NON-INTERVENTIONAL (NI) FINAL STUDY REPORT

Study Information

Title	The Acute Effects of Azithromycin Use on Cardiovascular Mortality, as Compared with Amoxicillin-Clavulanate in Veterans.
Protocol number	A0661211
Version identifier of the final study report	1.0
Date	10 February 2020
EU Post Authorization Study (PAS) register number	EUPAS17206
Active substance	Azithromycin (AZT): J01FA10 Amoxicillin-Clavulanate (AMX/CLV): J01CR02
Medicinal product	Zithromax
Research question and objectives	Primary Objective: The primary objective was to estimate hazard ratios (HRs) and risk differences (RDs) of CV death for azithromycin users as compared to amoxicillin-clavulanate users among persons 30-74 years of age within 1-5 and 6-10 days following the dispensed prescription, for a respiratory or ear-nose-throat (ENT) infection indication. Subgroup analyses: 1. CV death among those with a history of CV disease. 2. CV death among those with high baseline CV mortality risk as defined by a CV mortality risk score.

	Secondary Objective: The secondary objective was to estimate the HRs and RDs of non-CV death for azithromycin users as compared to amoxicillin-clavulanate users among persons 30-74 years of age within 1-5 and 6-10 days of dispensed prescription, for a respiratory or ENT infection indication. Subgroup analyses: 1. Non-CV death among those with a history of CV disease. 2. Non-CV death among those with high baseline CV mortality risk as defined by a CV mortality risk score.
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1. ABSTRACT (STAND-ALONE DOCUMENT)

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACE	Angiotensin Converting Enzyme
AE	Adverse Event
AEM	Adverse Event Monitoring
AMX	Amoxicillin
ARB	Angiotensin Receptor Blocker
AZT	Azithromycin
CABG	Coronary Artery Bypass Grafting
CDW	Corporate Data Warehouse
CI	Confidence Intervals
CIOMS	Council for International Organizations of Medical Sciences
COD	Cause of Death
COPD	Chronic Obstructive Pulmonary Disease
CPT	Current Procedural Terminology
CV	Cardiovascular
e-CRF	Electronic Case Report Form
ED	Emergency Department
EMA	European Medicines Agency
EMM	Effect Measure Modifiers
EMR	Electronic Medical Record
ENT	Ear-Nose-Throat
EU PAS	European Union Electronic Register of Post-Authorization Studies
FDA	Food and Drug Administration
GEP	Good Epidemiological Practice
GPP	Good Pharmacoepidemiology Practice
HR	Hazard Ratio
ICD	International Classification of Diseases
IEA	International Epidemiological Association

Abbreviation	Definition
IEC	Independent Ethics Committee
IPTW	Inverse Probability of Treatment Weights
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
KP	Kaiser Permanente
LLC	Limited Liability Company
NDI	National Death Index
NI	Non-Interventional
NIS	Non-Interventional Study
OR	Odds Ratio
PASS	Post Authorization Safety Study
PCI	Percutaneous Coronary Intervention
PI	Principal Investigator
PS	Propensity Score
QA	Quality Assurance
RCT	Randomized Control Trial
RD	Risk Difference
RR	Relative Risk
SAP	Statistical Analysis Plan
SCD	Sudden Cardiac Death
SSN	Social Security Number
US	United States
VA	Veterans Affairs
VHA	Veterans Health Administration
VSF	Vital Status File

3. INVESTIGATORS

Principal Investigator(s) of the Study

Name, degree(s)	Title	Affiliation	Address
Mei Sheng Duh, ScD, MPH	Principal Investigator	Analysis Group, Inc.	111 Huntington Avenue, 14th Floor Boston, MA 02199
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Alexander M. Walker, MD, DrPH	Co-Investigator	World Health Information Science Consultants (WHISCON)	3 Allied Drive, Suite 303 Dedham, MA 02026

4. OTHER RESPONSIBLE PARTIES

Not applicable

5. MILESTONES

Milestone	Planned date	Actual date	Comments
Initial IRB approval	14 December 2016	14 December 2016	IRB approval has been maintained over the course of the study
Final protocol	27 February 2017	27 February 2017	The protocol underwent revisions and amendments during the course of the study
Registration in the EU PAS register	14 March 2017	14 March 2017	
Start of data collection	12 April 2017	12 April 2017	
End of data collection	30 June 2019	30 June 2019	
Completion of feasibility assessment	11 February 2019	11 February 2019[1]	
Final study report	10 February 2020	10 February 2020	

Notes:
[1] The feasibility assessment was completed after the start of data collection. Data collected were used to conduct the feasibility analyses, which informed the final protocol.

6. RATIONALE AND BACKGROUND

This study compared the acute effects of azithromycin use versus amoxicillin-clavulanate use on cardiovascular (CV) mortality, both during and shortly after treatment, among dispensings to patients who received these antibiotics for a respiratory or ENT infection indication. The study was prompted by findings reported by Ray et al. (2012)[1] that showed an increased risk of CV deaths associated with 1-5 day administration of azithromycin, and was undertaken in the context of other observational studies following Ray et al. (2012), including Svanström et al. (2013),[2] Rao et al. (2014)[3], Mortensen et al. (2014)[4], Trifirò et al. (2017)[5], and Chou et al. (2015)[6].

Ray et al (2012)

Ray et al. (2012)[1] examined the acute effects of azithromycin and several comparator antibiotics on CV death among patients receiving health care coverage through Tennessee Medicaid. Patients treated with azithromycin had a higher risk of CV death than patients treated with amoxicillin during the 5 days or entire 10 days after therapy initiation, (hazard ratio [HR]: 2.49; 95% confidence interval [CI]: 1.38, 4.50 and HR: 1.87; 95% CI: 1.16, 3.01, for 5- and 10-day analyses, respectively). Based on these results, Ray and colleagues estimated there would be 47 additional CV deaths per million prescriptions of azithromycin when compared to amoxicillin, and 245 additional CV deaths among patients in the highest decile of CV risk score. The risk of CV death during the 5 days of azithromycin therapy dispensing was also higher relative to that of ciprofloxacin (HR: 3.49; 95% CI: 1.32, 9.26), but did not differ meaningfully or significantly from that of levofloxacin (HR: 1.27; 95% CI: 0.66, 2.47). Ray and colleagues posited that the link between azithromycin use and an increased risk of CV death was potentially due to QT prolongation that resulted in ventricular arrhythmia and sudden cardiac death (SCD).

