NON-INTERVENTIONAL (NI) STUDY REPORT

PASS information

Title	The Acute Effects of Azithromycin Use on Cardiovascular Mortality, as Compared With Amoxicillin
Protocol number	A0661209
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Active substance	Azithromycin (AZ): J01FA10 Reference product: Amoxicillin (AMX): J01CF05
Medicinal product	Azithromycin
Product reference	Appendix 12
Procedure number	EPITT Ref No 16156
Marketing Authorisation Holder (MAH)	Pfizer Limited

Joint PASS	No
Research question and objectives	Primary Objectives: The primary objectives were to estimate the relative and absolute risks of the following **adjudicated** outcomes for azithromycin users as compared to amoxicillin users, among persons aged 30-74 years old, within 5 days and within 6-10 days of dispensed prescription (Rx): 1. Cardiovascular (CV) death 2. Sudden cardiac death (SCD) Subgroup analyses: 3. CV death among those with prior CV disease 4. CV death among those with high baseline CV risk as defined by a CV risk score Secondary Objectives: The secondary objectives were to estimate the relative and absolute risk of the following outcomes for azithromycin users, as compared to amoxicillin users, among persons aged 30-74 years old; using **coded (not adjudicated)** outcome data. 1. Non-CV death and all-cause death, within 5 and within 6-10 days of dispensed prescription (Rx) 2. CV death within 365 days of Rx dispensed. Subgroup analyses: • Among those with prior CV disease • Among those with high baseline

	CV risk according to a CV risk score. • Among those with either diagnosed prior CV disease or with high baseline CV risk according to a CV risk score • Among those with chronic obstructive pulmonary disease (COPD) • Among those with community acquired pneumonia (CAP)
Country(-ies) of study	US
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Not applicable

1. ABSTRACT (STAND-ALONE DOCUMENT)

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
A-CVD	Adjudicated Cardiovascular Death Outcome
A-SCD	Adjudicated Sudden Cardiovascular Death Outcome
ACE	Angiotensin Converting Enzyme
ACS	Acute Coronary Syndrome
AIDS	Acquired Immune Deficiency Syndrome
ALOC	Altered Level of Consciousness
AM	Amoxicillin
ARB	Angiotensin Receptor Blocker
AZ	Azithromycin
BNP	B-type natriuretic peptide
C-CVD	Coded Cardiovascular Death Outcome
C-SCD	Coded Sudden Cardiac Death Outcome
CAD	Coronary artery disease
CAP	Community acquired pneumonia
CARDIA	Coronary Artery Risk Development in Young Adults
CHF	Congestive Heart Failure
CI	Confidence Intervals
CIOMS	Council for International Organizations of Medical Sciences
CK	Creatine Kinase
COD	Cause of Death
COPD	Chronic Obstructive Pulmonary Disease

CPT	Current Procedural Terminology
CT	Computed Tomography
CV	Cardiovascular
CVA	Cerebrovascular Accident
CVD	Cardiovascular Disease
CVRS	Cardiovascular Risk Score
DCT	Data Collection Tools
DOR	Division of Research
EAC	Events Adjudication Committee
e-CRF	Electronic Case Report Form
ED	Emergency Department
EKG	Electrocardiogram
EMA	European Medicines Agency
EMM	Effect Measure Modifiers
EMR	Electronic Medical Record
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FDA	Food and Drug Administration
GEP	Good Epidemiological Practice
GPP	Good Pharmacoepidemiology Practices
HF	Heart Failure
HH	Homonymous Hemianopia
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio

HX	History
ICD	International Classification of Diseases
ICH	Intracerebral Hemorrhage
IEA	International Epidemiological Association
IEC	Independent Ethics Committee
IOU	Indication of Use
IPH	Intraparenchymal Hemorrhage
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
JVD	Jugular Venous Distension
JVP	Jugular Venous Pressure
KASIS	Kaiser Permanente surgical procedures database
KP	Kaiser Permanente
KPNC	Kaiser Permanente Northern California
KPSC	Kaiser Permanente Southern California
MI	Myocardial Infarction
MRA	Magnetic Resonance Angiography
MRA	Medical Record Analysts
MRI	Magnetic Resonance Imaging
NLF	Nasolabial Fold
OR	Odds Ratio
ORSOS	Kaiser Permanente anesthesia database
PET	Positron Emission Tomography
PI	Principal Investigator

PIMS	Kaiser Permanente pharmacy database
PND	Paroxysmal Nocturnal Dyspnea
PPV	Positive Predictive Value
PS	Propensity Score
RD	Risk Difference
RX	Prescription
R&E	Research and Evaluation
QA	Quality Assurance
Rx	Prescription
SAH	Subarachnoid Hemorrhage
SAP	Statistical Analysis Plan
SCD	Sudden Cardiac Death
SD	Standard Deviation
SDH	Subdural Hemorrhage
SIEC	Serious Illness Exclusion Criterion
STD	Sexually Transmitted Disease
TIA	Transient Ischemic Attack
TRRS	Kaiser Permanente radiology database
U-CVD	Unclassifiable CV deaths
ULN	Upper Limit of Normal
VA	Veteran Affairs
VDW	Virtual Data Warehouse

3. INVESTIGATORS

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation
Jonathan Zaroff, MD	Principal Investigator	Kaiser Permanente Northern California (KPNC)
Niki Palmetto, PhD, MPH	Principal Investigator	Pfizer Inc.
Douglas Corley, MD PhD	Co-Investigator	KPNC Division of Research (DOR)
Charles Quesenberry, PhD	Co-Investigator	KPNC DOR
Craig Cheetham, PharmD MS	Co-Investigator	Kaiser Permanente of Southern California (KPSC)

4. OTHER RESPONSIBLE PARTIES

Responsible Party Name and Affiliation	Role in the study
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Lucy Almers, MPH KPNC DOR	Programmer Analyst
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Cecilia Portugal, MPH KPSC	Project Manager
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Anna Shuhua Liang, MS KPSC	Programmer Analyst
John Chang, MPH KPSC	Research Associate
Laura Sirikulvadhana, MPH KPSC	Research Associate

5. MILESTONES

Milestone	Planned date	Actual date	Comments
Date of Institutional Review Board (IRB) approval of protocol	14 MAY 2014	14 MAY 2014	None
Start of data collection	15 MAR 2015	01 May 2015	Due to delay in EU PAS registration (below)
End of data collection	30 JUN 2016	21 OCT 2016	Indication of use algorithm refinement
Registration in the EU PAS register	15 MAR 2015	16 APR 2015	Administrative time required for registration after protocol sign off on 19 March 2015
Final report of study results	30 NOV 2016	14 NOV 2018	Due to increased time required after data inconsistencies/ errors found, and post hoc analyses required. Agencies informed.

6. RATIONALE AND BACKGROUND

The purpose of this observational study was to examine the potential effects of azithromycin use on cardiovascular mortality. This observational study was preceded by seven recently published observational studies by Ray et al. (2012), [1] Svanstrom et al. (2013), [2] Rao et al. (2014), [3] Mortensen et al. (2014),[4] Chou et al. (2015), [5] Trifiro et al. (2017), [6] and Polgreen et al. (2018), [7] which examined this, or a related research question.

Ray et al. (2012) [1] examined the acute effects of azithromycin use on cardiovascular death within a Tennessee Medicaid population and found that within 5 and 10 days after the start of therapy, patients taking azithromycin had an increased risk of cardiovascular death as compared with those who took amoxicillin (Hazard Ratio (HR) 2.49; 95% CI: 1.38--4.50 and HR 1.87; 95% CI: 1.16--3.01, for 5 and 10 day analyses, respectively). It was estimated that there were 47 additional cardiovascular deaths per million prescriptions of azithromycin (when compared with amoxicillin), and 245 additional cardiovascular deaths per million

among patients in the highest decile of cardiovascular risk score. The risk of cardiovascular death during the 5 days of azithromycin therapy was also higher when compared with ciprofloxacin (considered to have minimal adverse electrophysiological effects) but did not differ significantly from that of levofloxacin (considered to have proarrhythmic effects). Ray et al. (2012) posited that the increased risk of cardiovascular death associated with azithromycin may be due to QT prolongation, resulting in ventricular arrhythmia and sudden cardiac death. The study conducted by Ray et al. (2012) had many methodological strengths, such as adequately powered analyses and stratification of effect by baseline cardiovascular (CV) risk (via a CV risk summary score) but lacked validation of CV deaths and contained missing indication of use (IOU) information for 30% of the population. This latter feature likely resulted in residual confounding by indication, whereby the underlying condition requiring antibiotic use, rather than the medication use itself, increases the risk of the outcome. In addition, the generalizability of the findings may be limited due to the unique clinical characteristics of the study population (Tennessee Medicaid recipients), a population with greater morbidity compared to the general US population.

Using a similar design to Ray et al. (2012),[1] Svanstrom et al. (2013)[2] examined the risk of cardiovascular death among patients taking azithromycin (compared to penicillin V) within a Danish general population sample and did not report an increased risk. When the risk of cardiovascular death was further examined among those with baseline cardiovascular disease (CVD), there was a trend toward an increased risk which was not statistically significant. Amoxicillin use was examined as an additional comparator group in a sensitivity analysis and yielded null findings. Strengths of the study included its population-based sample, stratification of CV death risk according to baseline CVD status, and multiple sensitivity analyses (examination of cardiac-specific deaths, propensity score matching, and an amoxicillin comparator group). However, investigators did not control for IOU or validate outcomes, and the analysis was likely underpowered to detect the small increase in risk found among those with prior CVD.

Rao et al. (2014)[3] conducted a retrospective cohort study among US veterans to examine the risk of all-cause death and serious arrhythmias, associated with azithromycin use within the first 5 days after drug dispensing (compared with amoxicillin), and reported an increased risk of both (HR 1.48; 95% CI 1.05--2.09, HR 1.77; 95% CI 1.20--2.62, respectively). Smaller effects which were not statistically significant were seen during the 6-10-day period. Similarly, among US veterans, Mortensen et al. (2014)[4] conducted a retrospective cohort study to examine the risk of CV and mortality outcomes associated with azithromycin use (compared to other antibiotic therapy use). Primary outcomes were 30-day and 90-day all-cause mortality, and cardiovascular events within 90 days of admission to a hospital. Those who received azithromycin had a lower 30-day mortality (OR 0.77, 95% CI 0.73--0.81) and 90-day mortality (OR 0.73, 95% CI 0.70--0.76), but increased odds of 90-day myocardial infarction (OR 1.17, 95% CI 1.08--1.25), compared to those not receiving azithromycin. Both the Rao et al.[3] and Mortensen et al.[4] studies, however, were potentially limited by residual confounding by indication of use (only 66% of patients had a recorded IOU in Rao et al.), and their lack of generalizability to the larger US population (nearly all VA patients are men, particularly of older age).

An observational study by Chou et al.[5] used data from the Taiwanese national health care system to compare the rates of ventricular arrhythmia and cardiovascular death after exposure to various macrolide and fluoroquinolone antibiotics in comparison to amoxicillin-clavulante and found that azithromycin was associated with both outcomes. An observational study by Trifiro et al. 2017[6] used a nested case-control design among new antibiotic users belonging to a network of 7 healthcare databases across Europe to examine the association between azithromycin use (compared with amoxicillin use) and risk of ventricular arrhythmia and reported no increased risk. Most recently, an observational study by Polgreen et al. 2018[7] investigated cardiac-related events after antibiotic exposure in a population of patients with acute myocardial infarction and reported no increased risk of any cardiac event or death after azithromycin exposure, after controlling for covariates.

The results from these studies are mixed (see table 1 below for summary of findings) and do not allow for a clear conclusion regarding the potential risk of cardiovascular death associated with the use of azithromycin.

Table 1. Summary of findings from prior studies examining the risk of cardiovascular outcomes associated with use of azithromycin

Author	Population	Primary Comparator	Exposure Window	Primary Outcome(s)	Main Results
Ray et al. 2012[1]	Medicaid	Amoxicillin	0-5 days, 6-10 days after dispensing	Cardiovascular death	CV death: HR 2.49 (95% CI: 1.38--4.50) CV death: RD 47 (95% CI not reported) deaths per million Rxs CV death among high baseline CV risk): RD 245 (95% CI 63--576) deaths per million Rxs
Svanstrom et al. 2013[2]	Danish general population	Penicillin V	0-5 days after dispensing	Cardiovascular death	CV death: RR 0.93 (95% CI 0.56--1.55) CV death among those with prior CV disease: RR 1.35 (95% CI 0.69--2.64)
Rao et al. 2014[3]	US veterans (Veteran Affairs database)	Amoxicillin	0-5 days, 6-10 days after dispensing	All cause death Serious arrhythmia	All cause death: HR 1.48 (95% CI 1.05--2.09) Serious arrhythmia: HR 1.77 (95% CI 1.20-- 2.62)

Mortensen et al. 2014[4]	US veterans (Veteran Affairs database), hospitalized with pneumonia	Guideline concordant antibiotics	30 days, and 90 days after dispensing	30-day mortality 90-day mortality 90-day MI 90-day Arrhythmia 90-day cardiac event	30-day mortality: OR 0.77 (95% CI 0.73--0.81) and 90-day mortality: OR 0.73 (95% CI 0.70--0.76) 90-day MI: OR 1.17 (95% CI, 1.08--1.25) 90-day arrhythmia: OR 0.99 (95% CI, 0.95--1.02) 90-day cardiac event: OR 1.01 (95% CI, 0.98--1.05)
Chou et al. 2015[5]	Taiwanese National Health Insurance Database	Amoxicillin-Clavulanate	7 days after dispensing	Ventricular arrhythmia Cardiovascular death	OR: 4.32 (95% CI, 2.95–6.33) OR: 2.62 (95% CI, 1.69–4.06)
Trifiro et al. 2017[6]	7 EU general populations	Amoxicillin	7 days after dispensing	Ventricular arrhythmia	OR: 0.90, 95% CI 0.48–1.71
Polgreen et al. 2018[7]	Medicare	No azithromycin exposure	7 days after dispensing	Death MI	OR 0.74 (95% CI 0.65-0.85 OR 1.10 (95% CI 0.91-1.33)

				Ventricular arrhythmia Atrial fibrillation or flutter	OR 1.13 (95%CI 0.92-1.40) 1.24 (95% CI 1.11-1.38)

Though no studies have reported long-term adverse cardiovascular effects associated with azithromycin use, 2 studies found long-term cardiovascular effects associated with clarithromycin, another macrolide.[8,9] Jespersen et al. 2005 conducted a randomized controlled trial (CLARICOR trial), which randomized patients with stable coronary heart disease to either a 2-week treatment of clarithromycin or placebo, and found an increased risk of CV mortality among those with clarithromycin treatment, 3 years post treatment (HR: 1.45, 95% CI 1.09--1.92).[9] Schembri et al. 2013 conducted 2 observational cohort analyses among patients hospitalized for chronic obstructive pulmonary disease (COPD) and community acquired pneumonia (CAP), treated with either clarithromycin or no macrolide during hospitalization.[8] Among those with COPD, clarithromycin was associated with an increased risk of CV mortality (HR: 1.52, 95% CI 1.02--2.26) 1 year post treatment. Among those with CAP, clarithromycin was not associated with increased CV mortality, however it was associated with an increased risk of CV events (acute coronary syndrome, cardiac failure, serious arrhythmia, or sudden cardiac death) (HR: 1.68; 95% CI 1.18--2.38).

An additional evaluation with sufficient power, adequate control of confounding, and the ability to adjudicate cardiovascular deaths, is required to further assess the potential cardiovascular signal. Qualitative and quantitative feasibility assessments determined the Kaiser Permanente (KP) database, both Northern California (KPNC) and Southern California (KPSC), to be an appropriate data source based on numerous strengths, including its comprehensive electronic medical record system (EMR), its large sample size, and its ability to link to death certificates. The Kaiser Permanente EMR system also allows for direct electronic capture of indication of use for a subset (approximately 1/3) of participants, as well as CV death adjudication using medical record review. Further, Kaiser's comprehensive EMR system allows for the capture, and therefore control of most clinical variables which may act as confounders.

This non-interventional study was designated as a Post-Authorization Safety Study (PASS) and was a Post-marketing Requirement of the FDA at the time of protocol submission. The sponsor also made a commitment to the EMA to provide further data on the possible association of azithromycin use with cardiovascular death, which included submission of this voluntary PASS protocol (A0661209).

7. RESEARCH QUESTION AND OBJECTIVES

Primary Objectives:

The primary objectives were to estimate the relative and absolute risk of the following **adjudicated** outcomes for azithromycin users as compared to amoxicillin users, among persons aged 30-74 years old, within 5 days and within 6-10 days of dispensed prescription (Rx):

1. Cardiovascular (CV) death
2. Sudden cardiac death (SCD)

Subgroup analyses:

3. CV death among those with a diagnosis of prior CV disease

4. CV death among those with high baseline CV risk as defined by a CV risk score

Secondary Objectives:

The secondary objectives were to estimate the relative and absolute risk of the following outcomes for azithromycin users, as compared to amoxicillin users, among persons aged 30-74 years old; **coded (not adjudicated)** outcome data were used for these analyses[1]:

1. Non-CV death and all-cause death, within 5 and within 6-10 days of dispensed prescription (Rx)

2. CV death within 365 days of Rx dispensed.

   Subgroup analyses:

   - Among those with prior CV disease
   - Among those with high baseline CV risk according to a CV risk score
   - Among those with prior CV disease or with high baseline CV risk according to a CV risk score
   - Among those with chronic obstructive pulmonary disease (COPD)
   - Among those with community acquired pneumonia (CAP)

8. AMENDMENTS AND UPDATES

Not applicable (there were no amendments to the Protocol)

9. RESEARCH METHODS

Please see Appendix 2. Protocol for additional details

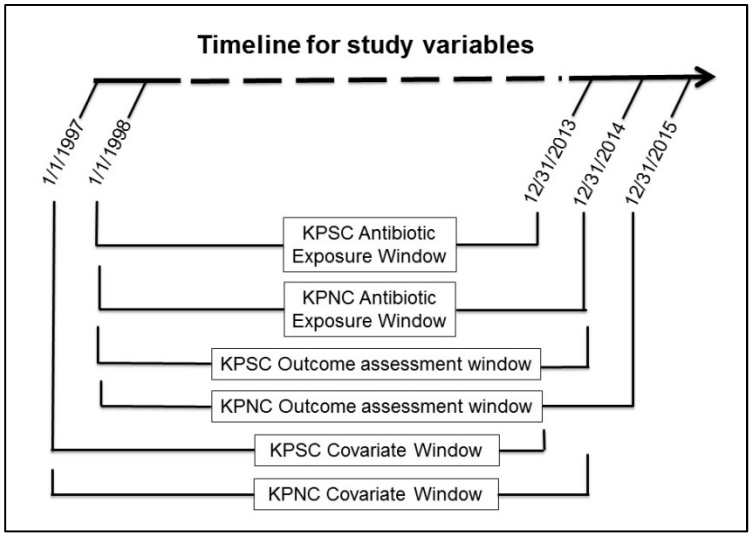
9.1. Study design

This study employed a retrospective cohort design to examine the effects of azithromycin on cardiovascular and sudden cardiac death (primary endpoints), as compared to amoxicillin, both within a general population of azithromycin users, and within a subset with high baseline CV risk. The secondary endpoints include non-cardiovascular mortality and all-cause mortality. This retrospective study design provided the ability to obtain the large

[1] Individual secondary objective analyses which merit further investigation will be adjudicated. These analyses will be submitted to regulatory authorities (FDA/PRAC), according to a later, agreed upon timeframe.

sample size needed (given the rarity of the outcome) in a timely manner. The temporal relationships between the study's exposure variable, outcomes, and covariates is shown in the schematic below (Figure 1).

Figure 1: Timeline for study variables



9.2. Setting

This study was conducted among KPNC and KPSC enrollees.

KPNC is a group practice integrated health program with approximately 4.1 million members annually; this represents about 30% of the insured population in 14 Northern California counties encompassing the greater San Francisco Bay Area and the upper central valley of California. Members receive almost all their care at KPNC facilities and inpatient and outpatient visits, and their corresponding diagnoses can be identified electronically. The membership's demographics closely resemble the underlying census population of Northern California.[10]

Kaiser Permanente Southern California (KPSC) is a nonprofit, integrated healthcare delivery system with a membership of over 4.2 million people in Southern California. KPSC provides integrated, comprehensive medical services through its own facilities, which includes 14 hospitals, 200 outpatient facilities and a centralized laboratory. All aspects of care and interaction with the healthcare delivery system are captured in a continuously updated research database. The KPSC membership represents an insured population that is racially and socio-economically diverse. Overall the demographic makeup of the KPSC membership closely mirrors the underlying population of Southern California.[11]

KPSC and KPNC are separate financial entities which share administrative practices (such as the EMR). The combined Kaiser Permanente California population possesses several advantageous qualities for pharmacoepidemiology studies. Kaiser Permanente's electronic information systems allow researchers to track patient enrollment, diagnoses, procedures, and prescriptions dispensed at Kaiser Permanente pharmacies. KPNC has a well-established

research unit, the Division of Research (DOR), with approximately 500 personnel, including research scientists/investigators, programmers, data analysts, and medical record analysts; this infrastructure permits the use of KPNC's electronic resources for research. KPSC's Department of Research and Evaluation (20 research scientists and 300 personnel) provides similar services to the DOR.

