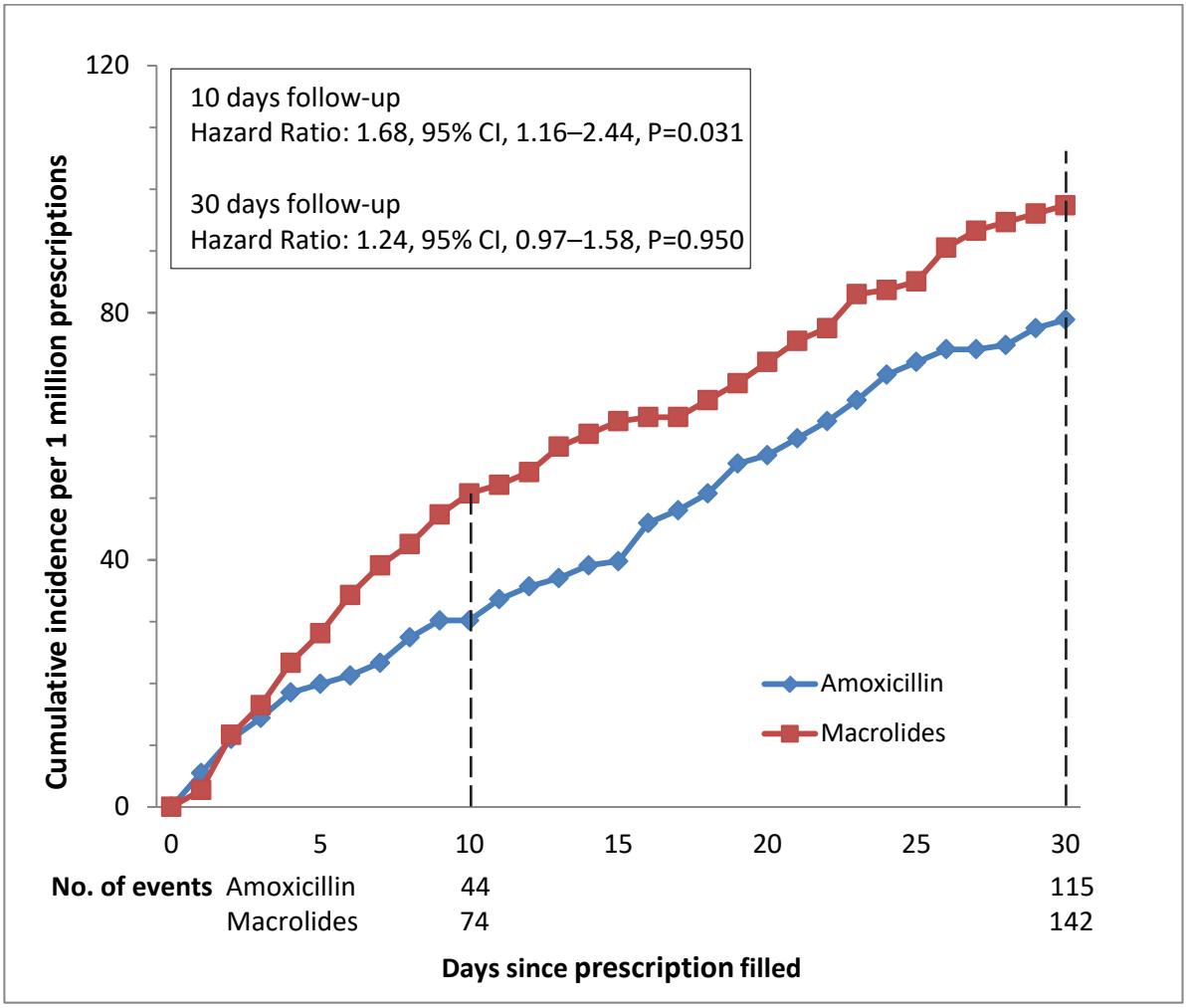


Figure 3.5 Cumulative incidences of ventricular arrhythmia and sudden death with fluoroquinolones and amoxicillin in all diagnoses



APPENDICES

Appendix A. List of medications and comorbidities associated with QT prolongation

Medications and comorbidities associated with QT prolongation
Macrolide antibiotics
Azithromycin
Clarithromycin
Erythromycin
Fluoroquinolone antibiotics
Ciprofloxacin
Gemifloxacin
Levofloxacin
Moxifloxacin
Ofloxacin
Antidepressants
Amitriptyline
Citalopram
Clomipramine
Desipramine
Doxepin
Escitalopram
Fluoxetine
Imipramine
Mirtazapine
Nortriptyline
Paroxetine
Sertraline
Trazodone
Trimipramine
Venlafaxine
Antipsychotics
Aripiprazole
Asenapine
Chlorpromazine
Clozapine
Droperidol
Haloperidol
Iloperidone
Lithium
Olanzapine
Paliperidone
Perphenazine
Pimozide
Promethazine
Quetiapine
Risperidone

Thioridazine
Ziprasidone
Antihistamines
Diphenhydramine
Hydroxyzine
Antiarrhythmics
Amiodarone
Disopyramide
Dofetilide
Dronedarone
Flecainide
Ibutilide
Procainamide
Quinidine
Sotalol
Comorbidities
Angina pectoris
Cardiac arrhythmia
Cardiomyopathy
Coronary artery disease (CAD)
Heart murmur
Heart valve disease (including aortic stenosis),
Palpitation
Ventricular septal defect (VSD)