Ray et al. (2012)[1] took steps to control for confounding bias and looked at the effects of antibiotics according to baseline CV mortality risk. There remain, however, ways in which they could have better analyzed the Medicaid data available to them. First, the study used a measurement period for covariates that was optimal only for chronic pre-existing conditions. The fixed 365-day period prior to antibiotic dispensing for covariate assessment did not distinguish between features that may have been present only in the relatively distant past, only in the recent past, or concurrently at the time of antibiotic dispensing. The study identified poor overlap of the propensity score (PS) distribution between azithromycin and amoxicillin that indicated imbalance in baseline characteristics, but retained amoxicillin as a primary comparator despite the consequent likelihood of confounding by unmeasured covariates. The study design failed to account for recently dispensed antibiotics, thereby lacking both a washout period and a proxy for prior treatment failure. Although 30% of the study population lacked data on indication, a potent possible confounder, these individuals were retained in the analysis, essentially guaranteeing a measure of residual confounding by indication.

Following the publication of Ray et al. (2012)[1], a number of studies examined the question of whether azithromycin is associated with a risk of CV mortality that differs from that associated with other antibiotics in similar people. Svanström et al. (2013)[2] concluded that Danish patients receiving azithromycin had the same risk of CV death as those taking penicillin V (HR: 0.93; 95% CI: 0.56, 1.55). Svanström and colleagues used a population-based sample, stratification by baseline CV disease, and a number of sensitivity analyses (e.g., examination of cardiac-specific deaths and PS matching for main analysis). The HR for CV death associated with azithromycin use was also not elevated when compared to penicillin V among those with CV disease (rate ratio: 1.35; 95% CI: 0.69, 2.64), as well as when compared to amoxicillin (rate ratio: 0.60; 95% CI: 0.29, 1.23). Svanström et al. (2013)[2] noted that the risk of CV death among the Tennessee Medicaid population in the previous study was approximately six times higher than among the Danish sample and suggested that

Ray et al's (2012) findings may have been particular to individuals with atypically high baseline CV mortality rates, such as in the Tennessee Medicaid population.

In a retrospective cohort study among US veterans, Rao et al. (2014)[3] examined the occurrence of serious arrhythmia and all-cause mortality in azithromycin recipients in comparison with persons who received amoxicillin or levofloxacin. In windows of 1-5 and 6-10 days following treatment start, the authors found that arrhythmia risks were higher for both levofloxacin and azithromycin than amoxicillin. The all-cause mortality risks were similarly discrepant between azithromycin and levofloxacin on the one hand and amoxicillin on the other. Rao and colleagues speculated that "[p]atients with high-risk comorbidities or/and higher disease severity may be more likely to be given prescriptions for such broad spectrum antibiotics as levofloxacin and azithromycin, which might bias the mortality results away from the null." Essentially this is an argument for residual confounding by indication. Rao and colleagues only had antibiotic indication information in two-thirds of their study population. In addition, the study also reported a lower than expected prevalence of almost all concomitant therapies and medical conditions, suggesting that the data available to them lacked information on critical medical covariates.

In a study of the US veterans population, Mortensen et al. (2014)[4] employed a retrospective cohort study design to compare the longer-term outcomes associated with azithromycin use and other antibiotic therapies conforming to standard prescribing guidance, both within 48 hours of hospital admission. The primary outcomes were 90-day all-cause deaths and CV events and all-cause deaths within 30 days following admission. Mortensen et al. (2014)[4] found that azithromycin use (versus non-use) was associated with diminished 30-day (odds ratio [OR]: 0.77; 95% CI: 0.73, 0.81) and 90-day all-cause mortality (OR: 0.73; 95% CI: 0.70, 0.76). There was an increased risk of myocardial infarction within 90 days (OR: 1.17; 95% CI: 1.08, 1.25) for those exposed to azithromycin, while other outcomes (e.g., any CV event, heart failure, cardiac arrhythmia) at 90 days were similar between the compared groups.

Trifirò et al. (2017)[5] used population-based health care databases in European countries to conduct a case-control study of new antibiotic users to investigate the relationship between azithromycin use and ventricular arrhythmia. Trifirò and colleagues compared azithromycin use with amoxicillin use or non-use of antibiotics, utilizing diagnoses for ventricular tachycardia or ventricular fibrillation as primary outcomes. After adjusting for demographic (age and sex) and clinical covariates (e.g., CV disease, metabolic diseases, and prior use of anti-arrhythmia drugs), Trifirò and colleagues found no increased risk relative to amoxicillin (OR: 0.90; 95% CI: 0.48, 1.71). Users of both products showed an increased risk of arrhythmia compared to non-use of antibiotics, likely reflecting risk patterns in patients to whom caregivers are more prone to treat with antibiotics generally.

Using information from the Taiwan National Health Insurance Database, Chou et al. (2015)[6] conducted a retrospective study to assess the risk of ventricular arrhythmia and CV death within 7 days among patients treated with amoxicillin-clavulanate in comparison to other antibiotics (azithromycin, clarithromycin, moxifloxacin, levofloxacin, and ciprofloxacin).

Chou and colleagues chose amoxicillin-clavulanate as the active comparator in order to increase the comparability among treatment groups with regard to the severity of infection,[6] and in particular, amoxicillin-clavulanate was chosen over amoxicillin because amoxicillin-clavulanate (unlike amoxicillin) is widely used to treat more severe infections. After PS adjustment for potential baseline confounders, the study found risks of ventricular arrhythmia and CV death that were similarly increased with azithromycin, moxifloxacin, and levofloxacin relative to amoxicillin-clavulanate.

A recent Pfizer-sponsored study conducted using the Kaiser Permanente California databases (Pfizer, Data on File) found that azithromycin was associated with an increased hazard of CV death (HR 1.82; 95% CI: 1.23, 2.67) and sudden cardiac death (HR 1.78; 95% CI: 1.05, 3.03) relative to amoxicillin within 5 days of exposure. Similar results were observed in patients within the top decile of CV risk (HR: 1.71; 95% CI: 1.06, 2.76). Azithromycin was also associated with an increased risk of non-CV death (HR: 2.17; 95% CI: 1.44, 3.26) and all-cause death (HR: 2.00; 95% CI: 1.51, 2.63) within 5 days of exposure. No statistically significant increases in risk were found 6-10 days after exposure. The authors concluded that causality could not be established due to the likelihood of residual confounding.