The study was conducted among Kaiser Permanente members who received azithromycin and amoxicillin prescriptions during the period of 1998–2014 for KPNC and1998-2013 for KPSC. The start date of 1998 was chosen based on availability of electronic KP medical record data, and to allow for exclusion criteria 3 (see exclusion criteria, below), which requires participants to have been enrolled in KP healthcare for at least 1 year prior to the index prescription date. The end dates of 2013-2014 were chosen based on the most recent cause-of-death information available in the California State Death Registry.

9.3. Subjects

9.3.1. Inclusion criteria

Patients must have met the following inclusion criteria to be eligible for the study:

Inclusion Criteria:

1. Dispensing of an outpatient prescription for azithromycin or amoxicillin between 01 January 1998 and 31 December 2014 (31 December 2013 at KPSC). If a patient had more than one prescription within this period, each exposure was counted separately (thus, individuals may have contributed multiple prescriptions to the analysis. For details regarding repeat exposures see Section 8.9.2.2).

2. Only oral prescriptions were included (not intravenous or ophthalmic) and amoxicillin-clavulanate prescriptions were also included in the amoxicillin group, consistent with the methodology of Ray and Svanstrom.[1,2]

9.3.2. Exclusion criteria

Patients meeting any of the following criteria were not included in the study:

Exclusion Criteria:

1. Missing date of birth or gender.

2. Age < 30 or >74 years on the index date (the date of the antibiotic prescription dispensing).

3. Not enrolled at KPNC or KPSC during the 365 days prior to the index date (allowing gaps of < 60 days). This criterion ensures capture of potential confounders and effect modifiers.

4. Any gap in prescription benefits coverage greater than 60 days during the 365 days prior to the index date, unless there was evidence of a filled prescription during that

period. This criterion ensures opportunities for capturing exposures to the medications of interest, as well as confounders and effect measure modifiers.

5. More than one type of study antibiotic prescribed on the index date or within the 10 days prior to the index date (i.e., wash-out period). The detailed methodology regarding repeat exposures is described in Section 8.9.2.2.

6. Hospitalization within 30 days prior to the index date. This criterion considers that medication changes and medications administered during hospital stays may not be captured.

7. Residing in a nursing home or other residential institution on the index date or at any time in the preceding 365 days, except for stays of <30 days following hospital discharge. This includes inferred nursing home stays, defined as 2 or more outpatient encounters in the year leading up the index prescription date with procedure codes indicating nursing home place of service separated by at least 28 days. It also includes external cause of injury diagnosis code indicating place of residence was an institution. This criterion considers that the cause of death information recorded on death certificates within a nursing home setting may be less accurate.

8. *Serious Illness Exclusion Criterion (SIEC): This was applied only to post-hoc analyses using the modified cohort (see section 9.3.3 below). The SIEC was developed using Ray's methodology and designed to exclude records of patients with diseases associated with a high risk of non-cardiovascular death. See Appendix 10 for details regarding the SIEC methodology.

9.3.3. Modified Cohort

Ray et al. (2012)[1] excluded all serious underlying illnesses, a possible source of confounding, from their study cohort. This exclusion criterion had not been replicated in the current study, per the protocol. For these reasons, post hoc analyses were designed for the present study to similarly exclude people with an underlying serious illness, and subsequently labeled the '*modified cohort.*' In addition, the *modified cohort* analyses censored prescriptions at the time of hospitalization of a patient. Censoring upon hospitalization was also done by Ray et al. (2012),[1] based on the belief that hospital deaths were likely related to non-cardiac conditions which led to the hospitalization, even if it was coded as a CV death on the death certificate. *Thus, the present study's post hoc analyses used a modified cohort which added a serious illness exclusion criterion to the study population and censored prescriptions associated with a hospitalization within 10 days of the prescription.*

9.4. Variables

9.4.1. Exposure definition

Any outpatient oral prescriptions for azithromycin or amoxicillin between 01 January 1998 and 31 December 2014 (31 December 2013 for KPSC), as described under "inclusion criteria"

9.4.2. Outcome definitions

The following outcomes were examined in this study:

1. (adjudicated, see definition below) cardiovascular death (*primary endpoint*)
2. (adjudicated) sudden cardiac death (*primary endpoint*)

3. (coded) all-cause death (*secondary endpoint*)
4. (coded) non-cardiovascular death (*secondary endpoint*)

5. (coded) cardiac death (*sensitivity analysis only*)
6. (coded) cardiovascular death (*sensitivity and post hoc analyses only*)
7. (coded) sudden cardiac death (*post hoc analyses only*)

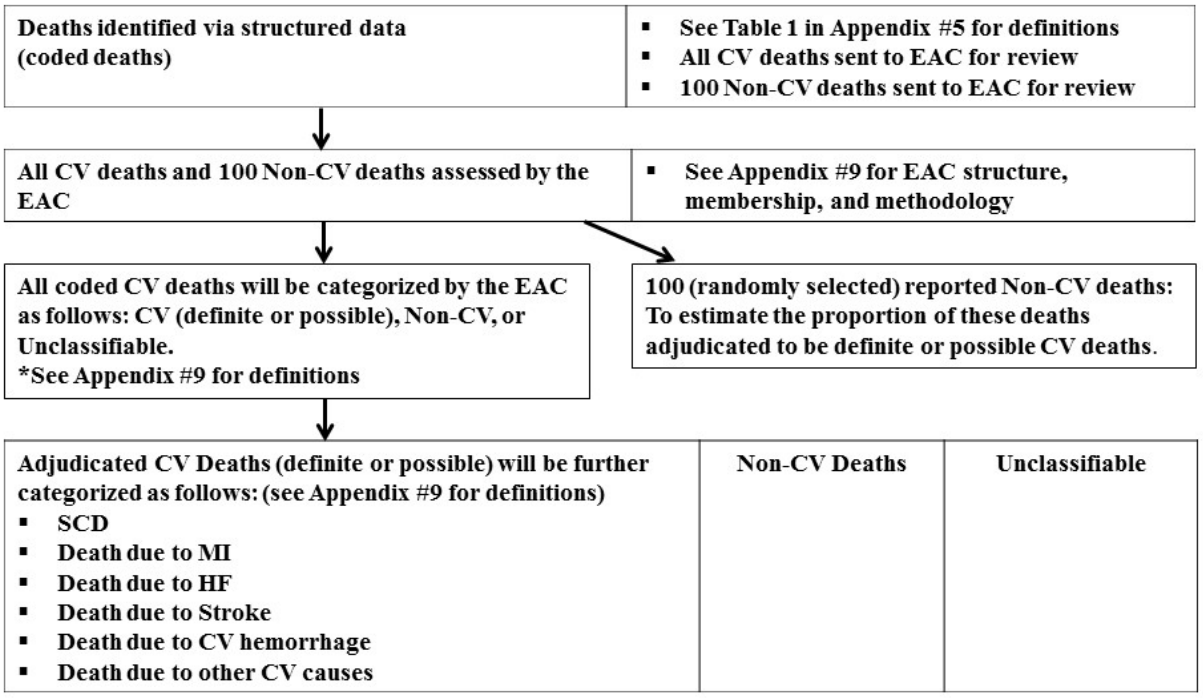
Coded outcomes were identified via structured data only. All coded cardiovascular deaths were initially identified using death certificate data. The subset of SCD outcomes were then identified through algorithms using ICD9/10 diagnostic and procedure codes, and other data obtained from Kaiser Permanente research databases (see Appendix 5 pp. 1-2 for outcome variable database programming definitions and database sources). In many cases, the databases were queried for both ICD9 codes and ICD10 codes to maximize sensitivity. In the KP databases, cause of death codes include both ICD9 and ICD10 (available starting in 2015) codes whereas non-fatal inpatient and outpatient encounters use only ICD9 codes.

Adjudicated outcomes are outcomes which after being identified as coded outcomes (see above) were manually adjudicated and confirmed using medical record review (see Appendix 9 for adjudication process details). Briefly, information regarding all coded CV deaths was summarized from the medical records by data abstractors (see Appendix 4 Table 1 for data collection form). These summarized data abstractions were then reviewed by the Events Adjudication Committee (EAC), comprised of KPNC Cardiologist reviewers who were blinded to antibiotic exposure status. The reviewers assigned a confirmed cause of death category in each case: CV (SCD), CV (non-SCD, subtype listed), non-CV, or unclassifiable. Any confirmed deaths with insufficient information in medical charts to determine cause of death, were categorized as unclassifiable (but remained in the all-cause mortality analyses).

- Primary analyses included only deaths adjudicated to be definitely or possibly CV in nature.
- Secondary analyses included all coded (not adjudicated) endpoints.
    - The non-CV death (secondary endpoint) analyses were conducted using coded outcomes, however a sample of 100 non-CV deaths also underwent adjudication to gain insight into the validity of the coded non-CV death outcome, and the potential misclassification of some CV deaths as non-CV deaths.

The process of death outcome determination is summarized in Figure 2, below.

Figure 2. Overview of death outcome determination and adjudication methodology



CV: cardiovascular
EAC: Event Adjudication Committee
SCD: sudden cardiac death
MI: myocardial infarction
HF: heart failure

9.4.3. Effect Measure Modifiers

Based on findings from prior studies such as Ray et al. (2012)[1] and Svanstrom et al.[2] the following subgroups were examined for the risk of cardiovascular death within 5 days, within 6-10 days, and within 365 days of azithromycin dispensing, compared to amoxicillin use: 1) prior CV disease and 2) baseline CV risk as defined by a CV risk score (CVRS). Also, based on findings from prior studies, the following subgroups were examined for the risk of cardiovascular death within 365 days of azithromycin dispensing, compared to amoxicillin use: 1) COPD and 2) CAP.[8,9]

9.4.3.1. Prior CV Disease

Individuals with prior CV disease were defined by an in- or outpatient encounter with an appropriate diagnostic code (see Appendix 6, pp. 1-3) within one year prior to the index date for each antibiotic prescription (t_0). This included emergency department encounters and non-acute institutional stay encounters but excluded telephone and email encounters. In the KP databases relevant to this study period, inpatient and outpatient encounters use only ICD9 codes. These codes have been used and validated in previous KP publications.[12-24]

9.4.3.2. High Baseline CV Risk according to CV Risk Score (CVRS)

Index prescriptions among individuals with a high baseline CV risk were defined by constructing a CV risk score (CVRS), which statistically summarizes the effects of numerous CV variables using the validated methodology of Arbogast, Ray and others.[1,25,26] Ray et al. (2012) constructed their CVRS in a primary comparator group of non-users of antibiotics, whereas the current study constructed the CVRS among its primary comparator group of amoxicillin users.

The CVRS regression model included all CV disease diagnoses (Appendix 6, pp.1-3), as well as additional elements (Appendix 6, pp.3-6), including various CV medications. Only oral forms of medication were included, except for nitroglycerin and insulin. CV emergency room visits and current smoking status were also included. As was the case with Ray's methodology, risk factors for heart disease such as hypertension, hyperlipidemia, and diabetes mellitus were not included in the CVRS but were included as covariates in the propensity score models.

Logistic regression was used to assess 10-day risk of coded cardiovascular death in relation to the list of CV risk factors (Appendix 6, pp. 1-6) and conducted using all study-eligible amoxicillin exposure periods. The resulting estimated regression coefficients were used to calculate a risk score for each eligible exposure (azithromycin and amoxicillin prescriptions), consisting of the sum of each regression coefficient multiplied by the associated covariate value (0 vs 1, with the exception of age [continuous]) assessed on the prescription fill date. As in Ray et al. 2012,[1] deciles of CVRS were formed, and all study-eligible exposures were assigned a risk category: low (CVRS deciles 1-5), medium (CVRS deciles 6-9), and high CV risk (CVRS decile 10). The high CV risk group (CVRS decile 10) was a subgroup of interest for the primary objective. Individuals could contribute more than 1 index prescription to the analysis (see Section 9.3.1) and a CVRS was calculated at the outset of each exposure period. See Appendix 6 for further details regarding the CVRS methodology.

In a sensitivity analysis, the high CV risk group was defined as patients who had a CV mortality rate of approximately 160 per million azithromycin exposures as a cutoff point, to approximate the CV risk of the top decile in the study by Ray et al. (2012).[1]

9.4.3.3. Individuals with COPD and Pneumonia

The study's secondary objectives included an analysis of CV death in the subgroups of patients with a history of chronic obstructive pulmonary disease (COPD) and pneumonia These conditions were defined by ICD9 codes (below) during an inpatient or outpatient encounter within one year prior to the index date for each antibiotic prescription (t_0).

Table 2. Coding definitions for COPD and Pneumonia

Variable	Role	Data Source	Operational definition
COPD	EMM	KPNC/KPSC VDW (Virtual Data	ICD9 codes: 491.xx -492.xx, 494.xx, or 496.xx

Variable	Role	Data Source	Operational definition
		Warehouse) diagnosis database	
Pneumonia	EMM	KPNC/KPSC VDW diagnosis databases	ICD9 codes: 480.xx - 488.xx, 500.xx- 508.xx, 510.xx - 511.xx, 513.xx, 515.xx, 010.xx - 012.xx, 073.xx, 517.1x

9.4.4. Covariates

Given the large number (> 100) of potential confounders, propensity scores were used for covariate adjustment. The propensity score models included basic demographics (age, gender, race/ethnicity, geographic service area), all variables included in the CV risk score, other medical conditions (e.g., respiratory, neurologic, and psychiatric conditions) and prescriptions, health care utilization variables (e.g. number of CV-related office visits), and the indication for antibiotic use (see section 9.5.1 and Appendix 8 for details). The detailed definition for each covariate included in the propensity score models can be found in Appendix 3 (Statistical Analysis Plan, pp.18-32). In brief, the covariates used by Ray et al. 2012[1] were used with minor differences when specific covariates (as defined by Ray) were not available in the KP databases. The present study added additional medications known to prolong the QT interval as covariates (see Appendix 3, pp. 31-32) because QT prolongation is associated with sudden cardiac death.

9.5. Data sources and measurement

This retrospective cohort study linked data from several KPNC and KPSC databases using medical record numbers. Azithromycin and amoxicillin prescriptions were captured in the pharmacy databases. This database captures filled prescriptions, medication quantities, and directions for use.

All coded outcome definitions and data sources can be found in Appendix 5. The measurement and capture of CV outcomes is well established in the KP EMR system. Studies conducted within the KP EMR system have previously used chart review to validate database programming codes for a broad range of cardiovascular disease variables, including myocardial infarction/unstable angina, congestive heart failure, hypertension, stroke, ventricular arrhythmias, and cardiovascular death.[10,12,13,16,20,22,23] Previous KP studies have explored associations between medication exposures and adverse CV outcomes, including myocardial infarction and sudden cardiac death.[14,21,26-30] The PI of this current study also completed a study with Pfizer which quantified rates of CV events in the KPNC cancer population. That study included chart review validation of over 1,000 CV events and provided validation estimates for acute coronary syndrome (87% Positive Predictive Value [PPV]), congestive heart failure (PPV 91%), and cardiac arrest/ventricular arrhythmia (PPV 70%).[31]

The capture of covariates comes from the KP virtual data warehouse (VDW) database, a resource with standardized data definitions for associated diagnoses, and similar details in the medical record. The specific variables are discussed in more detail in the section on confounding and bias.

9.5.1. Antibiotic Indication Assessments

An important limitation of prior related studies was partial or fully missing data on indications for antibiotic use, possibly resulting in residual confounding.[1-4]

Starting in 2008, medications prescribed within the KP electronic medical record (EMR) system could be directly linked to a single diagnosis code, allowing for direct capture of indication of use (IOU). Given that direct assignment of IOU to prescriptions was not consistently used by prescribers until 2009, analyses that were intended to evaluate results in the "direct link" era of the study period, examined data from 2009 and beyond. Prior to 2008, this direct linkage was not available. In this study, for prescriptions written prior to 2008, medical visit diagnostic codes available in the research databases were temporally linked to the antibiotic prescriptions (obtained from the pharmacy databases) by medical record numbers and date ranges (see below), thus allowing for an indirect ascertainment of IOU (as was used by Ray et al. 2012).[1]

Antibiotic prescriptions with a directly-linked or indirectly-linked infection diagnosis were categorized as having that specific type of infection as the IOU. Prophylactic antibiotic prescriptions were considered as two separate categories. The term "immediate prophylaxis" describes a prescription that was to be started immediately on dispensing to prevent an infection from developing. An example would be the routine use of antibiotics before or after an elective surgery to prevent a wound infection from developing. The term "delayed prophylaxis" describes a prescription that is to be started at an unknown future date, or possibly never, after dispensing to prevent or treat infection. One example is dispensing of azithromycin to someone at risk of developing traveler's diarrhea (which may or may not happen), who will use the drug only if needed. Another example of delayed prophylaxis is dispensing of amoxicillin for future use before dental cleanings to prevent endocarditis. If there was no infection or prophylaxis code associated with the prescription, the IOU was categorized as missing. The detailed methodology for the IOU algorithm and the summarized validation results are described in Appendix 8.

9.5.2. Cardiovascular Death Adjudication

All primary objective endpoints were adjudicated by cardiologists according to the *a priori* specifications documented in the Event Adjudication Committee (EAC) Charter (Appendix 9). In brief, data abstractors reviewed the charts of all coded CV death cases and a random sample of coded non-CV death cases (N=100), and then collected anonymized data that were relevant in determining the cause of death. See Appendix 4 for the data collection tool used by the data abstractors. A panel of cardiologists, blinded to the antibiotic type, then reviewed the anonymized, abstracted information to determine the cause of death (according to chart information). CV deaths were categorized as "definite CV deaths", "possible CV deaths", "non-CV deaths", or "unclassifiable." Only those deaths which were considered confirmed CV deaths (definite or possible CV deaths) by the EAC were included in the study's primary

analysis. See Appendix 9 for the detailed methodology used for death adjudication in this study.

9.6. Bias

Given the observational study design, several potential sources of bias and confounding were anticipated, including confounding (by indication, infection severity, channeling, or other clinical and demographic characteristics) and misclassification (outcome and exposure).

Confounding could occur if azithromycin and amoxicillin are prescribed for different populations of patients with respect to characteristics which are also independent risk factors for cardiovascular death. To address this, the present study controlled for a multitude of potential risk factors for CV death which may be unevenly distributed across exposure groups, including demographics, comorbidities, other medications, and health care utilization variables, using propensity scores (see sections 9.4.4 and 9.5.1).

One of these sources of confounding is 'confounding by indication,' whereby patients are more likely to be prescribed one antibiotic over the other, based on their indication, is of concern in this study. This could occur if both: 1) azithromycin and amoxicillin are used for different types of infections (i.e. there is an imbalance of certain types of infections across study antibiotic group) and 2) these types of infections which are imbalanced across study antibiotic group, also increase the risk of adverse cardiovascular events. To address this, a comparator group (amoxicillin) was chosen to most closely match azithromycin with regards to indication of use (IOU). Considerable attention was then paid to obtaining IOU information in a comprehensive and valid way, using chart review and iterative algorithm refinement (Appendix 8). This IOU variable was also included in the propensity score. However, despite these efforts to capture IOU information, some missing data persisted, and a degree of IOU misclassification was identified (Appendix 8). Two sensitivity analyses were planned to evaluate the potential effects of missing and misclassified IOU data. One sensitivity analysis restricted the primary analysis to the time period 2009-2014, when a direct link IOU was available in the KP EMR and thus missing IOU and misclassification were expected to be lower. An additional sensitivity analysis restricted the primary analysis to prescription records with an infection IOU, excluding prescriptions with a prophylaxis or missing IOU. This analysis attempted to assess if the missing data was associated with antibiotic choice and/or outcome, by including records with the likely highest validity, that is, records associated with an infection category.