Appendix B. Exclusion criteria for manuscript III

Disease	**Definition and ICD-9-CM diagnostic codes**
Cancer	Diagnosis of cancer (except for non-melanomous skin cancers) or selected antineoplastic agents. Includes neoplasms uncertain behavior, ICD9-CM codes 235-238, except: 238.2 (skin), 238.9 (site unspecified), 237.70, 237.71 (neurofibromatosis), 238.4 (polycythemia v.), 238.7 (lymphoproliferative disease), 285.22 (anemia in neoplastic disease)
AIDS	Diagnosis of AIDS or use of antiretroviral agents or pentamadine
Severe Hepatic disease	Diagnoses 570-573
Organ transplant	Includes kidney, heart, lung, liver, bone marrow, and pancreas. Includes 996.8
Serious neuromuscular	Multiple sclerosis (340), ALS (335.20), Duchenne's muscular dystrophy (335.21), Huntington's chorea (333.4), quadriplegia, paraplegia, or spinal cord injury. Recent stroke (inpatient with primary discharge diagnosis of 430, 431, 433.x1, 434, 436) with hemiplegia/hemiparesis (342,438.2)
Cardiovascular congenital anomalies	Common truncus (745.0) transposition great vessels (745.1), tetrology (745.2), common ventricle (745.3), endocardial cushion defect (745.6), pulmonary atresia (746.0), tricuspid atresia (746.1), hypoplastic left heart (746.7), coarctation of aorta (747.1), other anomalies of aorta (747.2), total anomalous pulmonary venous connection (747.41) . A single diagnosis is sufficient for exclusion
Other congenital anomalies/childhood conditions	Sickle cell (282.6), cerebral palsy (343), spina bifida (741), Down's syndrome (758.0), hydrocephalus (742.3), microcephalus (742.1), encephalocele (742.0), severe mental retardation (318.1, 318.2), cystic fibrosis
Other end-stage illness	a. Hospice care. b. Diagnosis of coma, vegetative state, debility (799.3). c. Total parenteral nutrition, PEG, enteral feeding, malnutrition (260, 261,262, 263) when these are for outpatients. d. Gangrene (040, gas gangrene; 785.4 gangrene: single diagnosis sufficient) e. Intravenous medications outside of the hospital, as indicated by procedures for IV access outside a hospital

	stay period
Drug abuse	Includes all medications and drugs with abuse potential and with the exception of alcohol (unless hospitalization with primary discharge diagnosis: 291.x, 303.x, 305.0, 980.0, 980.9, E860.0, E860.1, E860.9) and tobacco. Codes are 292.0 (drug withdrawal syndrome), 304.x (drug dependence), 305.2-305.9 (drug abuse, except alcohol/tobacco, 305.9 is abuse NOS, may be nonspecific, but better to exclude), 965.01 (accidental poisoning, heroin), 969.6 (poisoning, psychodysleptic [hallucinogens]), 970.81 (cocaine poisoning, added in 2010), E8500 (heroin poisoning), E8541 (psychodysleptic poisoning)

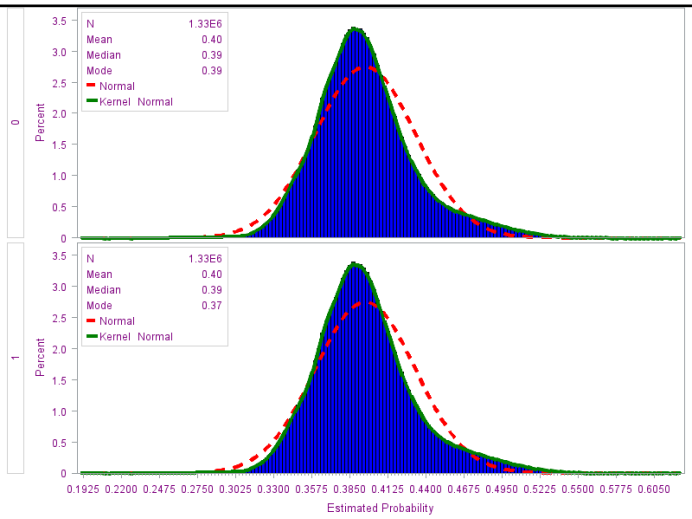
Appendix C. List of covariates for propensity score model

Covariates for propensity score model
Number of prescriptions for an unique patient
Age
Gender
Year
Month
Geographic region
Angina/angina pectoris
Acute myocardial infarction
Other coronary heart disease
Other cardiovascular disease
Heart valve disease
Conduction disorder
Atrial fibrillation
Cardiac arrhythmia
Congestive heart failure
Hemorrhagic stroke
Ischemic stroke
Transient ischemic attack
Obesity, diagnosed, not morbid
Morbid obesity, diagnosed
Hypertension
Malignant hypertension
Hyperlipidemia
Peripheral vascular disease
Diabetes mellitus
Diabetes, ocular complication
Diabetes, neurologic complication
Diabetes, skin complication
Diabetes, renal complication
Diabetes, other complication
Schizophrenia or other psychotic disorders
Alcohol abuse
Bipolar disorder
Unipolar depression and/or anxiety disorder
Parkinson's Disease
Seizure disorder
Dementia
Other cognitive disorders
Chronic lung disease
COPD and other respiratory conditions
Asthma
Diagnosed smoking
Rheumatic disease
Chronic liver disease
Chronic kidney disease