The aforementioned studies reflect the mixed body of evidence on this topic. Several critical limitations are noted across these observational studies, including potential conflation of effects by patients' use of multiple antibiotics in a short period of time, missing antibiotic indication information, a lack of adjustment for covariates occurring close to the index antibiotic dispensing, poor balance of baseline characteristics between comparator groups even after adjustment, and channeling of azithromycin use into high-risk indications. The results of these observational studies should also be considered in the context of two large-scale randomized clinical trials conducted to assess the short-term and long-term effect of azithromycin on a wide range of clinically important cardiovascular events, including cardiovascular death and sudden cardiac death. These studies found no association between azithromycin and CV and sudden cardiac death.[7,8]

The present study used data from the Veterans Health Administration (VHA) to address research questions regarding azithromycin and CV mortality risk. Since veterans are more similar to a Medicaid population with regards to CV risk than non-government insured populations,[9] the results of this analysis may serve as an appropriate point of comparison to findings from Ray et al. (2012)[1]. The VHA electronic medical record (EMR) database provided adequate information to examine the question of interest, including a large sample size, the ability to validate the algorithm used to determine antibiotic indication, and allowing the linking of various sources of data on hospitalizations, outpatient visits, and pharmacy dispensings for each individual. This study closely followed the methodology used in the study by Ray et al. (2012), while making improvements to enhance the validity of the analysis. These improvements included validation of antibiotic indication, improved control of confounding through a more granular assessment of baseline characteristics, and careful consideration of study population, exposure, and outcome definitions to reduce misclassification and minimize residual confounding.

The study design was developed following feasibility analyses aimed at ensuring comparability of the study treatment cohorts to reduce the impact of residual confounding on results and ensure that the most appropriate definition of the primary and secondary study endpoints was used to avoid outcome misclassification. Specifically, during the feasibility analysis phase, it was determined that using amoxicillin-clavulanate would be a more appropriate comparator due to increased comparability with azithromycin as seen through assessment of PS overlap; only dispensings for respiratory and ENT indications would be examined to reduce confounding by indication; and CV death would be identified via National Death Index (NDI) diagnosis codes. NDI codes were chosen to determine CV death rather than cardiologist-adjudicated outcomes due to the low proportion of adjudicable medical records for the classification of fatal CV events and the high level of agreement between NDI and adjudicated CV death in the small number of adjudicable records. Refer to Appendix 12 for further information regarding methods and findings of the feasibility assessment.

In this way, this study was designed to mitigate limitations of prior studies, such as confounding, particularly by indication, and outcome misclassification, and to thus increase the study's internal validity.

This non-interventional study was designated as a Post-Authorization Safety Study (PASS) and is a post marketing requirement of the Food and Drug Administration (FDA).

7. RESEARCH QUESTION AND OBJECTIVES

Primary Objective:

The study estimated the hazard ratios (HRs) and risk differences (RDs) of CV death for azithromycin users as compared to amoxicillin-clavulanate users among persons 30-74 years of age within 1-5 and 6-10 days of a dispensed prescription for a respiratory or ENT infection indication.

Subgroup analyses:

1. CV death among those with a history of CV disease.
2. CV death among those with high baseline CV mortality risk as defined by a CV mortality risk score.

Secondary Objective:

The study also estimated the HRs and RDs of non-CV death for azithromycin users as compared to amoxicillin-clavulanate users among persons 30-74 years of age within 1-5 and 6-10 days of dispensed prescription for a respiratory or ENT infection indication.

Subgroup analyses:

3. Non-CV death among those with a history of CV disease.

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

8. AMENDMENTS AND UPDATES

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
1	5/24/2017	Substantial	3, 7, 8.1	Added the following subgroup analyses to the secondary objective to estimate the relative and absolute risk of non-CV death and all-cause death, within 5 and within 6-10 days of a dispensed prescription among: (1) patients with a history of CV disease; and (2) patients with high baseline CV mortality risk as defined by a CV mortality risk score.	Per FDA request.
1	5/24/2017	Substantial	8.2.1, 8.2.2	Clarified that only a single study antibiotic prescription can be filled on the index date.	To replicate language used by Ray et al. (2012).
1	5/24/2017	Substantial	8.4.1	Indicated that the VHA and NDI data will be used to identify all endpoints.	To clarify data source for all study endpoints.
1	5/24/2017	Substantial	8.4.2, 8.9	Increased the number of antibiotic prescription encounters that will be randomly sampled to validate	Per FDA request to be consistent with Kaiser Permanente study protocol.

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
				the programmatic algorithm for antibiotic indication, from 100 to 300.	
1	5/24/2017	Substantial	8.7.4	Clarified that for unexposed periods used to construct CV mortality risk score, the first date on which exposure to azithromycin or amoxicillin did not occur for 30 days prior, were used as the index date, and the exposed and unexposed periods were matched on the index date.	To clarify language and ensure replication of Ray et al. (2012).
1	5/24/2017	Substantial	9.1, 9.3	Indicated that the VHA had approved the waiving of informed consent and that the protocol had received IRB approval.	To update IRB information.
1	5/24/2017	Substantial	Appendix 2	Updated serious illness exclusion criterion to not exclude patients with benign neoplasms or carcinoma in situ, to exclude patients with prior hospitalization due to alcohol abuse, and to correct ICD-9 code for occlusion and	Per FDA request to be consistent with serious illness exclusions as implemented by Ray et al. (2012).

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
				stenosis of precerebral arteries.	
1	5/24/2017	Substantial	Appendix 2	Specified that HCPCS codes would be used as available.	To clarify code sources for serious exclusion criterion.
1	5/24/2017	Substantial	3.0, 7.0, 8.3.3	Amended language of subgroup analysis among those with history of cardiovascular disease.	For consistency of language across high baseline CV risk subgroup analyses.
1	6/19/2017	Administrative	2.0	Updated list of investigators to include Alexander Walker, MD, DrPH as a co-investigator.	Alexander M. Walker, MD, DrPH has agreed to be a co-investigator.
2	7/19/2019	Substantial	3, 5	Updated the following milestone dates: start of data collection, end of data collection, and final study report.	Due to changes requested by the FDA and changes to the protocol based on feasibility and exploratory analyses.
2	7/19/2019	Substantial	3, 7, 8.1, 8.2, 8.2.1, 8.3.1, 8.3.3, 8.4.2, 8.5, 8.7.2, 8.7.3, 8.7.4, 8.7.5,	Changed the comparator from amoxicillin (with and without clavulanate) to amoxicillin-clavulanate.	Based on feasibility analyses, amoxicillin-clavulanate is a more appropriate comparator to azithromycin, due to greater comparability of baseline characteristics and overlap of propensity scores

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
			8.9, Appendix 1		(PS) distributions for azithromycin as compared to either amoxicillin (with and without clavulanate) or another evaluated antibiotic, levofloxacin.
2	7/19/2019	Substantial	3, 7, 8.1, 8.3.3, 8.7.5	Indicated that CV and non-CV death will be assessed during the 0-10 days following the index date rather than separately during the 0-5 and 6-10 day periods.	An outcome assessment period of 0-10 days is in line with the pharmacokinetics of the antibiotics included in the study, is considered to be more appropriate from a clinical perspective, and was used in previous publications on this topic.
2	7/19/2019	Substantial	3, 7, 8.1, 8.3.2	Removed sudden cardiac death (SCD) as an outcome.	Based on pilot study involving adjudication of 100 randomly selected NDI-coded CV deaths from the study population, there was low agreement between the NDI-coded SCD and the adjudicated SCD. SCD may not be reliably captured via NDI codes and therefore was removed as an outcome. See