Confounding by indication *severity* may have also occurred, if, even within infection type, patients were more likely to be prescribed one drug over the other for a more severe infection, and infection severity was associated with CV risk (i.e. if a more severe form of a given infection confers additional risk of CV death, compared to a milder form of the same infection). For example, the diagnosis of pneumonia (itself, a risk factor for CV death) includes a broad spectrum of severity, ranging from very mild to life threatening, with the latter conferring a higher risk of CV death than the former. If one study antibiotic was more likely to be prescribed to the more severe cases of pneumonia, this type of confounding could not be controlled for by simply controlling for indication of use. While direct control of IOU severity was not feasible, the extensive number of covariates included in the propensity score likely controlled for some factors associated with infection severity. For example, age and

renal failure are both covariates in the propensity score and are likely associated with greater infection severity. In addition, this study included a sensitivity analysis which attempted to assess this potential confounding by indication severity by examining health care utilization (emergency room and hospital visits as a proxy for high severity indications) in the 10-day window after the index date under the assumption that infections followed by emergency room or hospital visits are more severe.

Two forms of potential misclassification (i.e. measurement) bias were considered. Outcome misclassification may have occurred due to the known unreliability of death certificate coding, particularly for cardiovascular causes. This was addressed by cardiovascular death adjudication with professional data abstractors and cardiologist reviewers blinded to one another's assessment and to the type of study antibiotic exposure. Lastly, misclassification of study antibiotic use may have occurred in this study. Exposure to azithromycin or amoxicillin was ascertained via prescription dispensing records, which may not always result in the patient taking the medication, or taking it when, and as prescribed. While this potential bias is common to pharmacoepidemiology studies, it was of particular concern for this study, given that the medication of interest can be prescribed prophylactically, and therefore sometimes was not intended to be taken on the day of dispensation. The investigators performed a sensitivity analysis which attempted to exclude prophylactic prescriptions to help mitigate this potential bias.

9.7. Study Size

Minimum detectable risk differences and hazard ratios, with 80% and 90% power for detecting both adjudicated CV death and coded CV outcomes, are presented below in Tables 3 and 4, and compared to reported results from Ray et al. (2012).[1]

Based on the literature, a loss of approximately 20-50% of the cardiovascular deaths due to the adjudication process was expected (either CV deaths adjudicated to be non-cardiovascular deaths, or CV deaths with insufficient information to adjudicate).[31-33] However, during the death adjudication process, it was discovered that medical records from KPSC prior to 2007 had been largely destroyed, which increased the unclassifiable rate and decreased the number of charts available for adjudication.

Table 3. Minimum detectable Hazard Ratios based on 80% Power, compared to results reported in Ray et al. 2012[1]

	Coded CV death (C-CVD)	Adjudicated CV death (A-CVD)	Ray et al. 2012 results (C-CVD)
Amoxicillin Prescriptions	6,525,463	6,525,463	1,348,672
Azithromycin Prescriptions	1,922,425	1,922,425	347,795
Amoxicillin CV Mortality (#) Day 0-5	139	37	42
Amoxicillin CV Mortality Incidence* Day 0-5	21.40	5.70	31.5

Minimum HR detectable with **80% Power**	1.58	2.26	2.49
Minimum HR detectable with **90% Power**	1.67	2.48	2.49

*per 1,000,000 prescriptions

Table 4: Minimum detectable Hazard Ratios and Risk differences based on 80% and 90% Power, among the high CV risk subgroup‡, compared to results reported in Ray et al. 2012[1]

	Coded CV death (C-CVD)	Adjudicated CV death (A-CVD)	Ray et al. 2012 results
Amoxicillin Prescriptions	658,631	658,631	NR
Azithromycin Prescriptions	186,157	186,157	32,547
CV risk score in azithromycin users (mean)	18.5	18.5	18.5
CV risk score in amox users (mean)	18.5	18.5	NR
Amoxicillin CV Mortality (#) Day 0-5	101	29	NR
Amoxicillin CV Mortality Incidence* Day 0-5	154.20	44.28	165 †
Minimum HR detectable with **80% Power**	1.71	2.50	NR
Minimum Risk Difference detectable with **80% Power**	103	61	245 (63-576)
Minimum HR detectable with **90% Power**	1.83	2.76	NR
Minimum Risk Difference detectable with **90% Power**	123	65	245 (63-576)

NR = Not reported by Ray et al. 2012[1]
* Per 1,000,000 prescriptions
† Visually approximated from Figure 3 in Ray et al. 2012[1]
‡The CVRS was modified for the final analysis, resulting in slightly different sub-population sizes and outcome counts.

9.8. Data transformation

Detailed methodology for data transformations, particularly the two complex transformations (e.g., where many raw variables were used to derive an analytic variable), are documented in the Statistical Analysis Plan (SAP), which is dated, filed and maintained by the sponsor (Appendix 3). The first major transformation involved the CV risk score, which summarizes the effects of multiple CV risk factors to estimate a summary CV risk score associated with each eligible prescription record (see Appendix 6 for details). The second major transformation involved the propensity score, which summarizes the effects of many covariates (> 100) within the study's regression models (see section 9.10.2).

9.9. Statistical methods

Detailed methodology for summary and statistical analyses of data collected in this study are documented in the SAP (Appendix 3).

9.9.1. Main summary measures

The study's main results were presented as cumulative incidence proportions (e.g. of CV death) per 1,000,000 prescriptions, adjusted risk differences (ARD), and adjusted hazard ratios (HR) with 95% confidence intervals.

9.9.2. Main statistical methods

Cox proportional hazards regression was used to address the primary and secondary objectives, providing hazard ratios for azithromycin vs. amoxicillin in relation to study outcomes, adjusted for potential confounders. The regression analysis allowed for evaluation of heterogeneity in association between exposures and study endpoints over time, using time-dependent covariates (i.e. exposure by time interaction terms) to estimate hazard ratios separately within each of the time intervals: 0-5 days, 6-10 days, and 11-365 days (365-day end of follow-up for secondary outcome of un-adjudicated cardiovascular death, only [secondary objective]).

Unadjusted cumulative incidence, for days 0-5 and 6-10, was calculated by means of the product limit estimator.

Using the same approach as Ray et al (2012),[1] covariate-adjusted estimates of the adjusted difference in risk between azithromycin and amoxicillin for time intervals of interest were calculated as $(HR_a - 1) \times I_0$ where HR_a is the adjusted hazard ratio for azithromycin vs. amoxicillin, and I_0 is the unadjusted cumulative incidence among amoxicillin users.

9.9.2.1. Censoring

All analyses censored follow-up after a study-eligible prescription fill date at the earliest date of:

a. Outpatient dispensing of a subsequent study antibiotic
b. Date of inpatient study antibiotic fill, for hospital admission within days 1-10, for adjudicated cardiovascular deaths only (only these cases used chart review and could thus identify the inpatient prescriptions, see SAP Appendix 3, Section 8.1.C)
c. ≥ 60-day gap in prescription coverage

d. Nursing home admission
e. Termination of health plan membership
f. Death due to cause other than that for analysis objective (e.g. censoring due to non-cardiovascular death in the primary analysis of cardiovascular death)
g. End of risk interval of interest: 10 days for Primary Objectives and Secondary Objective 1, and 365 days for Secondary Objective 2.
h. End of study follow-up: (12/31/2014 (KPSC) and 12/31/2015 (KPNC), due to differential availability of the State of California death certificate file to the two healthcare systems.
i. *Upon entering the hospital. This censoring criterion was applied for sensitivity analysis #12 and all analyses conducted in the modified cohort (see section 8.3.3 above).

9.9.2.2. Repeat Antibiotic Exposures

Azithromycin and amoxicillin exposures occurring within 10 days after a prior exposure to a study eligible antibiotic prescription fill were excluded from the analysis per exclusion criterion #5 (Section 9.3.2), and event follow-up for the first exposure was censored at the date of the second prescription fill. Preliminary data from KP indicated that the number of repeat study antibiotic prescriptions within 10 days of any index prescription was very small.

Since antibiotic prescriptions ordered during hospitalizations and nursing home stays are often not available in the KP databases, this study censors upon nursing home admission, and includes a sensitivity analysis and modified cohort analyses which also censor prescriptions upon hospitalization. Additionally, if a patient had a cardiovascular death during hospitalization within 10 days of an index antibiotic exposure, the study's chart review process was designed to identify repeat study antibiotic prescription during the hospitalization and, if within 10 days of the index prescription, the censoring rule per exclusion criterion #5 would be applied and the death would be excluded from the analysis.

For each eligible study antibiotic exposure, the number of previous study exposures (dichotomized as: 0 or ≥1) was treated as a potential confounder in the propensity score (PS) models. The robust sandwich variance estimator for the Cox regression model was used to account for the effect of having multiple exposures per patient and address the violation of the assumption of independence between observations. The distribution of per-person number of study antibiotics during the study interval was reported, overall and for each study antibiotic.

9.9.2.3. Cox proportional hazards regression model

The regression analysis allowed for heterogeneity in association between exposures and study endpoints over time (e.g., 0–5 days vs. 6–10 days). See additional details in section 9.9.2.

9.9.2.4. Confounder control methods

Given the large number of potential confounders, propensity scores were used. Variables for inclusion in the propensity score logistic regression models were determined a priori, and included those covariates hypothesized to be associated with study exposures and outcomes, and not mediating the potential effects of interest (see Appendix 3 pp. 18-32 and Appendix 7 for propensity score variables and coefficients). For the primary analysis, PS deciles were included in the regression models for PS control. Standard approaches to covariate balance diagnostics were used to assess adequacy of the propensity score model specification (see Appendix 7 for propensity score diagnostics).

9.9.2.5. CVRS development

The summary CVRS was generated using methodology similar to that used by Arbogast, and Ray and others.[1,25] Some risk score elements were not explicitly defined using ICD codes by Ray et al. (2012), and therefore as a result, the ICD codes implemented may differ slightly in the present study.

Logistic regression was used to assess 10-day risk of coded CV death in relation to the component CVD diagnoses with analysis conducted using all study-eligible amoxicillin exposure periods. The resulting estimated regression coefficients were used to calculate a risk score for every exposure period under study (azithromycin and amoxicillin), consisting of the sum of each regression coefficient multiplied by the associated covariate value assessed on the prescription fill date. Deciles of risk score were formed, and all study-eligible exposure periods were assigned a risk category: low (CVRS deciles 1-5), medium (CVRS deciles 6-9), and high CV risk (CVRS decile 10).

See Appendix 6 for detailed CVRS methodology and model results.

9.9.3. Missing values

Based on preliminary data exploration, it was expected that there would be some missing IOU data and the approach for that specific variable is described in detail in Appendix 8. In brief, antibiotic indications were categorized as “infection,” “prophylaxis,” or “missing.”

For a very small number of KP members, there was a missing date of birth or gender, and those members were excluded from the analysis. In the feasibility analysis, less than 0.0001% of antibiotic prescriptions were excluded due to missing date of birth or gender data. Missing race/ethnicity data were categorized as “other/missing”.

All other variables are derived from ICD-9 codes and pharmacy database prescription records. If no code/record was present in the database that met the definitions in the SAP Appendix 3 (pp.18-32, propensity score variables), the variable was categorized as negative/absent. This study utilized electronic data, including all recorded relevant diagnoses and all recorded medications dispensed by the pharmacy. It was not possible to detect if data were missing from these data sources. Missing data in these circumstances would represent patients who had certain conditions which were not recorded by their physicians or medications taken by the patients which were not recorded and dispensed by the Kaiser Permanente Pharmacy system. However, prior studies indicate that few patients receive

medications outside of Kaiser Permanente pharmacies and the study excluded members' records if there was a greater than 60-day gap in KP prescription coverage in the year prior to the index date.

9.9.4. Sensitivity analyses

This study included several planned sensitivity analyses designed to test the robustness of the primary analysis findings, by way of alternative statistical methods and outcome definitions, and to further evaluate anticipated biases and limitations. Unless otherwise specified below, all sensitivity analyses included the entire study population and examined cardiovascular death within 5 days and 6-10 days of study antibiotic exposure (i.e. other outcomes of interest, and subgroup analyses were not conducted as part of sensitivity analyses).

1. Conducted primary analysis using propensity score as a stratifying variable (instead of a covariate in the regression equation) in the Cox model.

2. Examined the association between azithromycin use and cardiac death (a subset of cardiovascular death which excludes stroke, as used by Svanstrom et al. 2014,[2] and defined in Appendix 5, p.2) within 5 days, and 6-10 days, as compared to amoxicillin.

3. Conducted primary analysis (cardiovascular death within 5 days and 6-10 days), according to number of antibiotic Rxs (both study and non-study antibiotics) within the prior 30-day period:
    a. among those with no antibiotic Rx within the prior 30-day period (i.e., "new users")
    b. among those with 1 antibiotic Rx within the prior 30-day period
    c. among those with > 1 antibiotic Rx within the prior 30-day period

4. Evaluated the distribution of prescribed daily doses and duration of use (prescription length in days) of the study antibiotics. Because the observed distributions did not demonstrate significant variation in daily dose nor days' supply, an analysis regarding daily dose and duration of use was not performed (as planned in the protocol and SAP, with the contingency that those variables demonstrated significant variation).

5. Conducted primary analysis with alternative CV death definition to include confirmed (adjudicated) CV deaths (defined as definite or possible CV in nature), and unclassifiable CV deaths. This analysis thus excluded deaths classified as "Non-CV" during adjudication.

6. Conducted primary analysis with an alternative CV death definition to include all coded CV deaths (CV death according to structured data), as was done by Ray et al. (2012),[1] regardless of adjudication classification. Thus, this analysis included CV deaths determined to be non-CV during the adjudication process, and those that were deemed unclassifiable during the adjudication process.

7. Conducted primary analysis with alternative CVRS cut-off points for low, medium, and high CV risk categories. Specifically, the high CV risk group was created to

reflect Ray et al.'s (2012) high CV risk group profile as closely as possible. Therefore, a high CV risk category was created to reflect the CV mortality incidence of approximately 160 CV deaths per million amoxicillin prescriptions, as reported by Ray et al (2012).[1]

8. Conducted primary analysis restricted to antibiotic prescriptions within the time period of 2009 – 2013 (KPSC, -2014 KPNC). This time period within the Kaiser Permanente EMR system allowed for direct capture of indication of use (see Section 9.5.1).

9. Conducted primary analysis restricted to antibiotic prescriptions which had an infection indication of use and thus excluded prescriptions given for prophylaxis or missing indications (see Section 9.5.1). In addition, where there was substantial between-group imbalance in the distribution of antibiotic indication, analyses within categories of indication (i.e. analyses stratified by indication of use) were conducted.

10. Estimated the distribution of infection severity according to the type of antibiotic exposure. Because infection severity cannot be directly measured with KP's existing data, the study used a proxy for infection severity that captured each patient's health care utilization after study antibiotic exposure. Within each 10-day interval after antibiotic exposure, the patients' utilization status was categorized as: 0 (no emergency department visits or hospital admissions), 1 (any emergency department visit but no hospital admissions), or 2 (any hospital admission). The distribution of this utilization "score" was compared between antibiotic exposure groups, after excluding those antibiotic prescriptions made for prophylactic indications (as opposed to active infections). Because the score was not imbalanced between the two antibiotic exposure groups, it was not added as a variable to the propensity score model used for the primary analysis.

11. Conducted primary analysis with the Cox regression model stratified by the number of previous study antibiotic exposures (see SAP Appendix 3, section 8.1.C), allowing for separate, unspecified baseline hazard functions within each stratum. The number of study antibiotics filled prior to each antibiotic fill date was a time-varying covariate and was assessed at each index date with look-back from that date to the earliest available calendar date of data collection (January 1, 1997 [one year prior to earliest possible index date for study inclusion], or KP membership enrolment date, whichever is latest). In addition to examining number of prior exposures across the full range (0, 1, 2, 3….), we also broadly categorized this Cox stratification variable as: 0 and ≥ 1 previous study antibiotic fills.

12. Conducted primary analysis with hospital admission as an additional censoring criterion.

9.9.5. Amendments to the statistical analysis plan

None

9.9.6. Post Hoc Analyses

Post hoc analyses using the "modified cohort" (see Section 9.3.3) and coded cardiovascular deaths (defined via structured data, rather than 'per protocol' adjudicated cardiovascular deaths) were conducted to provide a more comparable cohort with Ray et al. 2012[1] (and increased control of confounding), and to overcome unanticipated limitations of the adjudication process (see Section 11 for further details).

9.10. Quality control

Data for the study were extracted from electronic databases maintained by Kaiser Permanente and by the Division of Research (DOR) and the Department of Research & Evaluation (R&E). The DOR Strategic Programming Group and the R&E routinely perform comprehensive QA of KP electronic databases, including the Virtual Data Warehouse (VDW) files. Each data content area in the VDW is subjected to similar checks, from high level variable name/type checks, to detailed trending comparisons. As an example, the diagnostic data is subject to the following checks:

- Referenced table exists.
- Diagnosis type correctly assigned by codes defining the diagnosis.
- Percentages and rates are as expected (check ranges and for missing).
- Both inpatient and outpatient diagnosis codes are captured. Referenced variables exist and are of appropriate length and type.

Data retrieval was coordinated by an experienced programmer/analyst. The analyst wrote programming for retrieval of each data element from the electronic databases. Data quality checks included comparisons of observed vs. expected numbers of prescriptions, outcomes, and patients, comparisons of electronic coding (pharmacy codes) with text string searches of drug names to confirm complete acquisition of medications of interest, and comparisons of estimates of person time from membership files with actual calculated membership time. All tables were reviewed by the project manager and the principal investigator to evaluate for internal consistency of counts and totals. All calculated variables were checked against the component variables (cross-tabs) to ensure accuracy. For example, categorical age was compared with continuous age to confirm that each category of age contained only persons of the expected age ranges within that category.

In addition to these measures, the database programming code and output were compared between the two sites (KPNC & KPSC) on a regular basis, legacy copies of the programming files were saved on the DOR servers as the programming evolved over time, and legacy copies of the descriptive and statistical analysis data tables were also saved on the server. The QA process for the CV death adjudications is detailed in Appendix 5.2.

Data Abstraction

All abstractions were conducted by professional, certified KPNC DOR and KPSC medical record analysts. Staff members had a minimum of one year of medical record coding/abstracting experience, but the department average is eight years, and some have 30 years of experience. Abstractors were trained by the principal investigator, with

review/re-abstraction of reports for the initial training to confirm accuracy. The Medical Record Analysts (MRAs) have expertise in health record content, health information management practices, ICD-9 coding, medical terminology, disease processes, drugs, abbreviations, and medical-record abstracting. See Appendix 5.2 for the detailed methodology of the Events Adjudication Committee.

9.11. Protection of human subjects

Subject information and consent

Not applicable

Independent Ethics Committee (IEC)/ Institutional Review Board (IRB)

The final protocol, any amendments, and informed consent documentation were reviewed and approved by an Institutional Review Board(s) (IRB) and/or Independent Ethics Committee(s) (IEC) for each site participating in the study.

The KPNC IRB approved the waiving of informed consent. The KPSC IRB ceded authority to the KPNC IRB for this study.

Ethical conduct of the study

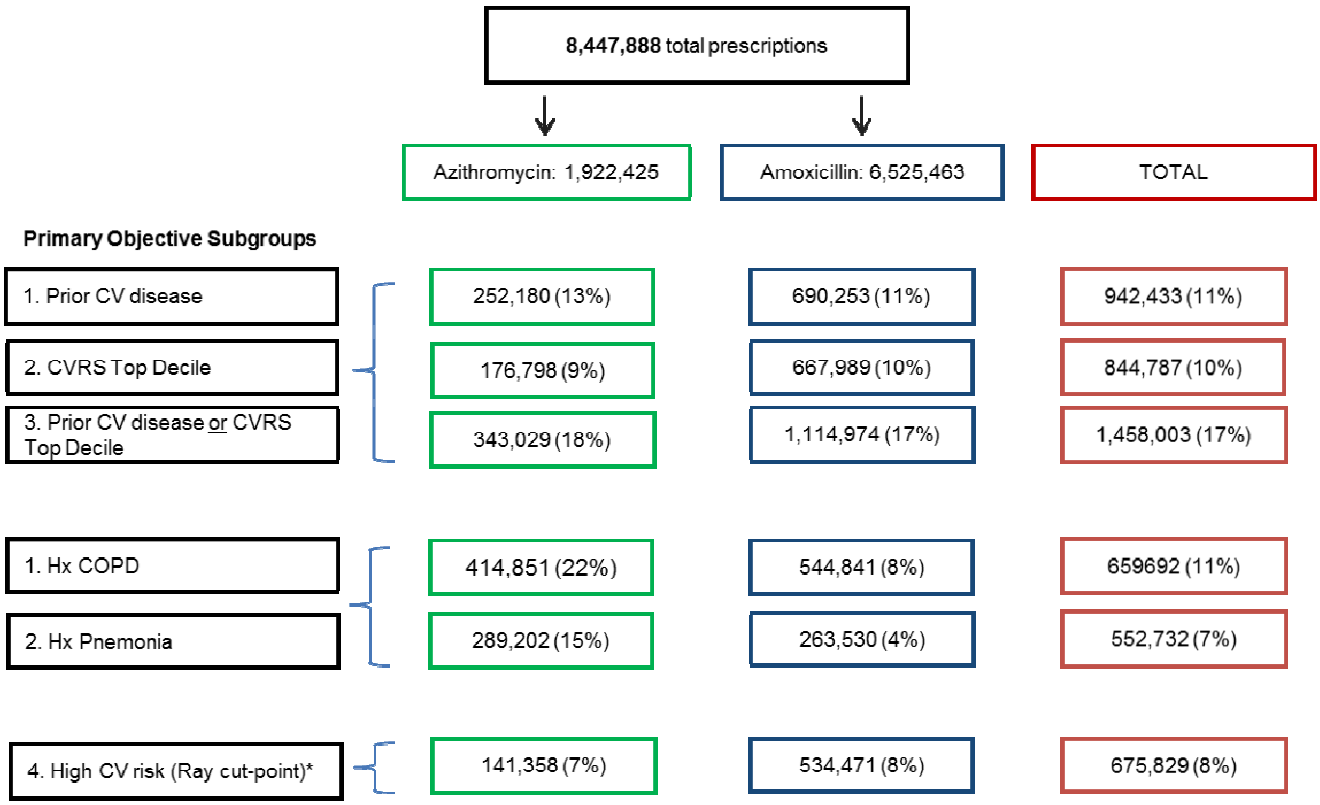
The study was conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA), International Ethical Guidelines for Epidemiological Research issued by the Council for International Organizations of Medical Sciences (CIOMS), European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, and FDA Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment, FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting of Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets.