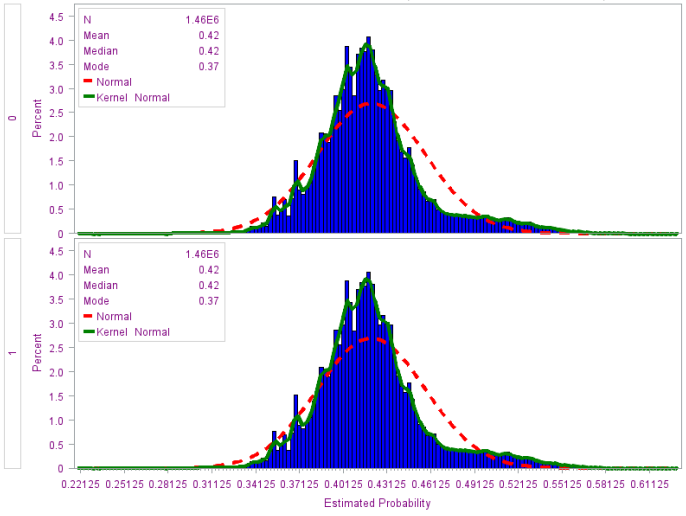
Acute kidney disease
Hypokalemia
Fluid and electrolyte disorders
Cardiac revascularization
ACE inhibitor
Anticoagulant
Angiotensin receptor blocker
Aspirin
Na^{+}-channel blocker
Beta-adrenergic blocker
K+-channel blocker
Ca^{2+}-channel blocker
Digoxin
Loop diuretic
Other diuretic
Insulin
Oral antidiabetic
Statin
Fibrate lipid-lowering agent
Nitrate anti-anginal
Other antihypertensive
Peripheral vasodilator
Platelet inhibitor, not aspirin
Tricyclic/tetracyclic antidepressant
SSRI/SNRI antidepressant
Trazodone antidepressant
Other antidepressant
Lithium antipsychotic
Atypical antipsychotics
Other antipsychotics
Benzodiazepine anticonvulsants
GABA agonist anticonvulsant
Hydroxyzine
Adrenergic beta-agonist
Other bronchodilator
Any prescription (other than study antibiotics) past 30 days
Any antibiotic use past 30 days
Any outpatient visit past 30 days
Any outpatient visits 30-365 days
Any ED visit past 7 days
Any hospitalization past 30 days
Any hospitalization past 30-365 days

ACE = angiotensin converting enzyme, COPD = chronic obstructive pulmonary disease, ED = emergency department, GABA = gamma-amino butyric acid

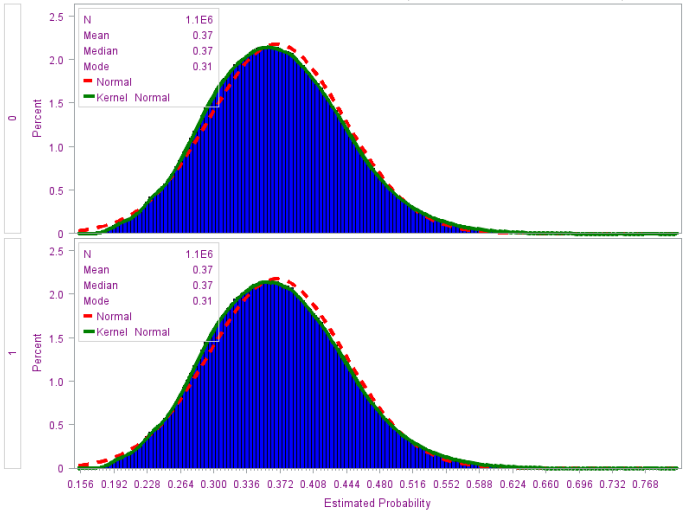
Appendix D. Distributions of propensity scores in matched study cohorts



Matched AMO-AZI cohort (0: AMO; 1: AZI)



Matched AMO-MAC cohort (0: AMO; 1: MAC)



Matched AMO-FLQ cohort (0: AMO; 1: FLQ)