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
					Appendix 1 for additional detail.
2	7/19/2019	Substantial	3, 7, 8.1, 8.3.2	Removed all-cause death as an outcome.	To ensure interpretability of study findings because all-cause death does not provide useful information beyond the assessment of CV death and non-CV death outcomes separately, and considering an aggregated outcome of CV and non-CV death may conflate the underlying clinical mechanisms.
2	7/19/2019	Substantial	3, 6, 7, 8.1, 8.2.1, 8.4.2, 8.5, 8.7, 8.7.3, 8.7.5, 8.9, Appendix 1	Included additional inclusion criteria of requiring respiratory or ear-nose-throat (ENT) indication.	Indication is an important confounder, which was considerably imbalanced across exposure cohorts and resulted in poor overlap of the PS distributions between antibiotic cohorts. This is indicative of intractable confounding by indication, which cannot be adjusted for using analytical techniques, and may bias results. Upon examination of the PS within

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
					subgroups defined by specific indications, the overlap in the distribution of PS between antibiotic cohorts was greatest in the respiratory and ENT indication subgroups. These were also the largest antibiotic indication groups in the study.
2	7/19/2019	Substantial	3, 8.7	Noted that primary, secondary, and sensitivity analyses would be conducted separately for each indication group (i.e., respiratory or ENT group). Standard meta-analytic techniques would then be used to pool estimates for the respiratory and ENT indication groups in order to provide a single overall estimate for the study.	To clarify statistical analyses methods.
2	7/19/2019	Substantial	3, 8.3.4	Indicated that study medications used for adjustment will be assessed in the 0, 1-7, 8-30, and 31-365 days prior to the index date for an antibiotic dispensing. Previously, the time periods	To account more granularly for both short-term and long-term values of key covariates.

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
				only assessed 0-30 and 31-365 day periods. In addition, any ED visit will be assessed on the index date (day 0), and day 1-7 prior to the index date, whereas this was only assessed during days 1-7 previously.	
2	7/19/2019	Substantial	3, 7	Noted that risk differences will be estimated in addition to the HR for the primary and secondary study objectives.	To provide a comparative estimate on the additive scale in addition to the multiplicative scale, as the risk difference can have greater importance to public health decision making.
2	7/19/2019	Substantial	3	Clarified and added additional detail regarding the study 'Rationale and Background' and 'Data Analysis'.	To expand upon the rationale of the study and clarify language regarding the data analysis.
2	7/19/2019	Administrative	3, 5	Updated the following milestone dates: start of data collection, end of data collection, and final study report.	Due to the changes in the study design and methods after the feasibility analyses.

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
2	7/19/2019	Administrative	3, 7, 8.1, 8.3.3, 8.5, 8.7.4, 8.7.5, 8.9, 13	Used the term "CV mortality risk score" rather than CV risk score.	To clarify language.
2	7/19/2019	Administrative	3, 8.3.2, 8.5, 8.7.5	Specified that "coded" deaths (identified through database programming) are "NDI-determined."	To clarify that cause of death for coded deaths will be identified using data from the NDI.
2	7/19/2019	Substantial	6	Further clarified statements regarding the importance of adjusting for antibiotic indication and provided estimates for associations from previous studies. Included information on recent Trifirò et al. (2017) study that examined a similar research question.	To make a coherent argument for the choice of study objectives and study design and ensure that all recent studies pertinent to the research question are discussed.
2	7/19/2019	Substantial	7	Noted that increased risk of non-CV death associated with any study antibiotics is likely to be indication of residual confounding.	To note the implication of an association between the study antibiotics and non-CV death.

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
2	7/19/2019	Administrative	8	Clarified description of research methods.	To ensure ease of understanding.
2	7/19/2019	Substantial	8.2.1	Noted that each outpatient dispensing of azithromycin or amoxicillin-clavulanate with a respiratory or ENT indication identified during the study period will be identified and evaluated for inclusion in the study.	To clarify the application of the study inclusion criteria.
2	7/19/2019	Substantial	8.2.2	Included additional exclusion criteria requiring patients to not have received any antibiotic 60 days before or on the index date.	To avoid conflation of effects from other antibiotics and exclude patients who might be very frail or have such severe disease that they receive multiple antibiotics in a short period of time.
2	7/19/2019	Substantial	8.2.2	Added having a date of death prior to the most recent index date as exclusionary criteria.	To exclude patients who were not alive on the date of the index dispensing.
2	7/19/2019	Administrative	8.3.2	Provided additional clarification about the ascertainment of death data in the CDW.	To provide greater clarity regarding outcome identification.

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
2	7/19/2019	Substantial	8.3.2	Added code (ICD-10: R98.xx) to the CV death definition in Table 1.	To ensure all relevant CV death codes are included.
2	7/19/2019	Substantial	8.3.3.2, 8.7.4	Specified that the CV mortality risk score will be calculated using coefficients estimated from the CV mortality risk model developed in the VHA feasibility assessment using data from 2000-2011 from a randomly sampled population unexposed to study antibiotics.	To increase efficiency by applying a previously developed CV mortality risk score estimated using data from antibiotic non-users (to whom the same study inclusion/exclusion criteria were applied) in the VHA database.
2	7/19/2019	Substantial	8.3.4	Added frailty index as a baseline covariate.	Frailty is likely to be associated with a patient's risk of CV death and may impact a physician's choice of antibiotic. Therefore it is a confounder that should be adjusted for in the analysis.
2	7/19/2019	Substantial	8.4.2	Clarified the application of algorithm to determine antibiotic indication.	To clarify that infection disease diagnosis codes will be given priority over prophylaxis codes.

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
2	7/19/2019	Substantial	8.5	Updated power calculation to account for use of amoxicillin-clavulanate as the comparator for azithromycin and for conducting analyses separately in the respiratory and ENT indication groups.	To reflect changes made to the antibiotic comparator of use and approximate anticipated sample sizes based on the feasibility analysis.
2	7/19/2019	Substantial	8.7.1	Created a new section (8.7.1: Absolute risks) which states that absolute risks (cumulative incidences) will be reported.	To clarify the analytical approach for the primary and secondary objectives.
2	7/19/2019	Administrative	8.7.2	Noted that with very low absolute risks, and with follow-up periods of identical length, the HR approximates the ratio of exposure-specific risks.	To aid with interpretation of hazard ratios if the cumulative incidence of outcomes is very low.
2	7/19/2019	Substantial	8.7.3	Indicated that confounding will be controlled using inverse probability of treatment weights (IPTW), calculated from PS models. Separate PS will be developed for the respiratory and ENT	To revise the method for confounding control, from PS adjustment to using IPTW adjustment. Using the PS as a covariate in the model requires correctly specifying the relationship between the PS and the outcome; an