10. RESULTS

10.1. Participants

The study sample included over 8 million unique azithromycin and amoxicillin prescriptions which met all inclusion and exclusion criteria. Sample size by study antibiotic and subgroups of interest is shown below in Figure 3.

Figure 3: Participant Flow Diagram



*CV mortality rate of 155.7 per million amoxicillin prescription exposures. This approximates the rate observed in Ray's top decile CVRS group (160 per million).

10.2. Descriptive data

The clinical and demographic characteristics of the patients receiving the prescriptions, according to study antibiotic type, are shown below in Table 5. The distribution of study antibiotic doses and durations is also included in these tables.

Table 5. Cohort characteristics of the study population (whole cohort and modified cohort)

	Whole Cohort		Modified Cohort	
Characteristic	**Azithromycin**	**Amoxicillin**	**Azithromycin**	**Amoxicillin**
Prescriptions (%)	1,922,425 (22.8%)	6,525,463 (77.2%)	1,736,976 (22.2%)	6,087,705 (77.8%)
Mean age, years (sd)	52.1 (12.0)	50.7 (11.8)	51.7 (12.0)	50.4 (11.7)
KPNC	62.9%	47.2%	63.0%	46.9%
KPSC	37.1%	52.8%	37.0%	53.1%
Female sex	62.8%	60.9%	63.6%	61.3%
Calendar year t0, mean (sd)	2008.3 (4.3)	2005.6(4.8)	2008.3 (4.4)	2005.5 (4.8)
Race				
Hispanic	19.6%	22.8%	19.6%	22.9%
Black	8.7%	10.0%	8.5%	9.9%
Hawaiian/Pacific Islander	0.9%	0.8%	0.9%	0.8%
Asian	12.4%	9.8%	12.8%	9.9%
Native American	0.5%	0.4%	0.5%	0.4%
White	53.3%	49.4%	52.7%	48.9%
Missing/Other	4.7%	6.9%	5.1%	7.2%
Study Antibiotic use				
Dose (most frequent)[±]				
Azithromycin 250 mg* (*two tabs typically taken on the 1st day) Azithromycin 500 mg Other	96.8% 2.5% 0.7%	-	97.1% 2.5% 0.4%	
Amoxicillin Trihydrate 500mg Amoxicillin-Clavulanate 875-125 mg Amoxicillin Trihydrate 250mg Amoxicillin-Clavulanate 500-125mg Other	-	80.3% 12.6% 3.8% 3.1% 0.2%		80.7% 12.3% 3.8% 3.0% 0.2%
Days' supply mean (sd)[±]	5.2 (6.9)	10.0 (6.0)	5.0 (5.8)	9.9 (5.8)
Days' supply, median[±]	5	10	5	10

	Whole Cohort		Modified Cohort	
Characteristic	**Azithromycin**	**Amoxicillin**	**Azithromycin**	**Amoxicillin**
Days' supply, days (%)[±]	<3 days (3.3%) 3 days (40.5%) 4-5 days (40.9%) 6-10 days (12.8%) >10 days (2.6%)	<7 days (9.1%) 7 days (17.5%) 8-10 days (62.9%) 11- 14 days (5.7%) >14 days (5.0%)	< 3 days (3.3%) 3 days (41.0%) 4-5 days (41.0%) 6-10 days (12.5%) > 10 days (2.2%)	< 7 days (8.8%) 7 days (17.4%) 8-10 days (63.3%) 11-14 days (5.7%) > 14 days (4.9%)
Current or past use (within 1 year) of medications (%)				
ACE inhibitor	18.3%	15.4%	17.5%	14.7%
Calcium-channel blocker	10.0%	8.0%	9.1%	7.3%
Digoxin	0.8%	1.1%	0.6%	1.0%
Loop diuretic	4.5%	3.0%	3.4%	2.3%
Other diuretic	18.0%	14.9%	17.5%	14.4%
Statin	26.1%	20.6%	24.9%	19.6%
Insulin	4.3%	3.1%	3.5%	2.7%
Oral hypoglycemic	10.7%	8.9%	10.2%	8.5%
Beta-agonist	41.1%	20.3%	40.7%	19.9%
Systemic Glucocorticoid	25.9%	15.3%	24.3%	14.3%
Angiotensin Receptor Blocker	6.2%	3.7%	5.8%	3.4%
Anticoagulant	4.0%	4.0%	2.9%	3.3%
Antiarrhythmic	1.0%	1.2%	0.8%	1.0%
Nitrate	4.0%	3.4%	3.5%	3.0%
Platelet inhibitor	1.4%	1.1%	1.2%	0.9%
Co-existing conditions coded within 1 year prior to index (%)				
Heart failure	2.2%	1.7%	1.6%	1.3%
COPD	21.6%	8.4%	20.6%	7.9%
Diabetes	14.5%	12.1%	13.4%	11.4%
Complications of diabetes	6.6%	4.8%	5.8%	4.2%
Incontinence of urine or feces	3.6%	2.6%	3.4%	2.4%
Use of wheelchair or walker	0.2%	0.1%	0.1%	0.1%
Asthma	23.1%	10.8%	22.6%	10.4%
Cardiac revascularization	0.5%	0.5%	0.4%	0.4%

	Whole Cohort		Modified Cohort	
Characteristic	**Azithromycin**	**Amoxicillin**	**Azithromycin**	**Amoxicillin**
Myocardial infarction	2.1%	1.6%	1.7%	1.4%
Other Coronary Heart Disease	4.1%	3.4%	3.5%	3.0%
Arrhythmia	3.7%	3.2%	3.1%	2.8%
Cardiac valve disease	1.2%	1.7%	1.0%	1.4%
Peripheral Vascular Disease	4.8%	3.1%	4.0%	2.6%
Stroke	0.4%	0.3%	0.2%	0.2%
TIA	0.6%	0.5%	0.5%	0.4%
Renal disease	4.9%	3.0%	3.7%	2.2%
Smoking	44.2%	36.8%	42.4%	35.6%
Prior Pneumonia	15.0%	4.0%	14.0%	3.5%
ED Visit for CV Disease within 31-365 days	1.3%	1.1%	1.0%	0.9%
ED Visit for CV Disease within 30 days	0.2%	0.1%	0.1%	0.1%
ED Visit for non-CV Disease within 31-365 days	16.9%	13.1%	15.2%	12.0%
ED Visit for non-CV Disease within 30 days	5.6%	2.2%	5.4%	2.1%
CV Disease hospitalization within 91-365 days	0.7%	0.7%	0.5%	0.5%
CV Disease hospitalization within 30-90 days	0.2%	0.2%	0.1%	0.1%
Non-CV Disease hospitalization within 365 days	4.0%	4.1%	3.0%	3.3%
Use of a study antibiotic within the past 30 days	4.3%	4.8%	4.2%	4.6%
Use of any other antibiotic within the past 30 days	7.0%	4.4%	6.8%	4.3%
Mean cardiovascular risk score (sd, median)	9.07 (6.03, 9)	9.63 (5.68, 10)	8.78 (5.97, 9)	9.45 (5.64, 9)

[±] Sensitivity Analysis (4) was a descriptive analysis of study antibiotic dose and duration. The dose distributions observed for both study drugs were as expected. Azithromycin was most commonly prescribed in 250 mg doses for 3 to 5 days. Amoxicillin was most commonly prescribed in 500 mg doses for 7 to 10 days.

Differences in cohort characteristics between antibiotic arms include the following: Mean calendar year t0 (AZ: 2008.3, AM: 2005.6), beta-agonist use (AZ: 41.1%, AM: 20.3%), systemic glucocorticoid use (AZ: 25.9%, AM:15.3%), asthma (AZ: 23.1%, AM: 10.8%), COPD (AZ: 21.6%, AM: 8.4%), prior pneumonia (AZ: 15.0%, AM: 4.0%), any non-CV ED visit in the past 30 days (AZ: 5.6%, AM: 2.2%), and use of a non-study antibiotic in the past

30 days (AZ: 7.0%, AM: 4.4). Azithromycin users also appear to have slightly more cardiovascular disease, as reflected by the greater use of ACE inhibitors, CCBs, loop and non-loop diuretics, statins, and ARBs, compared to amoxicillin users.

Compared to the whole cohort, the modified cohort has a small but consistent decrease in the rates of medication use, comorbid conditions, and health care utilization, resulting in a marginally lower mean CVRS for both azithromycin and amoxicillin. The variables with significant azithromycin vs amoxicillin frequency differences are very similar in the two cohorts (i.e. COPD: AZ 21.6%, AM 8.4% (Table 5, whole cohort) versus AZ 20.6%, AM 7.9% (Table 5, modified cohort)).

A total of 3,055,459 KP members met inclusion criteria for the study cohort. A single member could contribute records to both antibiotic groups. The proportions of study antibiotics dispensed to cohort members for the two study drugs individually and combined, is shown below:

Table 6A: Distribution of the number of study antibiotic prescriptions dispensed per KP member (whole cohort)

Number of Prescriptions Dispensed per KP Member	Azithromycin	Amoxicillin	Either Antibiotic
1	67.3%	47.6%	44.7%
2	18.3%	21.2%	21.1%
3	6.9%	11.2%	11.7%
4	3.1%	6.5%	7.0%
5	1.6%	4.1%	4.5%
>5	2.8%	9.4%	11.1%

67.3% of cohort members received exactly one azithromycin prescription during the study period, 47.6% received exactly one amoxicillin prescription, and 44.7% received exactly one prescription of either drug. Only 2.8% of members received more than 5 azithromycin prescriptions while 9.4% of members received more than 5 amoxicillin prescriptions and 11.1% of members received more than 5 prescriptions of the two drugs combined.

Table 6B: Distribution of the number of study antibiotic prescriptions dispensed per KP member (modified cohort)

Number of Prescriptions Dispensed per KP Member	Azithromycin	Amoxicillin	Either Antibiotic
1	68.6%	48.6%	45.8%
2	18.0%	21.2%	21.2%
3	6.6%	11.1%	11.5%
4	2.9%	6.4%	6.8%
5	1.5%	3.9%	4.3%
>5	2.5%	8.8%	10.3%

The distribution of the number of dispensed study antibiotics did not change substantially after the application of the SIEC.

Per protocol, the CVRS produced 10 deciles of CV risk and was used to divide the population into low (deciles 1-5), intermediate (deciles 6-9), and high (decile 10) CV risk groups. The distribution of the variables that compose the risk score is shown, by risk group, below.

Table 7. CVRS Variables According to Study Antibiotic Type and CVRS Subgroup*

	Low Risk: Deciles 1-5		**Medium Risk: Deciles 6-9**		**High Risk: Decile 10**	
	Azithromycin	Amoxicillin	Azithromycin	Amoxicillin	Azithromycin	Amoxicillin
Rx (n)	982,841	3,241,103	762,786	2,616,371	176,798	667,989
Summary CVRS score (mean)	3.89	4.69	13.57	13.48	18.50	18.50
Demographic						
Calendar year t0, mean	2009.0	2006.3	2008.1	2005.3	2005.6	2003.3
Age in years, mean	48.0	46.5	54.7	53.3	63.5	60.6
Male	28.9%	27.6%	41.3%	46.1%	65.3%	67.8%
White	49.8%	46.4%	56.8%	52.1%	57.3%	53.8%
Current or past use of cardiovascular medications						
Angiotensin Receptor	3.8%	2.1%	7.2%	4.3%	14.9%	8.8%

Blocker						
Anticoagulant	1.8%	1.7%	4.3%	4.4%	14.9%	13.4%
ACE inhibitor	10.6%	8.2%	21.5%	18.6%	47.6%	38.0%
Antiarrhythmic	0.4%	0.4%	1.0%	1.2%	4.8%	4.8%
Beta-blocker	9.1%	7.5%	19.0%	17.5%	47.8%	38.6%
Calcium-channel blocker	4.8%	3.1%	11.5%	9.8%	32.6%	24.1%
Digoxin	0.1%	0.1%	0.6%	1.0%	5.8%	6.5%
Loop diuretic	1.2%	0.7%	4.4%	2.9%	23.0%	14.4%
Other diuretic	12.4%	9.7%	21.2%	17.8%	36.1%	28.7%
Oral hypoglycemic	5.9%	4.4%	12.6%	10.9%	30.0%	23.0%
Statin	16.7%	12.3%	31.0%	24.7%	57.5%	44.5%
Nitrate	1.2%	0.9%	4.1%	3.6%	18.8%	14.6%
Platelet inhibitor	0.4%	0.3%	1.6%	1.2%	6.0%	4.1%
Cardiovascular diagnoses (%)						
COPD	16.2%	5.6%	24.7%	9.4%	38.1%	17.4%
Coronary revascularization	0.1%	0.2%	0.5%	0.5%	2.0%	2.0%
Cardiac valve disease	0.6%	0.9%	1.2%	1.7%	4.9%	5.5%
Arrhythmia	1.6%	1.2%	3.8%	3.4%	15.0%	12.5%
Coronary Heart Disease	1.0%	0.7%	4.2%	3.4%	21.2%	15.9%
MI	0.3%	0.2%	1.9%	1.4%	12.6%	8.8%
Stroke	0.2%	0.1%	0.4%	0.3%	1.3%	0.9%
TIA	0.2%	0.2%	0.7%	0.5%	2.4%	1.8%
Heart Failure	0.1%	0.1%	1.4%	1.1%	17.9%	12.0%
Peripheral Vascular Disease	2.1%	1.3%	5.2%	3.3%	18.2%	11.3%
Other comorbidity (%)						
Smoking	8.3%	4.3%	77.9%	61.7%	97.9%	97.5%
†Diabetes	8.3%	6.6%	16.9%	14.5%	38.9%	29.9%
†Prior Pneumonia	12.8%	3.3%	15.8%	4.1%	24.1%	7.5%
Medical care utilization (%)						
†Any ED visit in past year	17.8	13.2	22.7	15.9	33.4	22.0

ED visit for CVD within 31 - 365 days	0.5%	0.5%	1.3%	1.1%	5.4%	4.1%

*Note: The percentage results shown in each column are independent of the other columns.
†These variables are not in the CVRS model but are included to provide additional descriptive information

The mean summary CVRS was slightly higher for the amoxicillin than the azithromycin prescriptions for both the whole and modified cohorts (Tables 5A and 5B), although most of the CV risk factors comprising the CVRS were more prevalent in the azithromycin group. The small difference in the overall mean CVRS was driven by the higher mean summary CVRS for amoxicillin in the low risk CVRS sub-group (4.69 vs 3.89, Table 7). Unexpectedly, year of index prescription was the strongest predictor of the mean CVRS, as it is a predictor of CV death in the study population (OR 0.87 per one-year increase, P <0.001), as well as exposure (azithromycin vs amoxicillin). Specifically, azithromycin was prescribed proportionally more often during the later years of the study cohort compared to amoxicillin, during a period when the myocardial infarction death rate was also declining at KP. Given this strong temporal trend which resulted in year of prescription being the strongest predictor of the mean CVRS, a sensitivity analysis and a detailed discussion of the CVRS results is provided in the CVRS Appendix 6. Briefly, when year of prescription was removed from the CVRS, the mean summary CVRS for azithromycin was slightly higher than amoxicillin, as would be expected from the generally higher proportion of CV risk factors among azithromycin users, than amoxicillin users (Tables 6A and 6B).

The distribution of IOU by study antibiotic for the whole and modified cohorts is shown in Tables 8A and 8B, respectively.

Table 8A. Indication of Use, by study antibiotic (whole cohort)

	Infection Severity*	Azithromycin (N=1,922,425)	Amoxicillin (N=6,525,463)
Recorded indication			
Bronchitis	Low	22.3%	7.7%
Ear-Nose-Throat	Low	19.6%	35.8%
Respiratory symptoms	Low	12.2%	2.4%
COPD	High	10.6%	2.7%
Pneumonia	High	8.1%	0.4%
Unspecified/ other infections, Genitourinary, STDs	Low	4.8%	6.0%
Other serious infections, including Cardiac, Brain/Spinal, Blood	High	1.8%	1.0%
Gastrointestinal	Low	1.5%	2.4%
Skin/ soft tissue/ join/ bone, Wounds	Low	1.5%	4.4%
Other diseases of the respiratory track	Low	0.9%	0.4%
Pyrexia unknown origin	High	0.9%	0.2%
Immediate prophylaxis	Low	0.9%	1.0%
Delayed prophylaxis	Low	0.7%	0.5%
Missing diagnosis code	Low	14.0%	35.1%

*Infection severity classification per Ray et al. (2012)[1]

Approximately 20% of the azithromycin prescriptions were for high severity infections (per high severity classification used by Ray et al. 2012)[1] whereas only approximately 4% of amoxicillin prescriptions were for high severity infections. Bronchitis, (22.3%), ear-nose-throat infections, (19.6%), and respiratory symptoms (12.2%) were the most common indications for an azithromycin prescription. For amoxicillin, the most common indications were ear-nose-throat infections, (35.8%), bronchitis, (7.7%), and "unspecified/ other infections, genitourinary, and STDs" (6.0%). The overall rate of a missing diagnosis code was 30% and was disparate across antibiotic group (14.0% missing IOU in azithromycin, 35.1% missing indication of use in amoxicillin). See Appendix 8 for the IOU validation results.

Table 8B. Indication of Use, by study antibiotic (modified cohort)

	Infection Severity*	Azithromycin (N=1,736,976)	Amoxicillin (N= 6,087,705)
Recorded indication			
Bronchitis	Low	22.4%	7.8%
Ear-Nose-Throat	Low	20.1%	36.2%
Respiratory symptoms	Low	12.2%	2.4%
COPD	High	10.4%	2.6%
Pneumonia	High	8.0%	0.4%
Unspecified/ other infections, Genitourinary, STDs	Low	4.7%	5.8%
Other serious infections, including Cardiac, Brain/Spinal, Blood	High	1.6%	0.9%
Gastrointestinal	Low	1.5%	2.4%
Skin/ soft tissue/ join/ bone, Wounds	Low	1.4%	4.3%
Other diseases of the respiratory track	Low	0.9%	0.4%
Pyrexia unknown origin	High	0.9%	0.2%
Immediate prophylaxis	Low	0.9%	1.0%
Delayed prophylaxis	Low	0.7%	0.4%
Missing diagnosis code	Low	14.3%	35.4%

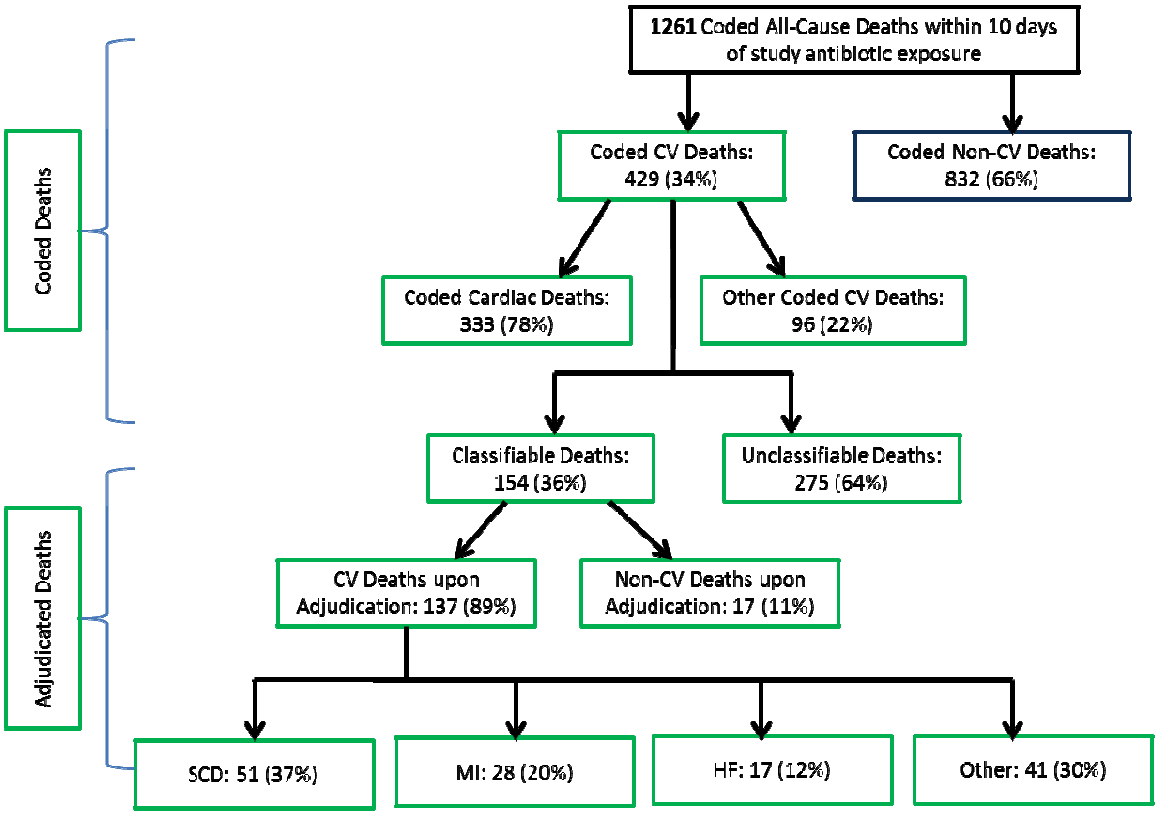
*Infection severity classification per Ray et al. 2012[1]

The application of the SIEC did not substantially change the distribution of the indications of use for the study antibiotics.