Appendix E. Demographics and clinical characteristics of the matched cohorts

Appendix Table E.1 Demographics and clinical characteristics of the matched AZI-AMO cohort			
Characteristics	**AMO**	**AZI**	**d**
Prescriptions (no.)	1,329,575	1,329,575	0.000
Mean prescriptions / patient (no.)*	1.68	1.67	0.002
Mean age*	43.0	43.1	0.009
Female (%)*	61.0	61.1	0.007
Year (%)*			
2011	32.3	32.1	0.005
2012	34.9	34.9	0.001
2013	32.8	33.0	0.004
Month (%)*			
January	10.8	11.0	0.006
February	9.7	10.1	0.011
march	9.5	9.6	0.004
April	8.1	8.1	0.001
May	8.0	7.8	0.006
June	7.0	6.7	0.011
July	6.6	6.2	0.016
August	7.0	6.7	0.012
September	7.4	7.3	0.001
October	8.3	8.3	0.000
November	8.9	9.0	0.004
December	8.8	9.2	0.015
Region (%)*			
Northeastern	11.1	12.1	0.034
Midwest	26.3	22.7	0.084
South	49.1	53.5	0.088
West	13.5	11.7	0.056
Comorbidities (%)			
Angina/angina pectoris*	0.6	0.6	0.000
Acute myocardial infarction	0.5	0.5	0.002
Other coronary heart disease	3.0	3.0	0.001
Other cardiovascular disease*	3.5	3.5	0.002
Heart valve disease*	2.3	2.4	0.002
Conduction disorder*	0.7	0.7	0.000
Atrial fibrillation	0.8	0.7	0.004
Cardiac arrhythmia*	3.5	3.5	0.000
Congestive heart failure	0.9	0.9	0.001
Hemorrhagic stroke	0.0	0.0	0.001
Ischemic stroke	0.3	0.3	0.002
Transient ischemic attack	0.3	0.3	0.002
Obesity, diagnosed, not morbid	5.0	5.0	0.000
Morbid obesity, diagnosed*	1.6	1.6	0.002
Hypertension*	22.0	22.5	0.011
Malignant hypertension*	0.8	0.8	0.002
Hyperlipidemia*	24.4	24.5	0.003

Peripheral vascular disease*	1.3	1.3	0.001
Diabetes mellitus	10.9	11.0	0.003
Diabetes, ocular complication	0.5	0.5	0.001
Diabetes, neurologic complication*	0.6	0.6	0.001
Diabetes, skin complication*	0.2	0.2	0.000
Diabetes, renal complication	0.3	0.3	0.000
Diabetes, other complication	0.5	0.5	0.001
Schizophrenia or other psychotic disorders	0.2	0.2	0.002
Alcohol abuse*	0.4	0.4	0.000
Bipolar disorder*	0.9	0.9	0.001
Unipolar depression and/or anxiety disorder	14.6	14.7	0.002
Parkinson's Disease*	0.1	0.1	0.001
Seizure disorder	0.7	0.7	0.003
Dementia	0.1	0.1	0.000
Other cognitive disorders	0.2	0.2	0.001
Chronic lung disease*	8.5	8.6	0.003
COPD and other respiratory conditions*	1.7	1.7	0.001
Asthma*	6.3	6.4	0.003
Diagnosed smoking*	3.8	3.9	0.006
Rheumatic disease	31.3	31.5	0.004
Chronic liver disease	2.4	2.4	0.002
Chronic kidney disease*	1.2	1.3	0.001
Hypokalemia	0.2	0.2	0.000
Fluid and electrolyte disorders	0.2	0.2	0.000
Cardiac revascularization	0.0	0.0	0.000
Medication use history (%)			
ACE inhibitor*	9.6	9.7	0.006
Anticoagulant*	0.8	0.8	0.001
Angiotensin receptor blocker*	5.7	5.8	0.003
Aspirin	0.4	0.4	0.001
Na^{+}-channel blocker*	0.1	0.1	0.002
Beta-adrenergic blocker*	8.3	8.4	0.004
K+-channel blocker*	0.1	0.1	0.004
Ca^{2+}-channel blocker	5.6	5.6	0.001
Digoxin*	0.1	0.1	0.002
Loop diuretic	1.7	1.7	0.002
Other diuretic*	10.8	10.9	0.004
Insulin*	1.7	1.7	0.000
Oral antidiabetic*	5.8	5.9	0.004
Statin*	14.4	14.5	0.003
Fibrate lipid-lowering agent	1.8	1.8	0.000
Nitrate anti-anginal*	0.7	0.7	0.001
Other antihypertensive*	1.9	1.9	0.000
Peripheral vasodilator	0.2	0.2	0.001
Platelet inhibitor, not aspirin	1.0	1.0	0.002
Tricyclic/tetracyclic antidepressant	2.2	2.2	0.006
SSRI/SNRI antidepressant	11.6	11.7	0.004
Trazodone antidepressant	1.8	1.7	0.005
Other antidepressant*	3.0	3.0	0.000

Lithium antipsychotic*	0.2	0.2	0.001
Atypical antipsychotics*	1.1	1.1	0.002
Other antipsychotics	0.3	0.3	0.001
Benzodiazepine anticonvulsants*	6.4	6.4	0.001
GABA agonist anticonvulsant	2.9	2.9	0.002
Hydroxyzine*	0.9	0.9	0.000
Adrenergic beta-agonist*	9.4	9.4	0.003
Other bronchodilator*	0.9	0.9	0.000
Healthcare Utilization (%)			
Any prescription (other than study ABX) past 30 days*	60.2	60.8	0.013
Any antibiotic use past 30 days*	6.9	7.1	0.007
Any outpatient visit past 30 days	41.5	41.7	0.003
Any outpatient visits 30-365 days*	88.4	88.0	0.010
Any ED visit past 7 days	1.0	1.0	0.000
Any hospitalization past 30 days*	0.3	0.3	0.000
Any hospitalization past 30-365 days*	7.1	7.0	0.003

* Covariates included the propensity score model

C-statistic: 0.547

Hosmer and Lemeshow Goodness-of-Fit (GOF) test: χ^2=121.7 (degree of freedom [df] = 8, p-value < 0.0001)