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
				indication groups, and for the subgroup analyses.	incorrectly specified relationship can lead to bias due to model misspecification. In addition, compared to PS matching, IPTW preserves sample size and generalizability (as unmatched patients may be dropped from the analysis if PS matching is used). IPTW will provide similar results to PS matching with replacement.
2	7/19/2019	Substantial	8.7.5	Noted that sensitivity analyses will only be conducted using the Cox model (i.e., to estimate HRs).	In order to prioritize the main measure of effect and simplify the interpretation of study findings.
2	7/19/2019	Substantial	8.7.5	Removed the sensitivity analysis related to conducting the analyses within PS deciles.	Based on literature, this approach can result in greater bias than other PS based methods for confounding control, such as IPTW, which will be applied in this study.
2	7/19/2019	Substantial	8.7.5	Removed the sensitivity analyses related to conducting the primary analysis	To reflect the fact that patients who received any antibiotic other than the study

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
				according to the number of antibiotic dispensings within the 30 days prior to index.	antibiotic 60 days before or on the index date will now be excluded from the analysis so these sensitivity analyses cannot be performed.
2	7/19/2019	Substantial	8.7.5	Removed sensitivity analysis related to classifying CV deaths as probable, possible, and unclassifiable.	To reflect the fact that the adjudication of CV death will no longer be conducted based on findings from the pilot adjudication.
2	7/19/2019	Substantial	8.7.5	Removed sensitivity analysis related to using coded CV death based on the NDI as the primary study outcome.	To reflect that coded CV death based on the NDI will now serve as the primary study outcome.
2	7/19/2019	Substantial	8.7.5	Removed sensitivity analyses related to restricting analysis to be among patients with an infection indication or an analysis around infection severity.	Because the main study analysis will be conducted within subgroups defined by respiratory and ENT indication, these sensitivity analyses will not be conducted.
2	7/19/2019	Substantial	8.7.5	Removed sensitivity analyses related to conducting the	To ensure study validity is not threatened by residual confounding from a heterogeneous analytic

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
				analysis among patients ≥65 years of age.	population. Patients ≥65 years of age may have greater variation in comorbidities, concomitant medication use, and frailty.
2	7/19/2019	Administrative	11	Elaborated on study dissemination plans.	Final study results will be made publicly available via the EU PAS Register and submitted for publication in a peer-reviewed medical journal.
2	7/19/2019	Administrative	5	Changed date of receipt of FDA comments to 17 June 2019.	To reflect the exact date on which comments on the protocol and SAP were shared.
2	7/19/2019	Administrative	8.3.4	Added frailty index definition.	To clarify how frailty index will be defined, as indicated in SAP Appendix A.
2	7/19/2019	Substantial	8.5	Updated power calculation to include minimum detectable risk differences.	To address the fact that the final study results reporting both hazard ratios and risk differences, the power calculation was updated to include minimum detectable risk differences in addition to

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
					minimum detectable hazard ratios.
2	7/19/2019	Administrative	8.5	Clarified that the incidence of CV death used in power calculations was obtained from the feasibility analyses.	To clarify the source of information on CV death incidence used for power calculations.
2	7/19/2019	Substantial	8.7	Elaborated that a generalized estimating equation with sandwich variance estimator and a Cox proportional hazards model with a random effect for indication will be used as checks on the meta-analysis.	To account for possible zero events when integrating results using meta-analytic techniques.
2	7/19/2019	Substantial	8.7.3	Noted that IPTW will be trimmed at the 1st and 99th percentile, which will lead to minimal data loss.	To account for incomplete overlap in the propensity score distributions, IPTW will be trimmed at the 1st and 99th percentile, such that observations with IPTW below the 1st percentile or greater than the 99th percentile will be excluded, leaving 98% of the observations in place. Trimming can also help

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
					increase the precision of estimates.
2	7/19/2019	Substantial	8.7.2	Clarified that a generalized estimating equations model with an independent correlation matrix will be used in the binomial regression model to estimate the RD, and that a robust sandwich variance estimator will be used with the Cox proportional hazards model.	To account for multiple exposure opportunities of patients included in the analysis and use a robust sandwich variance estimator.
2	7/19/2019	Administrative	8.7.3	Noted that all variables listed in Appendix A of the SAP will be included in propensity score models.7	To clarify that a variable selection process will not be applied to choose variables for adjustment. Rather, all covariates identified as confounders will be adjusted for.
2	7/19/2019	Administrative	8.7.4	Noted that covariates in the CV mortality risk score model and propensity score model will be allowed to overlap.	To clarify that the some of the same covariates will be included in the CV mortality risk score model and the propensity score model.

9. RESEARCH METHODS

9.1. Study Design

The study employed a retrospective cohort design to examine the acute effects on CV death of azithromycin relative to amoxicillin-clavulanate, dispensed for a respiratory or ENT indication, in the 1-5 days and 6-10 days following dispensing (i.e., the index date). Subgroup analyses were conducted to examine CV death among those with a history of CV disease and among those with high baseline CV mortality risk. The study considered non-CV death as a secondary outcome. For both primary and secondary outcomes, HRs and RDs were used as the measures of effect.

9.2. Setting

The study population consisted of veterans enrolled in the VHA.

Approximately 1 million inpatient encounters and 8 million outpatient encounters occur within the VHA annually. The VHA EMR system contains information on all outpatient visits, hospital stays, treatments, dispensed prescriptions (both inpatient and outpatient), and laboratory results rendered in VHA medical facilities, and can be linked to the NDI to obtain mortality data. The study period began on January 01, 2000 and ended on December 31, 2014. January 01, 2000 marked the start of the nationwide, fully functioning VHA EMR system. The VHA's Corporate Data Warehouse (CDW) had recorded substantial data to provide baseline covariate information for many years prior. Using data from 2000 to 2014 overlaps with the study periods considered by Ray et al. (2012)[1], from 1992 to 2006, by Svanström et al. (2013)[2], from 1997 to 2010, and by the recently completed study conducted by Kaiser Permanente (KP) to assess the relationship between CV death and azithromycin use, with data from 1998 to 2014.

9.3. Subjects

Inclusion Criteria

All outpatient prescription dispensings of azithromycin and amoxicillin-clavulanate (referred to as the study antibiotics) in the VHA system from January 01, 2000 to December 31, 2014 were identified. Eligibility was evaluated for each dispensing on the date of the first study antibiotic dispensing observed and re-evaluated on each subsequent date of dispensing of one of the study antibiotics, using the following criteria:

1. Dispensing of an outpatient prescription for azithromycin or amoxicillin-clavulanate between January 01, 2000 and December 31, 2014. If a patient had more than one prescription dispensing within this period, each exposure was counted separately (thus, a single individual may have contributed multiple prescription dispensings to the analysis), and the index date of each exposure was identified as the first day on which the dispensing met the inclusion criteria (only a single study antibiotic prescription could have been filled on the index date).