10.3. Outcome data

Figure 4, below, provides count and distribution details on the primary outcome of interest, adjudicated CV deaths within 10 days of study antibiotic. The upper part of the figure displays the number of coded death outcomes (i.e. per structured data only) and the lower part of the figure displays the distribution of causes of death as determined by the CV death adjudication process.

Figure 4: Outcomes occurring within 10 days of study antibiotic exposure



The 1261 coded all-cause deaths were the total deaths after censoring criteria (see section 9.9.2.1) had been applied. Censoring criteria removed 10 adjudicated CV deaths, 19 coded CV deaths, and 126 non-CV deaths from the analysis population. "Cardiac death" includes all CV deaths but excludes stroke-related deaths and other rare CV causes of death.

The overall confirmed CV death rate was 32% (137/429). This low confirmation rate was largely due to insufficient information for adjudication for the majority of deaths. Among patients coded for CV death, sufficient information for adjudication was available for only 36% (154/429) of deaths. Among those with sufficient information for adjudication, 89% were confirmed to be CV deaths. Further, the unclassifiable rate (64%) was unequal by antibiotic group; 59% of coded CV deaths among azithromycin users and 68% of coded CV deaths amongst amoxicillin users were categorized as unclassifiable. Please see Appendix 9 for detailed death adjudication results.

The study also included a secondary analysis of outcomes occurring between day 11 and 365 after the index date. Because of the much longer follow-up period in comparison with the day 0-10 analyses, there are substantially more coded CV deaths (3805) in the long-term follow-up analysis. Per protocol, these CV deaths were not adjudicated.

10.4. Main results

10.4.1. Primary Objectives

Table 9: Cardiovascular Death (adjudicated and coded) and Sudden Cardiac Death (adjudicated and coded), 0-5 and 6 – 10 days following Azithromycin and Amoxicillin Prescriptions for KPNC/KPSC Members Age 30-74 years old, all prescriptions, whole and modified cohorts.

Adjudicated CV and Sudden Cardiac Deaths (A-CVD and A-SCD), whole cohort							
	Azithromycin (n=1,922,425)		Amoxicillin (n=6,525,463)		Adjusted Risk Difference*† (95% CI)	Adjusted Hazard Ratio† (95% CI)	p-value
Outcome	Deaths (n)	Cumulative Incidence*	Deaths (n)	Cumulative Incidence*			
Cardiovascular Death[1]							
0-5 days	38	19.88	37	5.70	7.60 (2.17--16.77)	2.33 (1.38--3.94)	0.002
6-10 days	24	12.80	38	5.94	2.62 (-1.22--9.57)	1.44 (0.79--2.61)	0.23
Sudden Cardiac Death[1]							
0-5 days	18	9.41	21	3.23	3.55 (0.00--11.02)	2.10 (1.00--4.41)	0.050
6-10 days	4	2.13	8	1.25	0.29 (-0.77--3.70)	1.23 (0.38--3.96)	0.73
Coded CV and Sudden Cardiac Deaths (C-CVD and C-SCD), whole cohort							
	Azithromycin (n=1,922,425)		Amoxicillin (n=6,525,463)		Adjusted Risk Difference*† (95% CI)	Adjusted Hazard Ratio† (95% CI)	p-value
Outcome	Deaths (n)	Cumulative Incidence*	Deaths (n)	Cumulative Incidence*			
Cardiovascular Death[2]							
0-5 days	114	59.62	139	21.40	22.63 (11.27--37.96)	2.06 (1.53--2.77)	<0.001

6-10 days	60	31.97	116	18.13	5.48 (-1.56--15.53)	1.30 (0.91--1.86)	0.14
Sudden Cardiac Death[3]							
0-5 days	36	18.83	51	7.85	7.54 (1.77--16.78)	1.96 (1.23--3.14)	0.005
6-10 days	20	10.65	40	6.25	2.46 (-1.44--9.54)	1.39 (0.77--2.53)	0.27
Coded CV and Sudden Cardiac Deaths (C-CVD and C-SCD), modified cohort							
	Azithromycin (n=1,736,976)		Amoxicillin (n=6,087,705)		Adjusted Risk Difference*† (95% CI)	Adjusted Hazard Ratio† (95% CI)	p-value
Outcome	Deaths (n)	Cumulative Incidence*	Deaths (n)	Cumulative Incidence*			
Cardiovascular Death[3]							
0-5 days	62	35.91	95	15.68	12.79 (3.66--26.21)	1.82 (1.23--2.67)	0.002
6-10 days	31	18.34	68	11.41	3.15 (-2.31--11.91)	1.28 (0.80--2.04)	0.31
Sudden Cardiac Death[3]							
0-5 days	21	12.17	39	6.44	5.05 (0.33--13.07)	1.78 (1.05--3.03)	0.032
6-10 days	16	9.47	36	6.04	2.91 (-1.08--10.11)	1.48 (0.82--2.67)	0.19

*per 1,000,000 prescriptions
†Adjusted for propensity score decile, age, and gender
[1] primary analysis per SAP
[2]sensitivity analysis per SAP
[3] post hoc analysis

Patients taking azithromycin, as compared with those who took amoxicillin, had a significantly increased risk of CV death (A-CVD: HR 2.33, 95% CI 1.38--3.94; C-CVD: HR 2.06, 95% CI 1.53--2.77) and the subtype of sudden cardiac death (A-SCD: HR 2.10, 95% CI 1.00--4.41; C-SCD: HR 1.96, 95% CI 1.23--3.14) in the first five days after prescription dispensing. No significant increases in risks were found during the 6-10 day window for CV death (A-CVD: HR 1.44, 95% CI 0.79--2.61; C-CVD: HR 1.30, 95% CI 0.91--1.86) and SCD (A-SCD: HR 1.23, 95% CI 0.38--3.96; C-SCD: HR 1.39, 95% CI 0.77--2.53).

Comparable results were seen in the modified cohort, which excluded patients with an underlying serious illness (see modified cohort definition in Section 9.3.3 above), (0-5 day window, C-CVD: HR 1.82, 95% CI 1.23--2.67, C-SCD: HR 1.78, 95% CI 1.05-3.03) within the 6-10 day outcome window (C-CVD: HR 1.28, 95% CI 0.80--2.04, C-SCD: HR 1.48, 95% CI 0.82--2.67). For the combined 0-10 day outcome window the HR was 1.59, 95% CI 1.14--2.21.

Patients taking azithromycin had a significantly increased absolute risk; the adjusted risk differences for CV death in the 0-5 day window after index date ranged from 7.60-22.63 cases per 1,000,000 Rxs, depending on the analysis.

Table 10: High CV risk subgroup analysis. Cardiovascular Death (adjudicated and coded), 0-5 and 6 – 10 days following Azithromycin and Amoxicillin Prescriptions for KPNC/KPSC Members Age 30-74 years old, whole and modified cohorts.

Adjudicated CV deaths (A-CVD), whole cohort									
	Azithromycin			Amoxicillin			Adjusted Risk Difference*† (95% CI)	Adjusted Hazard Ratio† (95% CI)	p-value
Subgroup	Rx (n)	Deaths (n)	Cumulative Incidence*	Rx (n)	Deaths (n)	Cumulative Incidence*			
Prior CV disease[1]	252,180			690,253					
0-5 days		18	71.84		27	39.35	18.30 (-11.26--78.98)	1.47 (0.71--3.01)	0.30
6-10 days		17	69.43		21	31.25	24.54 (-5.83--91.18)	1.79 (0.81--3.92)	0.15
Top decile CVRS[1]	176,798			667,989					
0-5 days		19	108.16		29	43.66	18.38 (-12.10--78.32)	1.42 (0.72--2.79)	0.31
6-10 days		15	87.48		28	42.92	7.22 (-18.84--61.5)	1.17 (0.56--2.43)	0.68
Coded CV deaths (C-CVD), whole cohort									
	Azithromycin			Amoxicillin			Adjusted Risk Difference† (95% CI)	Adjusted Hazard Ratio† (95% CI)	p-value
Subgroup	Rx (n)	Deaths (n)	Cumulative Incidence*	Rx (n)	Deaths (n)	Cumulative Incidence*			
Prior CV disease[2]	252,180			690,253					
0-5 days		64	255.42		81	118.06	106.24 (30.77--219.96)	1.90 (1.26--2.86)	0.002
6-10 days		37	151.13		57	84.66	47.95 (-3.18--131.15)	1.57 (0.96--2.55)	0.07
Top decile CVRS[2]	176,798			667,989					
0-5 days		69	392.68		102	153.53	137.27 (47.93--266.24)	1.89 (1.31--2.73)	<0.001
6-10 days		37	215.54		87	133.22	26.34 (-29.47--112.17)	1.20 (0.78--1.84)	0.41
Coded CV deaths (C-CVD), modified cohort									
Prior CV disease[2]	197,379			571,728					
0-5 days		30	153.13		50	88.01	51.47 (-8.73--157.40)	1.58 (0.90--2.79)	0.11
6-10 days		17	89.57		31	55.82	25.69 (-14.10--103.43)	1.46 (0.75--2.85)	0.27
Top decile	139,290			574,234					

CVRS[2]									
0-5 days		37	268.33		69	120.91	85.48 (6.80--212.66)	1.71 (1.06--2.76)	0.03
6-10 days		20	149.83		51	91.20	24.00 (-25.79--111.68)	1.26 (0.72--2.22)	0.42

*per 1,000,000 prescriptions
†Adjusted for propensity score decile, age, and gender
CVRS: Cardiovascular Risk Score
[1] primary analysis per SAP
[2] post hoc analysis

There were no significant associations between azithromycin exposure and A-CVD in either high CV risk subgroup (Prior CV disease: HR 1.47, 95% CI 0.71--3.01, top decile CVRS: HR 1.42, 95% CI 0.72 --2.79). None of the hazard ratios among the high CV risk subgroups were higher than the effect in the overall population (A-CVD: HR 2.33, 95% CI 1.38--3.94; C-CVD: HR 2.06, 95% CI 1.53--2.77, Table 9). However, when examining the adjusted risk differences, a higher risk among those with high baseline CV risk (for both the CVRS and prior CV disease) can be observed, compared to the overall population (*Overall:* A-CVD: RD 7.60, 95% CI 2.17--16.77; *CVRS:* A-CVD: RD 18.38, 95% CI -12.10--78.32; *prior CV disease:* A-CVD: RD 18.30, 95% CI -11.26--78.98) (Table 9 and 10), indicating a higher risk among those with high baseline CV risk on the additive scale.

In the modified cohort, there was a significantly increased risk of C-CVD in the day 0-5 window in the high CVRS subgroup but not in the prior CV disease subgroup (*CVRS*: C-CVD HR 1.71, 95% CI 1.06--2.76, *prior CV disease:* C-CVD HR 1.58, 95% CI 0.90--2.79) and the associations were not significant in the 6-10 day window. None of the hazard ratios among the high CV risk subgroups were higher than in the overall population (C-CVD HR 1.82, 95% CI 1.23--2.67) (Table 9). There was also an increase in absolute risk in the high CVRS subgroup (RD 85.48, 95% CI 6.8--212.66), which was higher than the effect in the overall population (RD 12.79, 95% CI 3.66--26.21) (Table 9).

10.4.2. Secondary Objectives

Table 11: Non-Cardiovascular death (coded) and All-cause death (coded), 0-5 and 6 – 10 days following Azithromycin and Amoxicillin Prescriptions for KPNC/KPSC Members Age 30-74 years old (whole and modified cohort).

Coded non-CVD deaths and all-cause deaths, whole cohort							
	Azithromycin (n=1,922,425)		Amoxicillin (n=6,525,463)		Adjusted Risk Difference*† (95% CI)	Adjusted Hazard Ratio† (95% CI)	p-value
Outcome	Deaths (n)	Cumulative Incidence*	Deaths (n)	Cumulative Incidence*			
Non-Cardiovascular Death[1]							
0-5 days	221	115.62	213	32.80	23.78 (11.87--38.86)	1.72 (1.36--2.18)	<0.001
6-10 days	199	106.01	199	31.10	20.75 (9.41--35.26)	1.67 (1.30--2.13)	<0.001
All-cause Death[1]							
0-5 days	335	175.24	352	54.19	44.26 (27.52--64.42)	1.82 (1.51--2.19)	<0.001
6-10 days	259	137.97	315	49.23	28.28 (14.17--45.52)	1.57 (1.29--1.92)	<0.001
Coded non-CVD deaths and all-cause deaths, modified cohort							
	(n=1,736,976)		(n= 6,087,705)				
Non-Cardiovascular Death[2]							
0-5 days	83	48.06	68	11.22	13.13 (4.99--25.37)	2.17 (1.44--3.26)	<0.001
6-10 days	35	20.71	43	7.22	3.29 (-0.89--10.21)	1.46 (0.88--2.41)	0.15
All-cause Death[2]							
0-5 days	145	83.97	163	26.90	26.77 (13.74--43.97)	2.00 (1.51--2.63)	<0.001
6-10 days	66	39.05	111	18.63	6.37 (-0.89--16.59)	1.34 (0.95--1.89)	0.09

*per 1,000,000 prescriptions
[1] secondary analysis, per SAP
[2] post hoc analysis
†Adjusted for propensity score decile, age, and gender

Patients taking azithromycin had a significantly increased risk of non-CV death and all-cause death within the 0-5 day window (Non-CVD HR 1.72, 95% CI 1.36--2.18; all-cause HR 1.82, 95% CI 1.51--2.19) and the 6-10 day window (Non-CVD HR 1.67, 95% CI 1.30--2.13; all-cause HR 1.57, 95% CI 1.29--1.92).

In the modified cohort, patients taking azithromycin similarly had an increased risk of non-CV death and all-cause death during the 0-5 day window (Non-CVD HR 2.17, 95% CI 1.44--3.26, all-cause death HR 2.00, 95% CI 1.51--2.63), which was reduced to non-significant levels during the 6-10 window. A separate analysis was performed using the combined 0-10 day outcome window and produced HR 1.89, 95% CI 1.32--2.71.

Table 12: Cardiovascular death (coded), 11-365 days following Azithromycin and Amoxicillin Prescriptions for KPNC/KPSC Members Age 30-74 years old, subgroup analyses (whole and modified cohort).

	Azithromycin			Amoxicillin			Adjusted Risk Difference*†	Adjusted Hazard Ratio† (95% CI)	p-value
	Rx (n)	Deaths (n)	Cumulative Incidence*	Rx (n)	Deaths (n)	Cumulative Incidence*			
Cardiovascular death, whole cohort									
Whole Cohort[1]	1,922,425	1046	681.50	6,525,463	2759	538.66	39.08 (-10.34--93.12)	1.07 (0.98--1.17)	0.12
Subgroup									
Prior CV disease[1]	252,180	650	3429.56	690,253	1508	2962.83	386.40 (16.35--802.41)	1.13 (1.01--1.27)	0.040
Top decile CVRS[1]	176,798	717	5317.42	667,989	1995	4022.64	527.11 (66.64--1039.44)	1.13 (1.02--1.26)	0.024
Prior CV disease *or* top decile CVRS[1]	343,029	840	3242.06	1,114,974	2256	2735.27	305.27 (14.90--626.30)	1.11 (1.01--1.23)	0.039
Patients with COPD[1]	414,851	403	1254.42	544,841	536	1313.25	92.09 (-113.26--332.59)	1.07 (0.91--1.25)	0.40
Patients with CAP[1]	289,202	374	1640.97	263,530	372	1925.20	-6.04 (-347.69--409.60)	1.00 (0.82--1.21)	0.97
Cardiovascular death, modified cohort									
Modified cohort[2]	1,736,976	645	465.57	6,087,705	1977	415.46	18.86 (-26.20--69.15)	1.05 (0.94--1.17)	0.43
Subgroup									
Prior CV disease[2]	197,379	346	2309.37	571,728	928	2193.43	199.73 (-143.21--600.04)	1.09 (0.93-1.27)	0.27
Top decile CVRS[2]	139,290	429	3972.51	574,234	1397	3278.34	455.52 (-9.14--986.22)	1.14 (1.00--1.30)	0.06
Prior CV disease *or* top decile CVRS[2]	275,128	498	2373.46	957,415	1569	2216.06	243.55 (-46.74--572.68)	1.11 (0.98--1.26)	0.10
Patients with COPD[2]	356,871	235	843.12	478,768	335	932.71	91.87 (-95.93--321.82)	1.10 (0.90--1.35)	0.36

Patients with CAP[2]	242,875	189	991.89	213,275	162	1025.87	89.48 (-198.72--478.11)	1.09 (0.81--1.47)	0.58

*per 1,000,000 prescriptions
[1] secondary analysis, per SAP
[2] post hoc analysis
†Adjusted for propensity score decile, age, and gender

No significant increased risk of CV death was found for azithromycin users during the 11-365 days after dispensing (HR 1.07, 95% CI 0.98--1.17). This finding is similar within the modified cohort (HR 1.05, 95% CI 0.98--1.17). Among the high-risk subgroups, non-significant or borderline significant associations were observed in the whole cohort (HRs ranged from 1.00-1.13), and non-significant associations were observed in the modified cohort (HRs ranged from 1.05-1.14).

10.4.3. Sensitivity analyses

The sensitivity analysis results presented below include both the per protocol analyses (adjudicated CV death) as well as analyses conducted using the modified cohort (coded CV death with serious illness exclusion criteria applied).

Table 13: Adjudicated Cardiovascular Death (whole cohort) and Coded Cardiovascular Death (modified cohort), 0-5 and 6 – 10 days following Azithromycin and Amoxicillin Prescriptions for KPNC/KPSC Members Age 30-74 years old with Cox regression models using a propensity score stratified summary estimate. (sensitivity analysis #1)

Adjudicated CV Death (A-CVD), whole cohort[1]							
	Azithromycin (n=1,922,425)		Amoxicillin (n=6,525,463)		Adjusted Risk Difference*† (95% CI)	Adjusted Hazard Ratio† (95% CI)	p-value
Outcome	Deaths (n)	Cumulative Incidence*	Deaths (n)	Cumulative Incidence*			
0-5 days	38	19.88	37	5.70	8.46 (2.41--19.04)	2.49 (1.42--4.34)	0.001
6-10 days	24	12.80	38	5.94	1.97 (-1.98--9.87)	1.33 (0.67--2.66)	0.42
Coded CV Death (C-CVD), modified cohort[2]							
	(n=1,736,976)		(n=6,087,705)				
0-5 days	62	35.91	95	15.68	14.79 (4.48--30.39)	1.94 (1.29--2.94)	0.002
6-10 days	31	18.34	68	11.41	1.52 (-3.97--11.07)	1.13 (0.65--1.97)	0.66

*per 1,000,000 prescriptions
[1]sensitivity analysis, per SAP
[2]post hoc analysis
† Adjusted for age and gender

Using the PS as a stratifying variable within the Cox model did not substantially alter the results. Specifically, the 0-5 day risk of A-CVD in the whole cohort (HR 2.49, 95% CI 1.42--4.34) is similar to the primary analysis results shown in Table 9 (HR 2.33, 95% CI 1.3--3.94). The 0-5 day risk of C-CVD in the modified cohort (HR 1.94, 95% CI 1.29--2.94, is also similar to the results reported in Table 9 (HR 1.82, 95% CI 1.23--2.67).