ABX = antibiotics, ACE = angiotensin converting enzyme, AMO = amoxicillin, AZI = azithromycin, COPD = chronic obstructive pulmonary disease, ED = emergency department, GABA = gamma-amino butyric acid

Appendix Table E.2 Demographics and clinical characteristics of the matched MAC-AMO cohort			
Characteristics	**AMO**	**MAC**	**d**
Prescriptions (no.)	1,457,873	1,457,873	0.000
Mean prescriptions / patient (no.)*	1.7	1.7	0.037
Mean age*	43.0	43.0	0.004
Female (%)*	61.6	61.4	0.005
Year (%)			
2011	31.5	32.0	0.013
2012	34.9	34.8	0.002
2013	33.6	33.2	0.010
Month (%)*			
January	10.8	10.9	0.005
February	9.9	10.0	0.005
march	9.6	9.6	0.001
April	8.1	8.1	0.000
May	7.9	7.8	0.001
June	6.9	6.8	0.006
July	6.4	6.3	0.008
August	6.9	6.7	0.006
September	7.4	7.4	0.002
October	8.3	8.3	0.000
November	9.0	9.0	0.003
December	9.0	9.2	0.005
Region (%)*			
Northeastern	11.6	12.2	0.021
Midwest	24.2	22.7	0.044
South	51.3	53.3	0.058
West	12.9	11.9	0.038
Comorbidities (%)			
Angina/angina pectoris*	0.5	0.5	0.001
Acute myocardial infarction*	0.4	0.4	0.002
Other coronary heart disease*	2.7	2.7	0.001
Other cardiovascular disease*	3.1	3.2	0.001
Heart valve disease*	2.1	2.1	0.002
Conduction disorder*	0.6	0.6	0.001
Atrial fibrillation*	0.7	0.6	0.002
Cardiac arrhythmia*	3.2	3.2	0.002
Congestive heart failure	0.8	0.8	0.002
Hemorrhagic stroke	0.0	0.0	0.000
Ischemic stroke*	0.3	0.3	0.000
Transient ischemic attack	0.3	0.3	0.003
Obesity, diagnosed, not morbid	4.8	4.8	0.001
Morbid obesity, diagnosed*	1.6	1.5	0.001
Hypertension*	21.1	21.2	0.003
Malignant hypertension*	0.7	0.7	0.002
Hyperlipidemia*	23.6	23.5	0.001
Peripheral vascular disease*	1.2	1.2	0.000
Diabetes mellitus*	10.3	10.3	0.001

Diabetes, ocular complication*	0.4	0.4	0.000
Diabetes, neurologic complication	0.5	0.5	0.003
Diabetes, skin complication*	0.2	0.2	0.002
Diabetes, renal complication*	0.2	0.2	0.001
Diabetes, other complication	0.5	0.5	0.001
Schizophrenia or other psychotic disorders	0.2	0.2	0.001
Alcohol abuse*	0.4	0.4	0.002
Bipolar disorder	0.8	0.8	0.002
Unipolar depression and/or anxiety disorder	14.3	14.5	0.004
Parkinson's Disease	0.1	0.1	0.000
Seizure disorder	0.7	0.7	0.004
Dementia*	0.0	0.0	0.000
Other cognitive disorders	0.1	0.1	0.001
Chronic lung disease*	8.5	8.5	0.002
COPD and other respiratory conditions*	1.5	1.5	0.002
Asthma*	6.5	6.6	0.002
Diagnosed smoking*	3.5	3.6	0.007
Rheumatic disease*	30.7	31.1	0.007
Chronic liver disease*	2.2	2.2	0.003
Chronic kidney disease*	1.0	1.0	0.002
Hypokalemia	0.2	0.2	0.001
Fluid and electrolyte disorders	0.2	0.2	0.001
Cardiac revascularization*	0.0	0.0	0.001
Medication use history (%)			
ACE inhibitor*	9.1	9.2	0.003
Anticoagulant*	0.7	0.7	0.001
Angiotensin receptor blocker*	5.3	5.4	0.003
Aspirin	0.4	0.4	0.001
Na^{+}-channel blocker*	0.1	0.1	0.003
Beta-adrenergic blocker*	7.7	7.8	0.002
K+-channel blocker*	0.1	0.1	0.002
Ca^{2+}-channel blocker*	5.3	5.3	0.003
Digoxin	0.1	0.1	0.001
Loop diuretic*	1.6	1.6	0.002
Other diuretic*	10.2	10.3	0.004
Insulin*	1.5	1.6	0.002
Oral antidiabetic	5.6	5.6	0.001
Statin*	13.8	13.7	0.002
Fibrate lipid-lowering agent*	1.7	1.7	0.000
Nitrate anti-anginal	0.6	0.6	0.003
Other antihypertensive*	1.8	1.8	0.002
Peripheral vasodilator*	0.1	0.1	0.000
Platelet inhibitor, not aspirin*	0.9	0.9	0.001
Tricyclic/tetracyclic antidepressant*	2.0	2.0	0.005
SSRI/SNRI antidepressant*	11.4	11.5	0.003
Trazodone antidepressant*	1.7	1.7	0.005
Other antidepressant*	2.8	2.8	0.002
Lithium antipsychotic*	0.1	0.2	0.002
Atypical antipsychotics*	1.0	1.0	0.001