2. Only oral prescription dispensings were included (not intravenous or ophthalmic).

3. Dispensings to patients with regular use of VHA medical care, defined as at least two outpatient, non-emergency department (ED), or inpatient encounters in the one year prior to each index antibiotic prescription dispensing were included. The encounters or inpatient admission dates must have been separated by more than 30 days, and at least one was within six months prior to the index antibiotic prescription dispensing.

4. Dispensings associated with an antibiotic indication of respiratory or ENT infection as determined by an indication algorithm (see Section 9.5.2 for further details on antibiotic indications).

Exclusion Criteria

The criteria below were implemented for the entire candidate population of study antibiotic dispensings (see above).

Exclusion Criteria:

1. Dispensings to patients missing date of birth or gender.

2. Dispensings to patients <30 or >74 years of age.

3. Dispensings to patients who were not enrolled in or had disenrolled from VHA benefits during the 365 days prior to the index date.

4. Dispensings to patients with no pharmacy dispensings during the one year prior.

5. Dispensings to patients with evidence of a serious illness (see Appendix 8 for full list of serious illnesses and corresponding codes) on the dispensing date or the preceding 365 days.

6. Dispensings to patients with hospitalization within 30 days prior to the dispensing date.

7. Dispensings to patients 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. Since the VHA contains data only on VHA-paid nursing homes and nursing home residency in patients with Medicare, this definition also included inferred nursing home stays. Inferred nursing home stays were defined as two or more outpatient encounters in the year leading up to the index prescription dispensing date with procedure codes indicating nursing home place of service separated by at least 28 days. It also included external cause of injury diagnosis code indicating place of residence was an institution (i.e., ICD-9 E849.7: accidents occurring in residential institution).

8. Dispensings after the patient's date of death.

9. Dispensings to patients who received another antibiotic the same day or in the preceding 60 days.

9.4. Variables

9.4.1. Exposure

Outpatient prescription dispensings of azithromycin or amoxicillin-clavulanate occurring between January 01, 2000 and December 31, 2014 that fulfilled all inclusion and exclusion criteria were used to define exposure.

9.4.2. Outcomes

The study examined the following outcomes: (1) CV death, (2) non-CV death, (3) cardiac death (only used in sensitivity analysis).

All outcomes were identified from the VHA database, and cause of death was classified based on information as captured by the NDI. For specific codes used to identify the outcomes in the NDI, please see Table 1 in the protocol (Appendix 2).

9.4.3. Effect Measure Modifiers (EMM)

The following subgroups were examined for the risk of CV death within 1-5 and 6-10 days, compared to amoxicillin-clavulanate use: 1) high baseline risk as defined by history of CV disease; 2) high baseline CV mortality risk as defined by a CV mortality risk score.

9.4.3.1. High Baseline Risk as Defined by History of CV disease

Individuals with baseline history of CV disease were defined by an inpatient or outpatient encounter (ED encounters included) with the following CV disease indicators, identified by diagnostic codes or procedures within one year prior to the index antibiotic dispensing: acute coronary syndrome, other ischemic heart disease, percutaneous or surgical coronary revascularization, heart failure or cardiomyopathy, valvular heart disease or heart valve surgery, congenital heart disease, cerebrovascular disease, peripheral arterial disease, or arrhythmia. The specific codes used to identify these diseases are listed in Table 2 in the protocol (Appendix 2). All of the codes have been used and validated in previous publications.[10,11,12,13,14,15,16,17,18,19,20,21,22,23]

9.4.3.2. High Baseline CV Mortality Risk as Defined by CV Mortality Risk Score

High baseline CV mortality risk was determined by a CV mortality risk summary score calculated based on a model that was developed following the methodology of Ray et al. (2012).[1,24,25,26] This served to statistically summarize the effects of numerous CV variables and model the fitted probability of CV death, calculated as a function of selected baseline covariates in persons from outside the study population. For this purpose, a randomly sampled cohort of patients that were unexposed to study antibiotics were identified in VHA data from 2000-2011 and used to develop the CV mortality risk score model.

The CV mortality risk score methodology used in the sample size feasibility assessment phase of this study was described in detail in the statistical analysis plan (SAP) (Appendix 4).

9.4.4. Covariates

In addition to the CV conditions, CV medications, and CV mortality risk score described above, the statistical analyses adjusted for the following:

- Demographic factors (e.g., age, gender, race/ethnicity, marital status)
- Frailty index
    - The frailty index was defined as the sum of age-related health deficits present per patient divided by the total number of age-related health deficits assessed. The list of age-related health deficits was based on Clegg et al. (2016),[27] using ICD-9 diagnosis codes and medication dispensings. Disease comorbidities included in the frailty index were identified within 0-365 days prior to index date. Medication use included in the frailty index score was assessed within 0-30 days prior to index date.
- Other medical comorbidities (e.g., respiratory, neurologic, and psychiatric conditions)
- Other non-CV medications (e.g., opioids, psychiatric drugs, and medications known to prolong the QT interval) assessed on the day of antibiotic dispensing, and within 1-7 days, 8-30 days, and 31-365 days prior to antibiotic dispensing
- Health care utilization variables (e.g., number of CV-related office visits, non-CV ED visits assessed on the day of antibiotic dispensing, and all ED visits) within 1-7 days, 8-30 days, and 31-365 days prior to antibiotic dispensing

The definitions of specific variables as well as the timing of the covariates relative to the index antibiotic prescription dispensing date were included in the SAP (Appendix 4).

9.5. Data Sources

9.5.1. VHA EMR Database and NDI

The study used an EMR data cut obtained from the CDW at the initiation of data collection, April 12, 2017. The data cut was considered locked and no longer updated at that point. The study also used information reported from the NDI to the VHA in combination with CDW data to identify all study endpoints.

VHA EMR Database

The VHA is an integrated healthcare system that provides comprehensive services, including primary, specialty and inpatient care, rehabilitation, long-term and home care, and other services, to military veterans. As of September 2016, the VHA was comprised of

168 medical centers and 1,053 outpatient sites of care of varying complexity, serving more than 8.9 million veterans each year. In 2011, greater than 84% of these veterans were at least 45 years old and over 72% were at least 55 years of age. Female veterans represented about 10% of the VHA population.