Table 14: Cardiac Death± (coded), 0-5 and 6-10 days following Azithromycin and Amoxicillin Prescriptions for KPNC/KPSC Members Age 30-74 years old, all prescriptions, whole and modified cohorts (sensitivity analysis #2)

Cardiac Death, whole cohort[1]							
	Azithromycin (n=1,922,425)		Amoxicillin (n=6,525,463)		Adjusted Risk Difference*† (95% CI)	Adjusted Hazard Ratio† (95% CI)	p-value
Outcome	Deaths (n)	Cumulative Incidence*	Deaths (n)	Cumulative Incidence*			
0-5 days	83	43.41	112	17.24	14.76 (5.55--27.71)	1.86 (1.32--2.61)	<0.001
6-10 days	46	24.51	92	14.37	3.69 (-2.28--12.61)	1.26 (0.84--1.88)	0.26
Cardiac Death, modified cohort[2]							
	(n=1736976)		(n=6087705)				
0-5 days	64	37.04	98	16.17	11.21 (2.43--24.15)	1.69 (1.15--2.49)	0.008
6-10 days	25	14.79	61	10.23	0.71 (-3.62--7.88)	1.07 (0.65--1.77)	0.79

*per 1,000,000 prescriptions
[1]sensitivity analysis, per SAP
[2]post hoc analysis
†Adjusted for propensity score decile, age, and gender
± "cardiac death" includes all CV deaths but excluding stroke-related deaths and other rare CV causes of death

During the first 5 days of therapy, patients taking azithromycin had a significantly increased risk of coded cardiac death (HR 1.86, 95% CI 1.32--2.61), defined as C-CVD (HR 2.06, 95% CI 1.53--2.77, Table 9), excluding stroke-related deaths and other rare CV causes of death. Similar results were observed for the modified cohort (HR 1.69, 95% CI 1.5--2.49). For both cohorts, the results were non-significant in the 6-10 day window.

Table 15: Adjudicated Cardiovascular Death (whole cohort) and Coded Cardiovascular Death (modified cohort), 0-5 and 6 – 10 days following Azithromycin and Amoxicillin Prescriptions for KPNC/KPSC Members Age 30-74 years old, by the number of antibiotic prescriptions (including study antibiotics and other antibiotics) within the 30 days prior to index, subgroup analyses. (sensitivity analysis #3)

Adjudicated CV Death (A-CVD), whole cohort[1]									
	Azithromycin			Amoxicillin			Adjusted Risk Difference*† (95% CI)	Adjusted Hazard Ratio† (95% CI)	p-value
Outcome	Rx (n)	Deaths (n)	Cumulative Incidence*	Rx (n)	Deaths (n)	Cumulative Incidence*			
Cardiovascular Death 0-5 days									
0 abx rx	1,704,444 (89%)	34	20.06	5,927,440 (91%)	33	5.59	8.22 (2.34--18.44)	2.47 (1.42--4.3)	0.001
≥1 abx rx	217,981 (11%)	4	18.48	598,023 (9%)	4	6.72	4.63 (-4.27--45.82)	1.69 (0.36--7.82)	0.50
Cardiovascular Death 6-10 days									
0 abx rx	1,704,444 (89%)	21	8.99	5,927,440 (91%)	32	4.12	2.38 (-0.62--7.96)	1.58 (0.85--2.93)	0.15
≥1 abx rx	217,981 (11%)	3	14.18	598,023 (9%)	6	10.30	-1.57 (-8.84--41.93)	0.85 (0.14--5.07)	0.86
Coded CV Death (C-CVD), modified cohort[2]									
Cardiovascular Death 0-5 days									
0 abx rx	1,546,485 (89%)	53	34.47	5,546,587 (91%)	86	15.58	13.01 (3.38--27.52)	1.83 (1.22--2.77)	0.004
≥1 abx rx	190,491 (11%)	26	17.26	541,118 (9%)	57	10.49	3.84 (-1.93--13.52)	1.37 (0.82--2.29)	0.24
Cardiovascular Death 6-10 days									
0 abx rx	1,546,485 (89%)	9	47.58	5,546,587 (91%)	9	16.72	17.12 (-5.43--84.72)	2.02 (0.68--6.07)	0.21
≥1 abx rx	190,491 (11%)	5	27.22	541,118 (9%)	11	20.95	-1.53 (-14.48--37.39)	0.93 (0.31--2.78)	0.89

*per 1,000,000 prescriptions
†Adjusted for propensity score decile, age, and gender
abx rx = antibiotic prescriptions within 30 days prior to the index date

[1]sensitivity analysis, per SAP
[2]post hoc analysis
Note: due to cells with zero counts, categories 1 and >1 were collapsed into ≥1

The 0-5 day risk of A-CVD is higher in the subgroup of patients not exposed to any kind of antibiotic in the 30 days prior to index (HR 2.47, 95% CI 1.42--4.3) than the subgroup with one or more antibiotic exposures (HR 1.69, 95% CI 0.36--7.82). Similar results were observed for C-CVD in the modified cohort for both those with no antibiotic exposure in the 30 days prior to index (HR 1.83, 95% CI 1.22--2.77) and those with one or more antibiotic exposures (HR 1.37, 95% CI 0.82--2.29).

Note regarding **sensitivity analysis #4**: The distribution of dose and duration for the study antibiotics is described in Table 5, above. Because of the lack of significant variation in dose and duration, an analysis stratified by these variables was not performed.

Table 16: Adjudicated + Unclassifiable Cardiovascular Death[±], 0-5 and 6-10 days following Azithromycin and Amoxicillin Prescriptions for KPNC/KPSC Members Age 30-74 years old, all prescriptions, whole and modified cohorts (sensitivity analysis #5).

Adjudicated CV Death (A-CVD) + Unclassifiable CV Death (U-CVD), whole cohort[1]							
	Azithromycin (n=1,922,425)		Amoxicillin (n=6,525,463)		Adjusted Risk Difference*[†] (95% CI)	Adjusted Hazard Ratio[†] (95% CI)	p-value
Outcome	Deaths (n)	Cumulative Incidence*	Deaths (n)	Cumulative Incidence*			
0-5 days	110	57.52	136	20.94	22.14 (10.93--37.29)	2.06 (1.52--2.78)	<0.001
6-10 days	54	28.77	112	17.50	4.04 (-2.62--13.68)	1.23 (0.85--1.78)	0.27
Adjudicated CV Death (A-CVD) + Unclassifiable CV Death (U-CVD), modified cohort[2]							
	(n=1,736,976)		(n=6,087,705)				
0-5 days	62	35.91	95	15.68	12.79 (3.66--26.21)	1.82 (1.23--2.67)	0.002
6-10 days	31	18.34	68	11.41	3.15 (-2.31--11.91)	1.28 (0.80--2.04)	0.31

*per 1,000,000 prescriptions
[1]secondary analysis, per SAP
[2]post hoc analysis
[†]Adjusted for propensity score decile, age, and gender
U-CVD: unclassifiable CV deaths
[±] Includes coded CV deaths that were adjudicated to be CV deaths, and coded CV deaths with insufficient information in medical records to be classified as CV or non-CV deaths during the adjudication process

During the first 5 days of therapy, patients taking azithromycin had an increased risk of CV death, as defined as adjudicated CV deaths (A-CVD) plus those that were categorized as unclassifiable (HR 2.06, 95% CI 1.52--2.78). Similar results were observed in the modified cohort (HR 1.82, 95% CI 1.23--2.67). There was no significant effect during days 6-10 in either cohort.

Note regarding **sensitivity analysis #6**: These results are included in Table 9.

Table 17: Adjudicated Cardiovascular Death and Coded Cardiovascular Death, 0-5 and 6 – 10 days following Azithromycin and Amoxicillin Prescriptions for KPNC/KPSC Members Age 30-74 years old, among a very high CV risk subgroup, using alternative high CV risk score cut-off point based on Ray et al. (2012).[1] (sensitivity analysis #7).

Adjudicated CV Death (A-CVD), whole cohort[1]							
	Azithromycin (n = 141,358)		Amoxicillin (n = 534,471)		Adjusted Risk Difference*† (95% CI)	Adjusted Hazard Ratio† (95% CI)	p-value
Outcome	Deaths (n)	Cumulative Incidence*	Deaths (n)	Cumulative Incidence*			
Cardiovascular Death							
0-5 days	18	128.17	28	52.67	20.17 (-16.22--92.89)	1.38 (0.69--2.76)	0.36
6-10 days	15	109.50	28	53.68	8.54 (-23.92--76.44)	1.16 (0.55--2.42)	0.69
Coded CV Death (C-CVD), modified cohort[2]							
	(n=109,855)		(n=454,755)				
Cardiovascular death							
0-5 days	34	312.74	63	139.43	95.20 (3.94--244.54)	1.68 (1.03--2.75)	0.038
6-10 days	18	171.30	48	108.50	20.04 (-36.55--121.13)	1.18 (0.66--2.12)	0.57

*per 1,000,000 prescriptions
† adjusted for propensity score decile, age, and gender
[1]sensitivity analysis, per SAP
[2]post hoc analysis

The creation of a subgroup with an even higher CV risk than the top decile CVRS subgroup did not have a significant impact on the results. This subgroup was developed using the CVRS methodology (see Appendix 6) but used a higher cut point that would result in an amoxicillin cumulative incidence of C-CVD (0-5 days) of approximately 160 deaths per million prescriptions, matching what was observed in the population of Ray et al. (2012).[1] The exact cut-point used was 155.7 deaths per million prescriptions, including quantiles 46-50 of a 50 quantile distribution. The 0-5 day risk of A-CVD (HR 1.38, 95% CI 0.69--2.76) was similar to what was observed for the top decile of the CVRS in Table 10 above (HR 1.42, 95% CI 0.72--2.79).

After applying this cut point to the modified cohort, the derived subgroup had an amoxicillin cumulative incidence of C-CVD of 139.43 deaths per million prescriptions. Though this was somewhat higher than the 120.91 deaths per million prescriptions for the top decile CVRS group in the modified cohort (Table 10), the results are similar (higher risk cut point: HR 1.68, 95% CI 1.03--2.75, versus top decile CVRS: HR 1.71, 95% CI 1.06--2.76).

Table 18: Adjudicated Cardiovascular Death (A-CVD) (whole cohort) and Coded Cardiovascular Death (C-CVD) (modified cohort), 0-5 and 6-10 days following Azithromycin and Amoxicillin Prescriptions for KPNC/KPSC Members Age 30-74 years old, restricted to study antibiotics filled during 2009-2014 (2013 for KPSC) (sensitivity analysis #8).

Adjudicated CV Death (A-CVD), whole cohort[1]							
	Azithromycin (n = 1,102,633)		Amoxicillin (n = 2,093,737)		Adjusted Risk Difference*† (95% CI)	Adjusted Hazard Ratio† (95% CI)	p-value
Outcome	Deaths (n)	Cumulative Incidence*	Deaths (n)	Cumulative Incidence*			
Cardiovascular Death							
0-5 days	19	17.34	10	4.80	10.47 (1.86--30.19)	3.18 (1.39--7.29)	0.006
6-10 days	11	10.23	3	1.46	7.51 (0.84--33.52)	6.14 (1.58--23.95)	0.009
Coded CV Death (C-CVD) and Sudden Cardiac Death (C-SCD), modified cohort[2]							
	(n= 989,898)		(n=1,906,464)				
Cardiovascular death							
0-5 days	18	18.29	21	11.07	1.01 (-5.34--14.41)	1.09 (0.52--2.30)	0.82
6-10 days	7	7.24	5	2.69	2.12 (-1.29--13.86)	1.79 (0.52--6.16)	0.36
Sudden Cardiac Death							
0-5 days	2	2.03	9	4.74	-3.01 (-4.32--2.33)	0.37 (0.09--1.49)	0.16
6-10 days	3	3.09	3	1.61	1.05 (-1.24--17.73)	1.65 (0.23--12.02)	0.62

*per 1,000,000 prescriptions
† adjusted for propensity score decile, age, and gender
[1]sensitivity analysis, per SAP
[2]post hoc analysis

Restricting the population to the more recent era of KP's current electronic medical record does not meaningfully change the adjudicated results. For A-CVD in the whole cohort, the 0-5 day risk (HR 3.18, 95% CI 1.39--7.29) appears higher in comparison to the results reported in Table 9 (HR 2.33, 95% CI 1.38--3.94) but the confidence intervals are overlapping. The risk of A-CVD in the 6-10 day window (HR 6.14, 95% CI 1.58--23.95) also appears higher in comparison to the results reported Table 9 (HR 1.44, 95% CI 0.79--2.61) but, again, the confidence intervals are overlapping.
For the modified cohort, no significant differences were found, and the HR was 1.09, 95% CI 0.52--2.30. All of these analyses are limited by small sample sizes, resulting in large confidence intervals and limiting the interpretive utility of this analysis.

Table 19: Adjudicated Cardiovascular Death (whole cohort) and Coded Cardiovascular Death (modified cohort), 0-5 and 6-10 days following Azithromycin and Amoxicillin Prescriptions for KPNC/KPSC Members Age 30-74 years old, using only prescriptions which had an "infection" indication of use (i.e. excluding prescriptions with missing or prophylactic indication of use, sensitivity analysis #9).

Adjudicated CV Death (A-CVD), whole cohort[1]							
	Azithromycin (n = 1,623,254)		Amoxicillin (n=4,145,780)		Adjusted Risk Difference*† (95% CI)	Adjusted Hazard Ratio† (95% CI)	p-value
Outcome	Deaths (n)	Cumulative Incidence*	Deaths (n)	Cumulative Incidence*			
Cardiovascular Death							
0-5 days	36	22.32	30	7.27	8.8 (1.9--20.9)	2.21 (1.26--3.87)	0.006
6-10 days	20	12.65	31	7.64	1.47 (-2.81--9.53)	1.19 (0.63--2.25)	0.59
Coded CV Death (C-CVD), modified cohort[2]							
	(n=1,462,362)		(n=3,854,603)				
Cardiovascular death							
0-5 days	54	37.19	63	16.43	10.21 (0.92--24.49)	1.62 (1.06--2.49)	0.027
6-10 days	28	19.71	44	11.68	2.45 (-3.32--12.21)	1.21 (0.72--2.05)	0.48

*per 1,000,000 prescriptions
[1]sensitivity analysis, per SAP
[2]post hoc analysis
† adjusted for propensity score decile, age, and gender

Restricting the population to prescriptions with an infection, indicated by the coded indication of use, does not change the results. For A-CVD in the whole cohort, the 0-5 day risk was similar in comparison to the results reported in Table 9 (HR 2.21, 95% CI 1.26--3.87 versus HR 2.33, 95% CI 1.38--3.94). For C-CVD in the modified cohort, the 0-5 day risk was also similar in comparison to the results reported in Table 9 (HR 1.62, 95% CI 1.06--2.49 versus HR of 1.82, 95% CI 1.23--2.67).

Table 20: Distribution of emergency department (ED)/hospitalization admissions within 10 days of study antibiotic fill, sub-cohort with infection IOU (excludes prophylactic and missing indications, sensitivity analysis #10)

ED/hospitalization for the 10-day interval after the index date	Amoxicillin (n=4,145,780)		Azithromycin (n=1,623,254)	
	Count	**%**	**Count**	**%**
No ED or hospital visits	4061296	97.96%	1579888	97.33%
ED visit, no hospital visit	61263	1.48%	28195	1.74%
Hospital visit, no ED visit	8609	0.21%	3993	0.25%
Hospital and ED visit	14612	0.35%	11178	0.69%

There was no variation in hospital and ED visits across antibiotic groups. The large majority (>97%) had no ED or hospital stay within 10 days prior to the index date.

Table 21: Adjudicated Cardiovascular Death (whole cohort) and Coded Cardiovascular Death (modified), 0-5 and 6–10 days following Azithromycin and Amoxicillin Prescriptions for KPNC/KPSC Members Age 30-74 years old; Cox regression stratified by number of previous study antibiotic prescriptions (continuous variable and dichotomized as 0 or ≥1), (sensitivity analysis #11).

Adjudicated CV Death (A-CVD), whole cohort[1]							
	Azithromycin (n=1,922,425)		Amoxicillin (n=6,525,463)		Adjusted Risk Difference*† (95% CI)	Adjusted Hazard Ratio† (95% CI)	p-value
Outcome	Deaths (n)	Cumulative Incidence*	Deaths (n)	Cumulative Incidence*			
Cardiovascular Death / Cox stratified on previous fills (continuous)							
0-5 days	38	19.88	37	5.70	7.54 (2.12--16.71)	2.32 (1.37--3.93)	0.002
6-10 days	24	12.80	38	5.94	2.66 (-1.19--9.65)	1.45 (0.8--2.62)	0.22
Cardiovascular Death / Cox stratified on previous fills (dichotomous)							
0-5 days	38	19.88	37	5.70	7.57 (2.16--16.7)	2.33 (1.38--3.93)	0.002
6-10 days	24	12.80	38	5.94	2.63 (-1.23--9.63)	1.44 (0.79--2.62)	0.23
Coded CV Death (C-CVD), modified cohort[2]							
	(n=1,736,976)		(n=6,087,705)				
Cardiovascular Death / Cox stratified on previous fills (continuous)							
0-5 days	62	35.91	95	15.68	12.60 (3.48--26.06)	1.80 (1.22--2.66)	0.003
6-10 days	31	18.34	68	11.41	3.23 (-2.28--12.09)	1.28 (0.80--2.06)	0.30
Cardiovascular Death / Cox stratified on previous fills (dichotomous)							
0-5 days	62	35.91	95	15.68	12.75 (3.63--26.18)	1.81 (1.23--2.67)	0.003
6-10 days	31	18.34	68	11.41	3.15 (-2.33--11.93)	1.28 (0.80--2.05)	0.31

*per 1,000,000 prescriptions
† adjusted for propensity score decile, age, and gender
[1]sensitivity analysis, per SAP
[2]post hoc analysis

Stratification by the number of study antibiotic prescriptions dispensed within 30 days prior to the index date did not change the primary results. For A-CVD in the whole cohort, the 0-5 day risk was comparable to the results reported in Table 9 for both continuous (HR 2.32, 95% CI 1.37--3.93) and dichotomous (HR 2.33, 95% CI 1.38--3.93) stratification versus HR 2.33, 95% CI 1.38--3.94 in Table 9. For C-CVD in the modified cohort, the 0-5 day risk was also comparable to the results reported in Table 9 for both

continuous (HR 1.80, 95% CI 1.22--2.66) and dichotomous (HR 1.81, 95% CI 1.23--2.67) stratification versus HR of 1.82, 95% CI 1.23--2.67 in Table 9.

Table 22: Adjudicated and Coded Cardiovascular Death 0-5 and 6 – 10 days following Azithromycin and Amoxicillin Prescriptions for KPNC/KPSC Members Age 30-74 years old, whole cohort, outcomes censored upon hospital admission (sensitivity analysis #12)

Adjudicated CV Death (A-CVD), whole cohort[1]							
	Azithromycin (n=1,922,425)		Amoxicillin (n=6,525,463)		Adjusted Risk Difference*† (95% CI)	Adjusted Hazard Ratio† (95% CI)	p-value
Outcome	Deaths (n)	Cumulative Incidence*	Deaths (n)	Cumulative Incidence*			
Cardiovascular Death							
0-5 days	25	13.09	30	4.62	4.32 (0.13--12.21)	1.94 (1.03--3.64)	0.041
6-10 days	9	4.82	16	2.51	0.79 (-1.14--5.45)	1.32 (0.55--3.17)	0.54
Coded CV Death, (C-CVD) whole cohort[2]							
Cardiovascular Death							
0-5 days	90	47.12	121	18.64	17.54 (7.25--31.92)	1.94 (1.39--2.71)	<0.001
6-10 days	38	20.36	81	12.69	2.96 (-2.49--11.33)	1.23 (0.80--1.89)	0.34

*per 1,000,000 prescriptions
† adjusted for propensity score decile, age, and gender
[1]sensitivity analysis, per SAP
[2]post hoc analysis

Censoring outcomes occurring during a hospital admission did not meaningfully change the results. For A-CVD in the whole cohort, the 0-5 day HR was 1.94 (95% CI 1.03--3.64) versus HR 2.33 (95% CI 1.38--3.94) in Table 9. For C-CVD in the whole cohort, the 0-5 day HR was 1.94 (95% CI 1.03--3.64) versus a HR of 2.06 (95% CI 1.53--2.77) in Table 9.