Other antipsychotics*	0.3	0.3	0.001
Benzodiazepine anticonvulsants*	6.0	6.1	0.004
GABA agonist anticonvulsant*	2.6	2.7	0.003
Hydroxyzine*	0.8	0.8	0.002
Adrenergic beta-agonist*	9.6	9.6	0.000
Other bronchodilator*	0.8	0.8	0.001
Healthcare Utilization (%)			
Any prescription (other than study ABX) past 30 days*	60.8	60.6	0.004
Any antibiotic use past 30 days*	7.3	7.1	0.006
Any outpatient visit past 30 days*	41.5	41.4	0.001
Any outpatient visits 30-365 days*	88.1	88.0	0.001
Any ED visit past 7 days	1.0	1.0	0.003
Any hospitalization past 30 days	0.3	0.3	0.001
Any hospitalization past 30-365 days*	6.6	6.6	0.003

* Covariates included the propensity score model

C-statistic: 0.546

Hosmer and Lemeshow Goodness-of-Fit (GOF) test: χ^2=153.7 (df = 8, p-value < 0.0001)

ABX = antibiotics, ACE = angiotensin converting enzyme, AMO = amoxicillin, COPD = chronic obstructive pulmonary disease, ED = emergency department, GABA = gamma-amino butyric acid, MAC = macrolide antibiotics

Appendix Table E.3 Demographics and clinical characteristics of the matched FLQ-AMO cohort			
Characteristics	**AMO**	**FLQ**	**d**
Prescriptions (no.)	1,096,138	1,096,138	0.000
Mean prescriptions / patient (no.)*	1.7	1.7	0.005
Mean age*	45.6	45.7	0.007
Female (%)*	63.8	64.1	0.006
Year (%)			
2011	33.9	33.5	0.008
2012	35.0	34.9	0.001
2013	31.1	31.5	0.009
Month (%)*			
January	10.8	10.7	0.003
February	9.8	9.6	0.007
march	9.5	9.4	0.003
April	8.1	8.1	0.003
May	7.8	7.9	0.003
June	7.0	7.1	0.005
July	6.7	6.8	0.002
August	7.1	7.2	0.003
September	7.4	7.6	0.004
October	8.4	8.4	0.000
November	8.7	8.8	0.001
December	8.7	8.7	0.000
Region (%)*			
Northeastern	9.7	10.4	0.025
Midwest	25.5	22.7	0.065
South	49.3	53.4	0.081
West	15.5	13.5	0.057
Comorbidities (%)			
Angina/angina pectoris*	0.7	0.7	0.001
Acute myocardial infarction*	0.6	0.6	0.000
Other coronary heart disease*	3.8	3.8	0.000
Other cardiovascular disease*	4.5	4.5	0.002
Heart valve disease*	3.2	3.1	0.004
Conduction disorder*	1.0	0.9	0.001
Atrial fibrillation*	1.3	1.3	0.003
Cardiac arrhythmia*	4.5	4.5	0.003
Congestive heart failure	1.2	1.2	0.001
Hemorrhagic stroke	0.0	0.0	0.001
Ischemic stroke*	0.4	0.4	0.001
Transient ischemic attack	0.4	0.4	0.000
Obesity, diagnosed, not morbid	5.5	5.5	0.001
Morbid obesity, diagnosed*	1.9	1.9	0.001
Hypertension*	26.4	26.2	0.004
Malignant hypertension*	0.9	1.0	0.001
Hyperlipidemia*	28.6	28.3	0.006
Peripheral vascular disease*	1.7	1.7	0.001
Diabetes mellitus*	13.0	13.0	0.001

Diabetes, ocular complication*	0.6	0.6	0.000
Diabetes, neurologic complication	0.8	0.8	0.002
Diabetes, skin complication*	0.3	0.3	0.002
Diabetes, renal complication*	0.4	0.4	0.001
Diabetes, other complication	0.7	0.7	0.002
Schizophrenia or other psychotic disorders	0.2	0.2	0.001
Alcohol abuse*	0.5	0.5	0.000
Bipolar disorder	1.1	1.0	0.002
Unipolar depression and/or anxiety disorder	16.0	15.9	0.003
Parkinson's Disease	0.1	0.1	0.002
Seizure disorder	0.8	0.8	0.002
Dementia*	0.1	0.1	0.000
Other cognitive disorders	0.2	0.2	0.001
Chronic lung disease*	9.5	9.7	0.007
COPD and other respiratory conditions*	1.9	2.0	0.004
Asthma*	7.0	7.2	0.006
Diagnosed smoking*	4.3	4.3	0.001
Rheumatic disease*	35.6	34.5	0.023
Chronic liver disease*	2.7	2.8	0.004
Chronic kidney disease*	1.4	1.5	0.002
Hypokalemia	0.3	0.3	0.001
Fluid and electrolyte disorders	0.3	0.3	0.001
Cardiac revascularization*	0.1	0.1	0.000
Medication use history (%)			
ACE inhibitor*	11.8	11.6	0.005
Anticoagulant*	1.9	1.8	0.005
Angiotensin receptor blocker*	6.8	6.8	0.002
Aspirin	0.4	0.4	0.001
Na^{+}-channel blocker*	0.2	0.2	0.002
Beta-adrenergic blocker*	10.2	10.1	0.003
K+-channel blocker*	0.3	0.3	0.002
Ca^{2+}-channel blocker*	6.8	6.7	0.000
Digoxin	0.3	0.3	0.002
Loop diuretic*	2.1	2.2	0.003
Other diuretic*	12.9	12.8	0.004
Insulin*	2.1	2.1	0.001
Oral antidiabetic	7.1	7.1	0.001
Statin*	17.7	17.6	0.003
Fibrate lipid-lowering agent*	2.2	2.2	0.000
Nitrate anti-anginal	0.9	0.9	0.002
Other antihypertensive*	2.4	2.5	0.007
Peripheral vasodilator*	0.2	0.2	0.001
Platelet inhibitor, not aspirin*	1.2	1.2	0.000
Tricyclic/tetracyclic antidepressant*	2.6	2.6	0.002
SSRI/SNRI antidepressant*	12.9	12.8	0.004
Trazodone antidepressant*	2.1	2.1	0.001
Other antidepressant*	3.4	3.4	0.000
Lithium antipsychotic*	0.2	0.2	0.001
Atypical antipsychotics*	1.3	1.3	0.001