The CDW consolidates data from the VHA's EMR system and contains information on all outpatient visits, hospital stays, treatments, dispensed prescriptions, and lab results. Although the VHA may have financially covered/reimbursed care provided at non-VHA facilities, the EMR system (and thus the CDW) does not capture information on such visits. The CDW stores data in separate databases, one for each type of clinical information (e.g., inpatient medication, inpatient admission, outpatient medication, outpatient visit). Each patient is assigned a unique patient identification number to allow for longitudinal follow-up as well as to cross-reference to the various separate databases. For example, in each inpatient admission record, information on the primary discharge diagnosis (and as many as 15 secondary diagnoses), date of admission, date of discharge, and length of stay is available. This record can then be linked to other information of that inpatient stay located in other files, including procedures that the patient underwent during the hospitalization, medical specialty of the provider, and prescriptions dispensed (inpatient and outpatient). Other files are similarly structured, and therefore can be linked together to provide comprehensive information about the patient and his/her medical encounters.

NDI Data

The NDI is a centralized data resource that contains death record information from all US states. The NDI was established by the National Center for Health Statistics to aid epidemiologists and other researchers in mortality ascertainment. Records are currently available from 1979 through 2017. The NDI service is available to investigators for statistical analysis in medical and health research and can be obtained through an application process. Characteristics available in the NDI and used for matching individuals to the death records included social security number (SSN), date of birth, age at death, date of death, sex, marital status, race, state of residence, and state of birth. The NDI Plus file contained cause of death information, which was used for this study. The causes of death were recorded as ICD-10 codes.

9.5.2. Antibiotic Indication Assessments

Similar to Ray et al. (2012),[1] diagnosis codes were assessed from the visits that occurred within a specific date range around the date of antibiotic dispensing to indirectly capture indication for antibiotic use. Antibiotic dispensings with a temporally-associated infection diagnosis codes were categorized as having that specific type of infection as the indication. The algorithm yielded 16 different indication groups. Of these, respiratory and ENT indications together captured 40.9% of the azithromycin dispensings and 19.7% of amoxicillin-clavulanate dispensings. Dispensings associated with respiratory and ENT indications were retained, and the analyses were conducted within strata defined by indication. Details of the algorithm to assign antibiotic indication are described in Appendix 2 and specific codes can be found in Appendix 8.

A validation process was also implemented to ensure that the algorithm assigning antibiotic indication accurately captured the purpose of treatment. An infectious disease physician reviewed a random sample of 300 medical records for patients with an antibiotic dispensing to determine the indication, which was then compared to the assigned indication based on the algorithm. Of the 300 records, 208 (69.3%) were in agreement on indication. Among high severity infections, including respiratory infections, this was even higher at 87.5%. This validation exercise supported the approach for assigning indication, allowing for the appropriate selection of respiratory and ENT indications for azithromycin and amoxicillin-clavulanate dispensings into the study.

9.6. Bias

Several approaches were implemented in the study design and analyses to reduce bias in this study. Amoxicillin-clavulanate was selected as a comparator to azithromycin based on an assessment of the PS distribution overlap and comparability of baseline characteristics, which indicated greater similarity between amoxicillin-clavulanate and azithromycin, as compared to amoxicillin (with and without clavulanate). The feasibility assessment found indication to be an important contributing factor to imbalances in baseline characteristics across cohorts. Therefore, the study was restricted to dispensings for respiratory and ENT indications to strengthen the internal validity of the study and to overcome a weakness of prior studies wherein confounding by indication interfered with the interpretation of the results.

Inverse probability of treatment weighting (IPTW) was used to further adjust for confounding. IPTW, calculated from the PS, was used to weight the regression models in order to provide an appropriately adjusted comparison of the cohorts and estimate what would be the average treatment effect in the total respiratory and total ENT populations, separately, if covariates had been similarly distributed in the two antibiotic treatment groups. Details of the statistical analysis can be found in Section 9.9. The PS was estimated separately for dispensings with a respiratory and ENT indication. In addition, separate PS models were developed for each subgroup and sensitivity analysis. Variables for inclusion in the PS logistic regression models were determined a priori and defined in the study protocol, including covariates hypothesized to be associated with exposures and study outcomes that do not mediate the potential effects of interest. All variables listed in Appendix 14 were included in the PS models (also described in Section 9.4.4). Within each indication, IPTW was calculated for each dispensing as the inverse of their observed probability of being in their exposure group (i.e., azithromycin or amoxicillin-clavulanate), given the dispensing's status on all covariates. Hence, IPTW was calculated as 1/PS for the azithromycin group and 1/(1-PS) for the amoxicillin-clavulanate group. In addition, each dispensing's weight was stabilized by the marginal probability of being in their exposure group to enhance precision of the effect estimates. The stabilized weights were calculated as Pr(azithromycin=1)/PS for the azithromycin group and [1-Pr(azithromycin=1)]/(1-PS) for the amoxicillin-clavulanate group. The stabilized weights were applied to all of the dispensings such that all results, including counts and outcomes presented descriptively, are IPTW-adjusted.

To reduce variability in the IPTWs, weight trimming was performed at the 1st and 99th percentiles of the PS, resulting in the reduction of the sample to 98% of the original

observations. The distribution of IPTW after trimming is presented in Appendix 9, in addition to histograms of the PS examining the overlap between cohorts. After weighting, the distribution of baseline characteristics was evaluated among the antibiotic cohorts to ensure comparability. Standardized differences were estimated, with values >10% indicating a remaining imbalance.

Lastly, immortal time bias was precluded by restricting the observation period to 10 days following the index date for all antibiotic dispensings, and including a washout period of 60 days prior to each dispensing. Given that dispensings for patients with more than 1 type of antibiotic prescribed on the index date or in the 60 days prior were excluded, it is not possible that dispensings for patients using azithromycin as a 2nd line antibiotic for a more severe or difficult to treat infection were included in the study.

Further discussion of potential sources of bias in the study, including outcome misclassification, is provided in Section 11.2 Limitations.

9.7. Study size

The total number of dispensings for this study was 1,144,951 after applying all eligibility criteria, with azithromycin dispensings comprising 67.6% of the sample. For the 1-5 day outcome window, the incidence of CV death per million prescriptions in the amoxicillin-clavulanate group was 76.9, thereby allowing for a minimum detectable HR of 2.09 with 90% power. For the 6-10 day window, the corresponding minimum detectable HR was 2.28.

Based on the observation of 56.7 CV deaths per million in the amoxicillin-clavulanate group, the minimum detectable RD with 90% power for the study was 100 per million dispensings in the 1-5 day window. The corresponding minimum detectable RDs for the 6-10 day window was also 100. For additional power calculations for the various sensitivity and subgroup analyses see Table 1 and Table 2 below.