10.5. Other analyses

The analyses below are post hoc analyses conducted using coded outcome data, and not previously presented in the Main Results section.

Table 23: Coded CV death (C-CVD) and Non-CV death 0-5 and 6 – 10 days following Azithromycin and Amoxicillin Prescriptions for Members Age 30-74 years old, by KP site, modified cohort

KPNC	**Azithromycin** (n=1,093,980)		**Amoxicillin** (n=2,856,689)		**Adjusted Hazard Ratio†** **(95% CI)**	**p-value**
Outcome	Deaths (n)	Cumulative Incidence*	Deaths (n)	Cumulative Incidence*		
C-CVD						
0-5 days	32	29.46	34	11.97	2.01 (1.17--3.47)	0.012
6-10 days	18	16.93	30	10.74	1.29 (0.68--2.44)	0.43
Non-CV death						
0-5 days	45	41.41	36	12.65	1.83 (1.08--3.11)	0.025
6-10 days	29	27.27	24	8.61	1.78 (0.97--3.26)	0.06
KPSC	**Azithromycin** (n=642,996)		**Amoxicillin** (n=3,231,016)		**Adjusted Hazard Ratio†** **(95% CI)**	**p-value**
Outcome						
C-CVD						
0-5 days	30	46.87	61	18.95	1.74 (1.01--3.01)	0.048
6-10 days	13	20.75	38	12.00	1.22 (0.61--2.46)	0.58
Non-CV death						
0-5 days	38	59.37	32	9.95	2.75 (1.47--5.13)	0.002
6-10 days	6	9.57	19	6.00	0.74 (0.26--2.09)	0.56

*per 1,000,000 prescriptions
† adjusted for propensity score decile, age, and gender

The risk of C-CVD was similar across KP sites, within the first 5 days (KPNC: HR 2.01, 95% CI 1.17--3.47, KPSC: HR 1.74, 95% CI 1.01--3.01), as well as within 6-10 days after dispensing (KPNC: HR 1.29, 95% CI 0.68--2.44, KPSC: HR 1.22, 95% CI 0.61--2.46). The risk of coded Non-CVD appeared to vary across KP sites within the first 5 days (KPNC: HR, 1.83 95% CI 1.08--3.11, KPSC: HR

2.75, 95% CI 1.47--5.13), and within the 6-10 days following dispensing (KPNC: HR 1.78, 95% CI 0.97--3.26, KPSC: HR 0.74 95% CI 0.26--2.09) but the confidence intervals are overlapping.

Table 24: Coded CV Death (C-CVD), 0-5 and 6-10 days following Azithromycin and Amoxicillin Prescriptions for KPNC/KPSC Members Age 30-74 years old with no prior CV disease, modified cohort.

	Azithromycin (n= 1,539,597)		Amoxicillin (n= 5,515,977)		Adjusted Risk Difference*† (95% CI)	Adjusted Hazard Ratio† (95% CI)	p-value
	Deaths (n)	Cumulative Incidence*	Deaths (n)	Cumulative Incidence*			
C-CVD							
0-5 days	32	20.92	45	8.20	9.09 (2.01--21.07)	2.11 (1.25--3.57)	0.005
6-10 days	14	9.33	37	6.85	0.88 (-2.89--8.24)	1.13 (0.58--2.20)	0.72

*per 1,000,000 prescriptions
† adjusted for propensity score decile, age, and gender

These data are complementary to those reported in Table 10 (C-CVD in the subgroup with prior CV disease). As demonstrated by overlapping confidence intervals, there was no significant difference in the 0-5 day effect in the population without prior CV disease (HR 2.11, 95% CI 1.25--3.57) versus those with prior CV disease (HR 1.58, 95% CI 0.90--2.79). Confidence intervals also overlapped for the adjusted risk difference in those without (9.09, 95% CI 2.01--21.07) versus with prior CV disease (51.47, 95% CI -8.7--157.40).

Table 25: Non-Cardiovascular Death (coded), 0-5 and 6 – 10 days following Azithromycin and Amoxicillin Prescriptions for KPNC/KPSC Members Age 30-74 years old, by CVRS subgroup, modified cohort.

Non-Cardiovascular deaths									
	Azithromycin			Amoxicillin			Adjusted Risk Difference*† (95% CI)	Adjusted Hazard Ratio† (95% CI)	p-value
Subgroup	Rx (n)	Deaths (n)	Cumulative Incidence*	Rx (n)	Deaths (n)	Cumulative Incidence*			
Low CVRS	921,914			3,099,598					
0-5 days		12	13.07		9	2.92	4.13 (-0.56--18.17)	2.42 (0.81--7.23)	0.11
6-10 days		5	5.56		4	1.32	1.68 (-0.54--10.27)	2.27 (0.59--8.79)	0.23
Medium CVRS	675,772			2,413,873					
0-5 days		29	43.20		21	8.74	7.35 (-0.26--21.82)	1.84 (0.97--3.50)	0.06
6-10 days		20	30.44		13	5.51	5.83 (-0.22--18.82)	2.06 (0.96--4.42)	0.06
High CVRS	139,290			574,234					
0-5 days		42	304.17		38	66.57	90.02 (21.3--212.49)	2.35 (1.32--4.19)	0.004
6-10 days		10	74.92		26	46.62	-7.99 (-29.66--41.34)	0.83 (0.36--1.89)	0.65

*per 1,000,000 prescriptions
† adjusted for propensity score decile, age, and gender

There is a consistent risk associated with azithromycin exposure in the day 0-5 window across the spectrum of CV risk, though the small number of outcomes in the lower risk groups provided limited power to evaluate associations (low CV risk: HR 2.42, 95% CI 0.81--7.23, medium CV risk: HR 1.84, 95% CI 0.97--3.50, high CV risk HR 2.35, 95% CI 1.32--4.19). The adjusted risk difference data show a large increase in risk when baseline CV risk becomes high (ARD 90.02, 95% CI 21.3--212.49). For the 6-10 day outcome window, the pattern appears different, but no observed differences were statistically significant and confidence intervals were overlapping between the groups (low CV risk: HR 2.27, 95% CI 0.59--8.79, medium CV risk: HR 2.06, 95% CI 0.96--4.42, high CV risk: 0.83, 95% CI 0.36--1.89.

Table 26: **Coded CV Death (C-CVD), 0-5 and 6 – 10 days following Azithromycin and Amoxicillin Prescriptions for KPNC/KPSC Members Age 30-74 years old, all prescriptions with Cox regression models using propensity score as a continuous covariate**

Coded CV Death (C-CVD)							
	Azithromycin (n=1,922,425)		Amoxicillin (n=6,525,463)		Adjusted Risk Difference*† (95% CI)	Adjusted Hazard Ratio† (95% CI)	p-value
Outcome	Deaths (n)	Cumulative Incidence*	Deaths (n)	Cumulative Incidence*			
C-CVD							
0-5 days	114	59.62	139	21.40	22.05 (10.94--36.97)	2.03 (1.51--2.73)	<0.001
6-10 days	60	31.97	116	18.13	5.17 (-1.79--15.08)	1.29 (0.90--1.83)	0.17

*per 1,000,000 prescriptions
† adjusted for propensity score decile, age, and gender

Using the PS as a continuous variable in the Cox model produces similar results to treating PS as a categorical variable (deciles) in the primary analysis (continuous: HR 2.03, 95% CI 1.51--2.73, categorical: HR 2.06, 95% CI 1.53--2.77).

Table 27: Coded CV Death (C-CVD), 0-5 and 6 – 10 days following Azithromycin and Amoxicillin Prescriptions for KPNC/KPSC Members Age 30-74 years old, by CVRS subgroup, modified cohort.

Coded CV Death (C-CVD)									
	Azithromycin			Amoxicillin			Adjusted Risk Difference*† (95% CI)	Adjusted Hazard Ratio† (95% CI)	p-value
Subgroup	Rx (n)	Deaths (n)	Cumulative Incidence*	Rx (n)	Deaths (n)	Cumulative Incidence*			
Low CVRS	921,914			3,099,598					
0-5 days		4	4.36		8	2.59	-0.71 (-2.03--3.69)	0.73 (0.22--2.42)	0.60
6-10 days		2	2.22		2	0.66	0.30 (-0.49--4.72)	1.46 (0.26--8.13)	0.67
Medium CVRS	675,772			2,413,873					
0-5 days		21	31.22		18	7.48	11.96 (1.75--33.48)	2.60 (1.23--5.47)	0.012
6-10 days		9	13.69		15	6.35	2.19 (-3.01--15.51)	1.35 (0.53--3.44)	0.54
High CVRS	139,290			574,234					
0-5 days		37	268.33		69	120.91	85.48 (6.80--212.66)	1.71 (1.06--2.76)	0.029
6-10 days		20	149.83		51	91.20	24.00 (-25.79--111.68)	1.26 (0.72--2.22)	0.42

*per 1,000,000 prescriptions
† adjusted for propensity score decile, age, and gender

Note: The high CVRS sub-group results (Table 27) are the same results shown in Table 10. These results show a non-linear relationship such that the 0-5 day risk appears higher in the medium CVRS group (HR 2.60, 95% CI 1.23--5.47) than both the low (HR 0.73, 95% CI 0.22--2.42) and high (HR 1.71, 95% CI 1.06--2.76) CVRS groups but with overlapping confidence intervals. This non-linear relationship may be explained by estimation instability due to the small number of outcomes in the lower risk groups. The adjusted risk differences are similar in the high CVRS group (85.48, 95% CI 6.80--212.66) and the medium CVRS group (11.96, 95% CI 1.75--33.48). The 6-10 results were non-significant across the spectrum of CV risk.

Table 28: Coded CV death (C-CVD) and Non-CV death, 0-5 and 6 – 10 days following Azithromycin and Amoxicillin Prescriptions for Members Age 30-74 years old, high CVRS subgroup, by study site, modified cohort

KPNC	**Azithromycin** (n=88,979)		**Amoxicillin** (n=290,820)		Adjusted **Hazard Ratio**[†] **(95% CI)**	**p-value**
Outcome	Deaths (n)	Cumulative Incidence*	Deaths (n)	Cumulative Incidence*		
C-CVD						
0-5 days	20	227.42	24	83.09	1.94 (0.96--3.93)	0.06
6-10 days	10	117.45	20	70.58	1.18 (0.52--2.67)	0.70
Non-CV death						
0-5 days	23	260.93	21	72.59	2.06 (0.98--4.31)	0.06
6-10 days	8	93.82	13	46.14	1.17 (0.43--3.20)	0.76
KPSC	**Azithromycin** (n=50,311)		**Amoxicillin** (n=283,414)		**Hazard Ratio**[†] **(95% CI)**	**p-value**
Outcome						
C-CVD						
0-5 days	17	340.65	45	159.66	1.53 (0.79--2.97)	0.21
6-10 days	10	207.17	31	112.31	1.33 (0.61--2.89)	0.47
Non-CV death						
0-5 days	19	380.60	17	60.39	2.87 (1.16--7.09)	0.023
6-10 days	2	41.44	13	47.10	0.40 (0.08--2.02)	0.27

*per 1,000,000 prescriptions
[†] adjusted for propensity score decile, age, and gender

There were no significant differences in C-CVD and Non-CV death results by KP site, among the high CVRS subgroup.

Table 29: Coded CV death (C-CVD), 0-5 and 6 – 10 days following Azithromycin and Amoxicillin Prescriptions for KPNC/KPSC Members Age 30-74 years old, infection severity subgroup analyses, modified cohort.

	Azithromycin (n=1,736,976)			Amoxicillin (n=6,087,705)			Adjusted Risk Difference*† (95% CI)	Adjusted Hazard Ratio† (95% CI)	p-value
Subgroup	Rx (n)	Deaths (n)	Cumulative Incidence*	Rx (n)	Deaths (n)	Cumulative Incidence*			
Patients with Pneumonia	139,625			21,452					
0-5 days		18	130.81		1	48.62	90.44 (-30.99--1047.81)	2.86 (0.36--22.55)	0.32
6-10 days		6	45.04		4	202.62	-155.31 (-188.97---38.66)	0.23 (0.07--0.81)	0.022
Patients w/o Pneumonia	1,597,351			6,066,253					
0-5 days		44	27.68		94	15.57	11.83 (2.47--26.05)	1.76 (1.16--2.67)	0.008
6-10 days		25	16.06		64	10.77	5.13 (-0.97--15.03)	1.48 (0.91--2.40)	0.11
Patients w/o Pneumonia, IOU‡	1,279,026			3,596,778					
0-5 days		34	26.73		55	15.37	8.12 (-1.12--23.33)	1.53 (0.93--2.52)	0.10
6-10 days		21	16.87		38	10.80	4.01 (-2.35--15.17)	1.37 (0.78--2.4)	0.27
Patients with respiratory infection	937,740			825,321					
0-5 days		47	50.48		25	30.50	26.66 (2.06--69.83)	1.87 (1.07--3.29)	0.029
6-10 days		25	27.45		21	26.09	4.99 (-9.75--33.04)	1.19 (0.63--2.27)	0.59
Patients with non-respiratory infection	799,236			5,262,384					
0-5 days		15	18.84		70	13.36	11.58 (0.57--31.29)	1.87 (1.04--3.34)	0.036
6-10 days		6	7.70		47	9.12	1.07 (-4.81--14.97)	1.12 (0.47--2.64)	0.80
Patients with	480,911			2,792,909					

non-respiratory infection, IOU‡									
0-5 days		5	10.47		31	11.15	3.31 (-5.90--28.68)	1.30 (0.47--3.57)	0.61
6-10 days		2	4.29		21	7.69	-1.76 (-6.33--18.13)	0.77 (0.18--3.36)	0.73
Patients with Ray's high severity infection¥	335,642			192,309					
0-5 days		27	81.23		8	42.14	44.13 (-4.98--158.16)	2.05 (0.88--4.75)	0.10
6-10 days		13	40.30		12	64.64	-22.11 (-46.68--36.11)	0.66 (0.28--1.56)	0.34
Patients with non-Ray's high severity infection¥	1,401,334			5,895,396					
0-5 days		35	25.10		87	14.82	12.62 (2.6--28.39)	1.85 (1.18--2.92)	0.008
6-10 days		18	13.16		56	9.70	4.71 (-1.36--15.19)	1.48 (0.86--2.57)	0.16
Patients with non-Ray's high severity infection¥, IOU‡	1,083,009			3,425,921					
0-5 days		25	23.22		48	14.08	8.07 (-1.59--25.23)	1.57 (0.89--2.79)	0.12
6-10 days		14	13.26		30	8.95	3.71 (-2.41--15.54)	1.41 (0.73--2.74)	0.30

*per 1,000,000 prescriptions
† adjusted for propensity score decile, age, and gender
‡Excludes missing and prophylactic indications of use
¥See Tables 8A and 8B for Ray et al.'s (2012) definition of a high severity infection

There are largely non-significant associations between azithromycin exposure and C-CVD in subgroups with infections of different severity. Due to the large number of subgroups and small sample sizes these results have less precision and reduced statistical power.

Table 30: Non-Cardiovascular death, 0-5 and 6 – 10 days following Azithromycin and Amoxicillin Prescriptions for KPNC/KPSC Members Age 30-74 years old, infection severity subgroup analyses, modified cohort.

	Azithromycin (n=1,736,976)			**Amoxicillin (n=6,087,705)**			**Adjusted Risk Difference*† (95% CI)**	**Adjusted Hazard Ratio† (95% CI)**	**p-value**
Subgroup	Rx (n)	Deaths (n)	Cumulative Incidence*	Rx (n)	Deaths (n)	Cumulative Incidence*			
Patients with Pneumonia	139,625			21,452					
0-5 days		19	137.58		5	235.64	-75.00 (-173.17--177.43)	0.68 (0.27--1.75)	0.43
6-10 days		3	22.63		1	51.16	-24.45 (-48.56--223.31)	0.52 (0.05--5.36)	0.58
Patients w/o Pneumonia	1,597,351			6,066,253					
0-5 days		64	40.28		63	10.43	13.43 (5.17--26.07)	2.29 (1.50--3.50)	<0.001
6-10 days		32	20.55		42	7.08	5.11 (0.25--13.21)	1.72 (1.03--2.87)	0.036
Patients w/o Pneumonia, IOU‡	1,279,026			3,596,778					
0-5 days		52	40.91		40	11.17	9.29 (1.35--22.28)	1.83 (1.12--2.99)	0.016
6-10 days		28	22.49		23	6.54	4.71 (-0.46--14.27)	1.72 (0.93--3.18)	0.08
Patients with respiratory infection	937,740			825,321					
0-5 days		62	66.61		20	24.37	17.74 (-0.74--50.67)	1.73 (0.97--3.08)	0.06
6-10 days		25	27.47		13	16.18	1.18 (-7.69--19.31)	1.07 (0.52--2.19)	0.85
Patients with non-respiratory infection	799,236			5,262,384					
0-5 days		21	26.35		48	9.16	14.17 (4.55--30.53)	2.55 (1.50--4.33)	0.001
6-10 days		10	12.81		30	5.83	5.54 (-0.37--17.82)	1.95 (0.94--4.06)	0.07
Patients with respiratory infection, IOU‡	480,911			2,792,909					
0-5 days		9	18.78		25	8.99	5.38 (-2.49--22.78)	1.60 (0.72--3.54)	0.25
6-10 days		6	12.81		11	4.03	5.80 (-0.52--23.49)	2.44 (0.87--6.83)	0.09
Patients with Ray's high severity infection¥	335,642			192,309					
0-5 days		38	114.40		16	83.92	2.06 (-39.02--80.71)	1.02 (0.54--1.96)	0.94

6-10 days		9	27.97		9	48.73	-27.73 (-40.50--4.87)	0.43 (0.17--1.10)	0.08
Patients with non-Ray's high severity infection¥	1,401,334			5,895,396					
0-5 days		45	32.26		52	8.86	16.02 (6.92--30.35)	2.81 (1.78--4.43)	<0.001
6-10 days		26	19.00		34	5.90	8.78 (2.66--19.26)	2.49 (1.45--4.27)	0.001
Patients with non-Ray's high severity infection¥, IOU‡	1,083,009			3,425,921					
0-5 days		33	30.64		29	8.50	11.52 (2.84--26.84)	2.36 (1.33--4.16)	0.003
6-10 days		22	20.83		15	4.48	9.15 (2.22--23.24)	3.04 (1.50--6.19)	0.002

*per 1,000,000 prescriptions
† adjusted for propensity score decile, age, and gender
‡Excludes missing and prophylactic indications of use
¥See Tables 8A and 8B for Ray et al.s (2012) definition of a high severity infection

The results are different for Non-CVD than for C-CVD (Table 29). In general, stronger associations were observed for the subgroups with lower infection severity. For example, the subgroup with a high severity infection according to Ray et al. (2012) criteria had a smaller azithromycin HR (1.02, 95% CI 0.54--1.96) than the subgroup without a high severity infection (2.36, 95% CI 1.33--4.16). Due to the large number of subgroups and small sample sizes, the results have decreased precision and reduced statistical power.

Table 31: Coded Cardiovascular death (C-CVD), 0-5 and 6 – 10 days following Azithromycin and Amoxicillin Prescriptions for KPNC/KPSC Members Age 30-74 years old, with index antibiotic prescription year as a covariate, modified cohort.

	Azithromycin (n=1736976)		Amoxicillin (n=6087705)		Adjusted Risk Difference*† (95% CI)	Adjusted Hazard Ratio† (95% CI)	p-value
Outcome	Deaths (n)	Cumulative Incidence*	Deaths (n)	Cumulative Incidence*			
Cardiovascular death							
0-5 days	62	35.91	95	15.68	12.58 (3.70--25.54)	1.80 (1.24--2.63)	0.002
6-10 days	31	18.34	68	11.41	3.11 (-2.28--11.67)	1.27 (0.80--2.02)	0.31

*per 1,000,000 prescriptions
† adjusted for propensity score decile, age, and gender

Adding index year to the model as a separate covariate (outside of the PS) does not change the results (model with index year: HR 1.80, 95% CI 1.24--2.63 versus HR 1.82, 95% CI 1.23--2.67, Table 9).

Table 32: Coded CV death (C-CVD) and Non-cardiovascular death, 0-5 and 6 – 10 days following Azithromycin and Amoxicillin Prescriptions for KPNC/KPSC Members Age 30-74 years old, with infection category as a covariate, modified cohort.