Other antipsychotics*	0.4	0.4	0.002
Benzodiazepine anticonvulsants*	7.3	7.2	0.004
GABA agonist anticonvulsant*	3.5	3.5	0.002
Hydroxyzine*	0.9	0.9	0.000
Adrenergic beta-agonist*	10.4	10.5	0.002
Other bronchodilator*	1.0	1.0	0.003
Healthcare Utilization (%)			
Any prescription (other than study ABX) past 30 days*	67.9	66.2	0.036
Any antibiotic use past 30 days*	8.6	8.3	0.008
Any outpatient visit past 30 days*	45.0	45.1	0.002
Any outpatient visits 30-365 days*	90.4	90.2	0.004
Any ED visit past 7 days	1.1	1.1	0.001
Any hospitalization past 30 days	0.4	0.4	0.003
Any hospitalization past 30-365 days*	8.6	8.5	0.000

* Covariates included the propensity score model

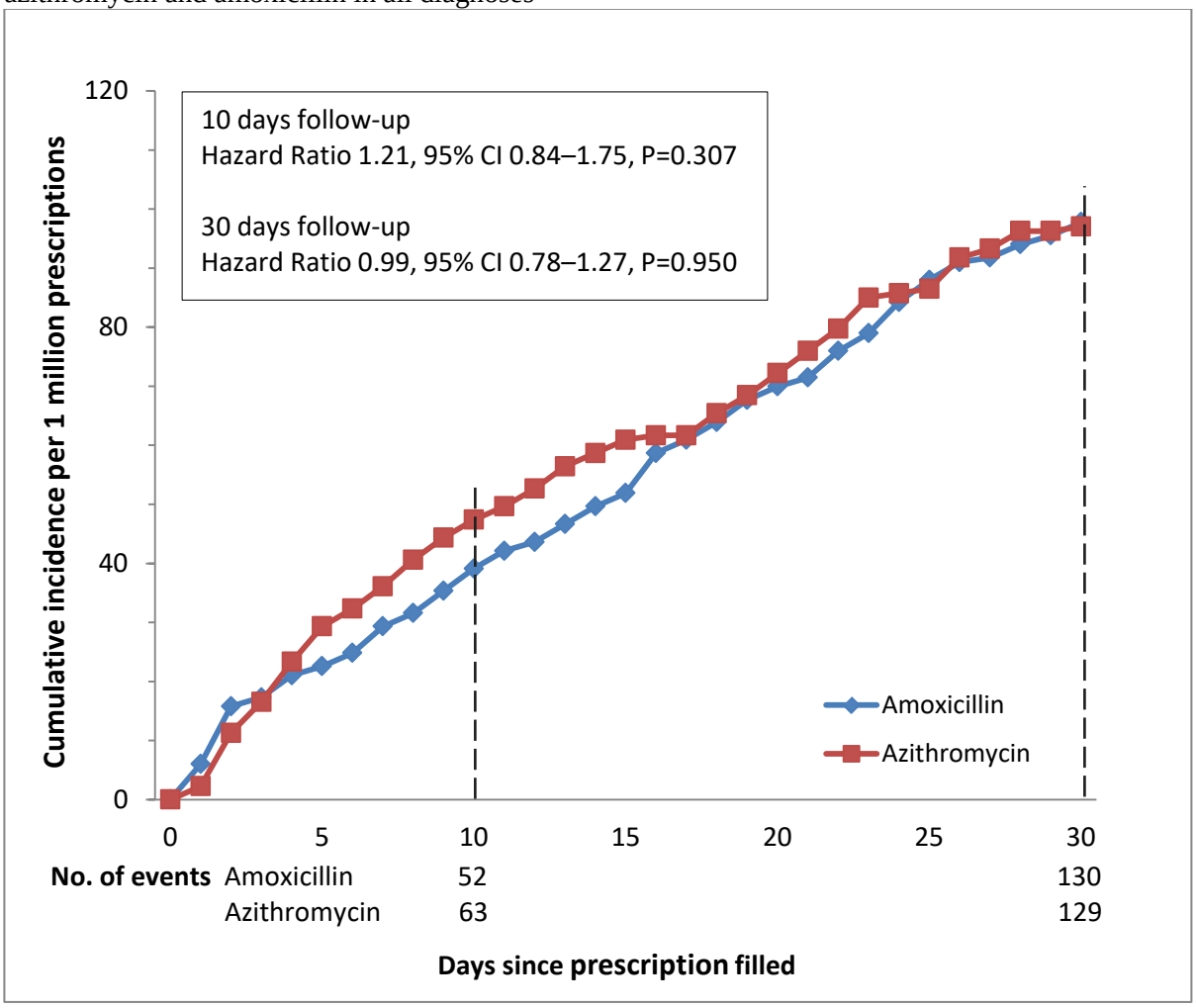
C-statistic: 0.602