	Azithromycin (n=1736976)		Amoxicillin (n=6087705)		Adjusted Risk Difference*† (95% CI)	Adjusted Hazard Ratio† (95% CI)	p-value
Outcome	Deaths (n)	Cumulative Incidence*	Deaths (n)	Cumulative Incidence*			
Cardiovascular death							
0-5 days	62	35.91	95	15.68	12.37 (3.36--25.65)	1.79 (1.21--2.64)	0.003
6-10 days	31	18.34	68	11.41	2.95 (-2.45--11.61)	1.26 (0.79--2.02)	0.34
Non-cardiovascular death							
0-5 days	83	48.06	68	11.22	12.84 (4.76--25.02)	2.14 (1.42--3.23)	<0.001
6-10 days	35	20.71	43	7.22	3.17 (-0.97--10.04)	1.44 (0.87--2.39)	0.16

*per 1,000,000 prescriptions
† adjusted for propensity score decile, age, and gender

Adding infection category (type of infection) to the multivariable model as a separate covariate (outside of the PS) did not change the C-CVD results (model with infection category as separate covariate: HR 1.79, 95% CI 1.21--2.64; main model without infection category as separate covariate: HR 1.82, 95% CI 1.23--2.67, Table 9).

10.6. Adverse events / adverse reactions

No reportable events were found during medical record review.

11. DISCUSSION

11.1. Key results

Ray et al. (2012) reported an increased risk of cardiovascular death associated with azithromycin (compared to amoxicillin) in a Medicaid population. Several other observational studies have since examined this, or a related research question, which have resulted in mixed, however largely non-corroborative findings (see Section 6, Table 1). While the study by Ray et al. (2012) was well-conducted, it had several limitations upon which this study attempted to improve. These efforts included attempts to adjudicate key endpoints to minimize outcome misclassification, and more comprehensive capture of indication of use to minimize confounding.

The presents study's results show an association between azithromycin use and acute cardiovascular and non-cardiovascular mortality. This association did not appear greater in those with high baseline CV risk, and there was no evidence of long-term effects of azithromycin on CV death. A detailed discussion of these findings follows below.

11.1.1 Primary Objectives

In this retrospective cohort study of over 8 million antibiotic exposures, the primary results suggest an increased relative and absolute risk of CV death associated with azithromycin exposure, as compared with amoxicillin, within 5 days of dispensing (the typical duration of azithromycin treatment) ((A-CVD (HR 2.33 [95% CI 1.38--3.94], RD 7.60 CV deaths per million prescriptions [95% CI 2.17--16.77]) and C-CVD (HR 2.06 [1.53--2.77], ARD 22.63 [11.27--37.96]). Similar effects were observed for both adjudicated (HR 2.10 [1.00--4.41], ARD 3.55 [0.00--11.02]) and coded cardiac deaths (HR 1.96 [1.23--3.14], ARD 7.54 [1.77--16.78]) outcomes. The post hoc analyses using the modified cohort also found associations between azithromycin and both C-CVD (HR 1.82 [1.23--2.67], RD 12.79 CV deaths per million prescriptions [3.66-26.21]) and C-SCD (HR 1.78 [1.05--3.03], RD 5.05 CV deaths per million prescriptions [0.33-13.07]). Thus, we observed an increase in the absolute risk of CV death ranging from 7.60 – 12.79 deaths per million azithromycin prescriptions.

No significantly increased risk of CV death and SCD was found during the 6-10 day window after prescription dispensing, which is consistent with Ray et al. (2012) findings. The proposed mechanism of action (MOA) by Ray et al. (2012)[1] was that azithromycin might increase risk for cardiovascular death via a cardiotoxic effect during the first 5 days after dispensing, when the drug is most likely to be taken.

While the observed significant association between azithromycin and CV death was similar to that observed by Ray et al. (2012)[1] (HR 2.49 [1.38--4.50], amoxicillin comparator) in a Tennessee Medicaid population,[1] it differed from the findings reported by Svanstrom et al. in 2013 (HR 0.93 [0.56--1.55], penicillin comparator) in a Danish general population sample.[2] When examining the findings across these studies, it is important to note key differences between populations and studies. KP's coded CV death incidence was 59.6 per million azithromycin exposures, which was lower than the incidence found by Ray (85 per million azithromycin exposures) yet higher than the incidence found by Svanstrom (15.4 per million azithromycin exposures).[2] These differences are likely explained by inter-study differences in population characteristics contributing to the risk of CV outcomes, such as age, diabetes, and baseline CV disease. Thus, the different results reported in these studies may be a consequence of differences in the health of the populations.

This study's SCD findings were similar to those observed for the larger CV death analysis. An increased risk was observed within the first 5 days of exposure (A-SCD HR 2.10 [1.00-4.41], C-SCD HR 1.78 [1.05--3.03]), which decreased to non-significant levels during days 6-10. Only 147 of the 429 coded CV deaths (34%) were SCD (see Appendix 9, Figure 4). Thus, while SCD (which is consistent with Ray et al. (2012) posited MOA) made up a large minority of CVD, there were also non-SCD causes of CVD that are inconsistent with this MOA, such as heart failure and MI. Thus, the possible arrhythmic MOA to explain the azithromycin effect, if valid, cannot be the sole mechanism of cardiotoxicity.

CV death among high baseline CV risk subgroups

There was no significant increase in the relative risk of A-CVD associated with azithromycin among those with prior CV disease or a high CVRS. There was an increased risk of C-CVD associated with azithromycin use within 5 days of dispensing among those with prior CV disease (HR 1.90 [1.26--2.86], ARD 106.24 [30.77--219.96]) or a high CVRS (HR 1.89 [1.31--2.73], ARD 137.27 [47.93--266.24]), which decreased to non-significant levels during the 6-10 day window. In the modified cohort, the only significant result was an increased risk of C-CVD in the high CVRS group during the 0-5 day window (C-CVD HR 1.71 [1.06-2.76], RD 85.48 [6.80-212.66]). While Ray et al. (2012)[1] did not report hazard ratios for a high CV risk subgroup, Svanstrom et al. (2013)[2] reported a possible trend for increased risk among those with baseline CV disease (HR 1.35 [0.69–2.64]).

The hazard among those with high baseline CV risk was not higher than the effect in the overall population, suggesting that those with baseline CV risk do not have an increased likelihood of a CV death outcome. However, those with high baseline CV risk appeared to have an increased absolute risk of C-CVD compared to the overall population, which is to be expected given the higher baseline CV risk in those subgroups.

11.1.2 Secondary Objectives

Non-CV death and All-cause cause death

Contrary to expectation and hypothesized MOA, the present study found an increased risk of non-CV death among azithromycin users, which was consistent across exposure periods (*0-5 days* HR 1.72 [1.36--2.18], RD 23.78[11.87--38.86], and *6-10 days* HR 1.67 [CI 1.30--2.13], RD 20.75 [9.41--35.26]). These results were supported by comparable results from the modified cohort analyses for the 0-5 day window, though the 6-10 day window results were not significant in the modified cohort.

These findings differed from Ray et al. (2012) who did not report an increased relative risk of non-CV death (HR 0.74 [0.33--1.67]; no antibiotic comparator).[1] Svanstrom et al. did not report non-CV death outcomes in their study.[2] Given the increased risk of CV death and non-CV death, the present study also reported an increased risk of all-cause death, which persisted across exposure periods (*0-5 days* HR 1.82 [1.51--2.19], RD 44.26 [27.52--64.42] and *6-10 days* HR 1.57 [1.29--1.92], RD 28.28 [14.17--45.52]). While Ray et al (2012) also reported an increase in all-cause death (HR 2.02 [1.24--3.30]), it was driven solely by an increased risk of CV death. Rao et. al also reported an increased risk of all-cause death (HR 1.48 [1.05--2.09]) but did not report the breakdown of CV vs non-CV causes.[3] Svanstrom et al.[2] did not report all-cause mortality outcomes in the Danish study.

A descriptive post-hoc analysis of the causes of non-CV death in the present study (Appendix 9, Tables 9 and 10), shows that only a minority of the non-CV deaths were related to infection and the most common cause of death was cancer, which is not plausibly the result of antibiotic exposure. Given the lack of a plausible mechanism of action whereby azithromycin would increase non-CV mortality, and prior studies such as Mortensen's and Polgreen's[4] (see Table 1) which have reported that azithromycin is associated with lower mortality compared to other antibiotics in patients with community-acquired pneumonia, these findings may be the result of residual confounding (see Limitations Section 11.3).

However, another potential explanation for the increased risk of non-CV death is that some of the non-CV deaths may have a contributing cardiac component. For example, if azithromycin causes cardiotoxicity manifested as worsening heart failure or ischemic heart disease, those co-morbid conditions could increase the risk of death attributed to primary non-cardiovascular conditions such as cancer, chronic lung disease, or severe infection.

CV mortality within 365 days of antibiotic dispensing overall, and in high CV risk subgroups

To examine possible long-term effects of azithromycin exposure on CV death, a secondary analysis of C-CVD occurring within 11- 365 days after exposure was conducted (Table 11). This analysis included a much larger sample size (>3700 coded CV deaths) and resulted in no significant increase in risk for the whole cohort (HR 1.07 [0.98--1.17]) and for the modified cohort (HR 1.05 [0.94--1.17]). There were insignificant or borderline significant increased risks for the high CV risk subgroups using the adjudicated CV death outcome (HR range 1.00 to 1.13), but no significant effects using the coded CV death outcome in the modified cohort (HR range 1.09 to 1.14).

11.1.3 Summary

The present study results are consistent with Ray et al. (2012)[1]: An increased risk of CV death was associated with outpatient azithromycin exposure compared to amoxicillin. There was also an increased risk of non-CV death associated with azithromycin exposure, results not found by Ray et al. (2012).[1] There was no increased risk of CV death during the 11-365 days following azithromycin dispensation.

11.2. Limitations

There were several limitations to the present study.

11.2.1 Cardiovascular Death Definition

While the adjudication of CV deaths was anticipated to be a strength of this study, the unforeseen high rate of unclassifiable deaths makes results of the primary analysis difficult to interpret. Specifically, the adjudication process resulted in an unexpectedly high rate of unclassifiable deaths (64%, detailed in Appendix 9). The high rate of unclassifiable deaths was likely multifactorial in nature. First, the definitions used to determine cause of death were strict, and likely best suited for clinical trials or prospective cohort studies which have more robust data collection around cause of death. For example, if a subject dies in a clinical trial or prospective cohort study, family members can be contacted to provide information regarding cause of death. In this retrospective observational study, patient data was captured through routine medical care/visits, and further information regarding cause of death could not be captured (e.g. from family members). The lack of information was particularly notable for SCDs occurring outside of the hospital setting.

A second important factor is that after the study began, it was discovered that most KPSC paper charts prior to 2007 had been destroyed by KPSC. This resulted in little to no data available in the medical records to be used for adjudication purposes in KPSC charts preceding the adoption of an electronic medical record in 2007.

There was also a difference in unclassifiable deaths between the exposure groups (azithromycin: 59%, amoxicillin: 68%), likely a consequence of temporal trends in antibiotic utilization and the introduction of a new electronic medical record at Kaiser Permanente (azithromycin use was more prevalent later in the study period, when the quality of medical records was higher). This could result in some degree of bias away from the null, though the association was also observed using coded outcomes. The high rate of unclassifiable deaths resulted in smaller numbers of confirmed outcomes and reduced power for CV risk subgroup analyses of adjudicated outcomes; affecting the generalizability of the findings.

However, given that the majority (89%) of reported CV deaths that could be classified were confirmed as CV deaths by adjudication, it is likely that the majority of the unclassifiable CV deaths were indeed true CV deaths. For detailed results of the death adjudication process, please see Appendix 9, section 4. In the present study, the analyses using coded outcomes produced similar results as the analyses using adjudicated outcomes. Therefore, due to the interpretability issues associated with the adjudicated outcome results, the results based on

coded CV deaths (classification based on death certificate; the outcome used in Ray et al. 2012[1] and all other prior related research) may be more valid than the analogous adjudicated estimates.

11.2.2 Residual Confounding

Residual confounding is important to consider and address in any observational study. Plausible sources of confounding in this study include: 1) indication of use, 2) severity of infection within indication categories, 3) the underlying health of the study population.

11.2.1.1. Residual Confounding by Indication of Use

Indication of use was found to be different across antibiotics exposures in this study with pneumonia, COPD, bronchitis, and respiratory symptoms being more common among azithromycin users, and ear-nose-throat infections being the primary indication for amoxicillin prescriptions. Pneumonia and COPD are associated with adverse cardiovascular outcomes.[21,33] Indication of use (IOU) was included in the propensity score, although full control of this potential confounder may not have been possible because 30% of the records had a missing IOU and the rate of missingness was imbalanced across antibiotics (14% for azithromycin and 35% for amoxicillin, see Table 7).

Two sensitivity analyses were undertaken to address the issue associated with missing indication of use. Sensitivity analysis #8 restricted the cohort to the study period of 2009-2014, when indication of use was systematically captured via a direct link in the electronic medical record, rather than determining indication by (see Table 18). For A-CVD in the whole cohort, use of a more accurate indication of use variable resulted in a higher risk for the azithromycin exposed within 5 days (A-CVD HR 3.18 [1.39--7.20]) in comparison to the primary analysis results (A-CVD HR 2.33 [1.38--3.94]). However, for C-CVD in the modified cohort, use of a more accurate indication of use variable resulted in a lower and non-significant risk for the azithromycin exposed within 5 days (C-CVD HR 1.09 [0.52--2.30]) in comparison to the primary analysis results (C-CVD HR 1.82 [1.23--2.67]). However, restricting the analysis to the years 2009-2014 reduced the sample size and the number of outcomes leading to unstable point estimates and wide confidence intervals.

In sensitivity analysis #9 the analytic cohort was restricted to prescriptions exposures which had an infection indication (prescriptions exposures with a missing indication or those with prophylactic indications were removed). The results after removing missing and prophylactic indications from the analysis are shown in Table 19. The results were similar to those observed in the primary analysis, for C-CVD in the modified cohort: the HR was 1.62 [1.06 --2.49] once missing and prophylactic indications were removed (compared to C-CVD HR 1.82 [1.23--2.67] in the primary analysis). Thus, removing prescriptions with prophylactic or missing IOU did not meaningfully change the results. While these sensitivity analyses address the issues of accuracy and missing indication of use they do not account for channeling where azithromycin is preferentially used different types of infections, such as pneumonia, COPD, respiratory infections, and bronchitis.

The increased risk found within the first 5 days, which diminishes within the 6-10 day window, could also be consistent with residual confounding by indication, which would manifest itself most strongly within the first 5 days of antibiotic exposure, when the infection is most severe. While Ray et al. proposed that this pattern of findings is consistent with the posited causal mechanism that azithromycin increases CV death via a cardiotoxic effect during the first 5 days after dispensing, when the drug is most likely to be taken, this interpretation does not fully consider the half-life of azithromycin. Azithromycin is still systemically present 6-10 days after index date, as the average half-life is 68 hours. Therefore, on day 8, only half of the azithromycin dose taken on day 5 has been metabolized (and drug accumulation over the first 5 days of dosing would be substantial. In the present study, approximately 85% of azithromycin prescriptions were for a total of 5 days or less (see Table 5, above).

11.2.1.2. Confounding by Infection Severity

Infection severity was not captured and therefore was not included and could not be controlled for in the propensity score adjustment. Differential prescribing may occur for mild cases of pneumonia versus more severe cases. Severe cases of pneumonia are at a greater risk factor for CV death, and plausibly more likely to receive azithromycin,[34] could not be controlled for due to lack of severity measures relevant to outpatient care within the KP database, such as the white blood cell count. This same phenomenon of differential prescribing based on severity of infection may occur in the other types of respiratory infections, which are also independent risk factors for CV death. The lack of relevant severity measures in outpatient care and the inability to capture different pneumonia etiologies could bias the results away from the null. However, the concern regarding unmeasured infection severity should be tempered by the fact that this study only included oral antibiotics prescriptions for outpatients; very severe infections are treated in the hospital and were not included in this study.

11.2.1.3. Residual Confounding by Underlying Health Status of Patients

In analyses conducted in the whole cohort, underlying serious illness (pre-existing medical conditions) is a potential source of confounding. Azithromycin appears to have been prescribed more to those with serious underlying illnesses compared to amoxicillin (see Table 5). Beta-agonist use, systemic glucocorticoid use, asthma, prior pneumonia, and any ED visit in the past year were notably higher among azithromycin users. In addition, there were many other, albeit smaller, imbalances in clinical characteristics between the two groups. To address this potential source of residual confounding, post-hoc analyses created a modified cohort by removing patients with underlying serious illnesses as was done in Ray et al. (2012).[1] By eliminating those with serious underlying conditions, proportionally more azithromycin prescriptions were removed from the analysis (7% of amoxicillin prescriptions vs. 10% of azithromycin prescriptions). The modified cohort analyses, which more closely matched the methods by Ray et al. (2012),[1] produced largely similar results compared to the primary analysis results, although the associations between azithromycin and the study

outcomes was slightly attenuated (C-CVD whole cohort: HR 2.06, 95% CI 1.53--2.77, C-CVD modified cohort: HR 1.82, 95% CI 1.23--2.67).

The PS diagnostic tables (Appendix 7) show that even after PS adjustment there were residual imbalances in some of the study variables, including infection category, antibiotic use within 30 days prior to index, outpatient medical visit utilization, opioid use, and index year. Because these imbalances may indicate the presence of residual confounding, the study investigators also created additional Cox models adding every imbalanced variable into the model as a separate covariate. Adding these variables into the model as covariates had no impact on risk of C-CVD and non-CVD. The results for the models which included index year and infection category as separate covariates are shown in Tables 31 and 32, respectively.

Serious underlying illnesses (one proxy for underlying health status), and all clinical characteristics captured in the propensity score, were assessed in the 12 months prior to the index date. Underlying health status within the prior year is likely correlated with, but and may not fully reflect the health of the person at the time of the infection. Since the current health status at the time of infection may be associated with both azithromycin prescribing, and the outcome of CV death, it may be a source of residual confounding

11.2.3 Temporal Changes Over Time

During the time period for this study (1998-2014), there was a significant decline in the rate of CV events such as MI and MI-associated 30 day mortality at Kaiser Permanente.[35] In the present study, there was a clear temporal trend for reduced CV death rates over time. As discussed above, there were other temporal trends over the course of the study including a higher rate of azithromycin prescriptions, an improved rate of cause of death adjudication, and an improved ability to categorize the IOU. Though these temporal trends may have introduced bias into the results, the investigators completed a range of sensitivity analyses to address these concerns, including analyses restricted to 2009-2014 (Table 18), adjudicated vs coded deaths (Table 9) and infection IOU category (Table 19), along with an analysis which included index year as a separate covariate in the models (Table 31). These analyses did not produce important changes to the results, though were conducted on much smaller sample sizes, resulting in less stable estimates.

11.3 Strengths

This study also had many strengths, including its large sample of antibiotic users, generalizability to the general population of the US, indication of use validation, and the extensive efforts which were made to address confounding. While this study had approximately 30% missing indication of use (similar to Ray et al. 2012;[1] other studies did not capture it), extensive chart review was conducted to improve and validate the algorithm's performance, and notably allowed capture of some prophylactic use (not captured by Ray et al. 2012,[1] or others). Most importantly, the majority of prescriptions written after 2009 allowed for direct capture of IOU, which is a strength of KP compared to other databases. In this study, indications of use derived via the algorithm had a 72% PPV, while the direct capture of IOU had a 97% PPV (Appendix 8, Table 4). Based on these validation results, it is reasonable to assume that this study's indication of use capture was more accurate than the

study by Ray et al. (2012),[1] which was solely based on algorithm. In addition, while the adjudication process ultimately resulted in limited interpretability of the adjudicated findings, it was able to provide a degree of reassurance about the validity of the coded outcomes in the present study, as there was an 89% confirmation rate among those records which had sufficient information to allow adjudication. Lastly, this study included an extensive set of sensitivity and post hoc analyses, which varied statistical, temporal, and population aspects of the multivariable models, allowing for an in-depth examination of potential biases and confounders.

11.4 Interpretation

Azithromycin was found to be associated with an approximately 2-fold increased risk of both acute cardiovascular and non-cardiovascular death, for outpatient azithromycin use compared to outpatient use of amoxicillin (within a 5 day window after dispensation). This study did not show a higher relative risk of cardiovascular death associated with azithromycin use among those with high baseline CV risk, compared to the overall cohort population. This study did not find an increased risk of cardiovascular death within the 11-365 days after azithromycin dispensation. Due to the observational study design and the potential for residual confounding, causality cannot be determined.

11.5 Generalisability

Given the study cohort characteristics, these study findings are largely generalizable to the US general population.

12 OTHER INFORMATION

Not applicable

13 CONCLUSIONS

Azithromycin was found to be associated with an increased risk of both acute cardiovascular and non-cardiovascular death, compared to amoxicillin, in this study. Due to the observational study design and the potential for residual confounding, causality cannot be determined.

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