Hosmer and Lemeshow Goodness-of-Fit (GOF) test: χ^2=167.4 (df = 8, p-value < 0.0001)

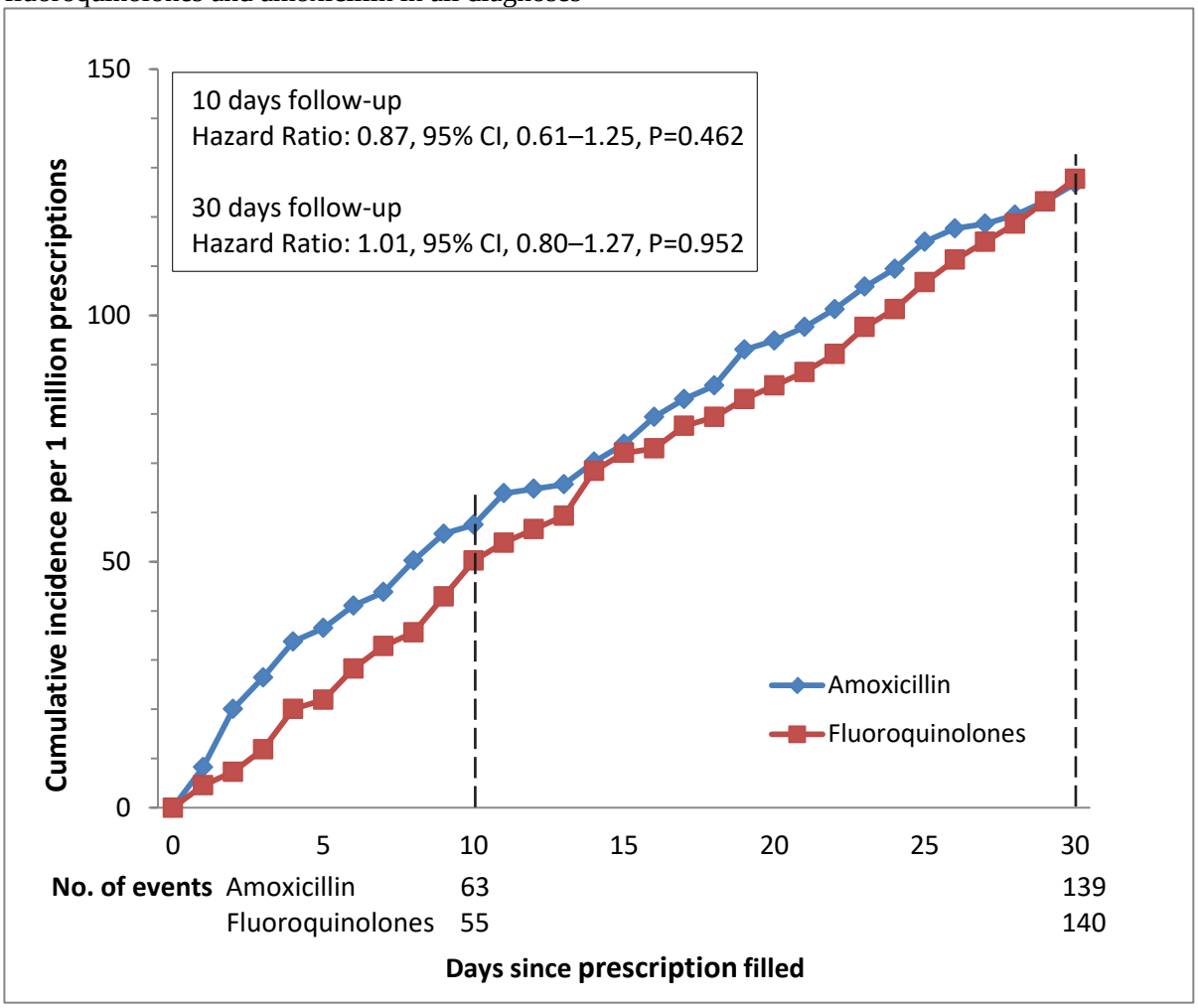
ABX = antibiotics, ACE = angiotensin converting enzyme, AMO = amoxicillin, COPD = chronic obstructive pulmonary disease, ED = emergency department, FLQ = fluoroquinolone antibiotics, GABA = gamma-amino butyric acid

Appendix F. Sensitivity analysis

Appendix Figure F.1 Cumulative incidence of ventricular arrhythmia and sudden death with azithromycin and amoxicillin in all diagnoses



Appendix Figure F.2 Cumulative incidence of ventricular arrhythmia and sudden death with fluoroquinolones and amoxicillin in all diagnoses



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