Table 1. Pooled power calculation for hazard ratios among dispensings to patients with a respiratory or ENT indication

	Total sample size	Proportion of azithromycin in total sample	Incidence of CV death per million dispensings in amoxicillin-clavulanate group	Minimum detectable hazard ratio with 90% power
Amoxicillin-Clavulanate vs. Azithromycin: Within 1-5 days of index date				
Total dispensings	1,144,951	67.6%	76.9	2.09
Subgroup with CV disease at baseline	313,425	68.6%	137.2	2.90
Subgroup in top decile of CV mortality risk score	114,660	64.7%	200.6	4.11
Amoxicillin-Clavulanate vs. Azithromycin: Within 6-10 days of index date				
Total dispensings	1,047,517	67.5%	66.8	2.28
Subgroup with CV disease at baseline	287,361	68.4%	135.7	3.05
Subgroup in top decile of CV mortality risk score	105,049	64.4%	266.5	3.59
Amoxicillin-Clavulanate vs. Azithromycin: Within 1-10 days of index date (sensitivity analysis)				
Total dispensings	1,144,951	67.6%	138.0	1.73
Subgroup with CV disease at baseline	313,425	68.6%	261.6	2.16
Subgroup in top decile of CV mortality risk score	114,660	64.7%	444.8	2.58

Abbreviations: CV = Cardiovascular; ENT = Ear-Nose-Throat.

Table 2. Pooled power calculation for risk differences among dispensings to patients with a respiratory or ENT indication

	Total sample size	Proportion of azithromycin in total sample	Incidence of CV death per million dispensings in amoxicillin-clavulanate group	Minimum detectable risk difference per million dispensings with 90% power
Amoxicillin-Clavulanate vs. Azithromycin: Within 1-5 days of index date				
Total dispensings	1,144,951	67.6%	56.7	100
Subgroup with CV disease at baseline	313,425	68.6%	101.7	200
Subgroup in top decile of CV mortality risk score	114,660	64.7%	148.1	400
Amoxicillin-Clavulanate vs. Azithromycin: Within 6-10 days of index date				
Total dispensings	1,047,517	67.5%	73.3	100
Subgroup with CV disease at baseline	287,361	68.4%	121.3	200
Subgroup in top decile of CV mortality risk score	105,049	64.4%	294.3	500
Amoxicillin-Clavulanate vs. Azithromycin: Within 1-10 days of index date (sensitivity analysis)				
Total dispensings	1,144,951	67.6%	124.1	100
Subgroup with CV disease at baseline	313,425	68.6%	213.6	200
Subgroup in top decile of CV mortality risk score	114,660	64.7%	419.6	500

Abbreviations: CV = Cardiovascular; ENT = Ear-Nose-Throat.

9.8. Data transformation

Not applicable.

9.9. Statistical methods

The study followed the methodology laid out in the previously submitted SAP, which was dated, filed, and maintained by Pfizer, and is submitted alongside this study report as Appendix 4. Results were estimated separately for respiratory and ENT indications and summarized across indication groups using pooling techniques.

9.9.1. Main summary measures

HRs and RDs were used to estimate the relative risk and absolute risk of the outcomes for azithromycin compared to amoxicillin-clavulanate.

Risks (cumulative incidences) were reported for the primary analysis as the number of outcome events divided by the number of dispensings at risk.

9.9.2. Main statistical methods

The study used regression analyses to estimate the risks of CV death and non-CV death associated with azithromycin versus amoxicillin-clavulanate. Specifically, HRs for azithromycin vs. amoxicillin-clavulanate were estimated using a Cox proportional hazards model, allowing for occasional right-censoring (for instance, upon hospitalization). Separate models were used for each indication group. In the cases of very low absolute risks, little censoring, and follow-up periods of identical lengths, the HR will closely approximate the ratio of exposure-specific risks. RDs comparing azithromycin to amoxicillin-clavulanate were estimated for the primary and secondary outcomes using a binomial regression model with an identity link, separately for each indication.

A generalized estimating equation (GEE) model with an independent covariance structure was used in the binomial regression model and a robust sandwich variance estimator was used with the Cox proportional hazards model to account for multiple dispensings for the same patient included in the analysis. Since the endpoint is death, we note that there is no opportunity for repeated within-person events.

Results were pooled across indications using a random-effects meta-analysis following the methodology of DerSimonian and Laird[28] to provide a single overall estimate for the study. In addition, a pooled HR was also estimated by including a random effect in the Cox proportional hazards model to account for clustering by indication. The RD across indication groups was estimated using a GEE model that included an indicator variable for each indication stratum to obtain the overall risk difference and its sandwich-variance-derived estimator (to estimate 95% CIs).

9.9.3. Missing values

Key information was checked to be non-missing prior to the analysis. For example, the inclusion and exclusion criteria required that information regarding age, gender, and a known

respiratory or ENT indication for the antibiotic received were available. A known cause of death was required for identification of study events (i.e., CV death, non-CV death, and cardiac death). Patients were censored at dates of death with missing or unknown case of death information.

All other variables were derived from healthcare encounter, diagnosis, procedure, or pharmacy dispensing records in the VHA CDW. The absence of a characteristic in the database indicated that the variable being evaluated did not occur (e.g., a patient did not have the comorbidity considered). Though data could be missing from the database if a patient received healthcare outside of the VHA system, the eligibility criteria requiring multiple encounters during the baseline period helped ensure the patients regularly received care within the system and that data were not missing for patients. The sensitivity analysis examining dispensings to Priority Group 1 veterans (patients who are the highest priority for VHA care due to the highest levels of service-connected disability, ensuring they are more likely to receive all of their care from a VHA facility) also supports this (see Section 9.9.4).

9.9.4. Sensitivity analyses

10. The following sensitivity analyses were conducted for the comparison of azithromycin vs. amoxicillin-clavulanate within indication (respiratory and ENT) using the proportional hazards model (i.e., to estimate HRs).

1. Conducted primary analysis of CV death within 1-5 and 6-10 days of index dispensing using PS as a continuous covariate in the Cox regression model (rather than weighted by IPTW).

2. Examined the association between azithromycin versus amoxicillin-clavulanate use and cardiac death within 1-5 and 6-10 days of index dispensing.

3. Conducted primary analysis (CV death within 1-5 and 6-10 days) with alternative CV mortality risk score cut-off points for low, medium, and high CV mortality risk categories. Specifically, the high CV mortality risk group was intended to closely follow Ray et al. (2012)'s high CV mortality risk group profile.

4. Conducted primary analysis (CV death within 1-5 and 6-10 days) after restricting to dispensings to patients who are in Priority Group 1.

5. Conducted primary analysis (CV death within 1-5 and 6-10 days) in the subgroup of dispensings to patients <65 years of age, as veterans become eligible for Medicare at 65 years of age and thus may be more likely to seek care outside the VHA (which would not be captured in the CDW).

6. Conducted all primary, secondary, subgroup, and sensitivity analyses using outcomes occurring within 1-10 days of index antibiotic dispensing.

All sensitivity analyses were conducted separately for dispensings with a respiratory or ENT indication, followed by analyses to pool indication groups.

9.9.5. Amendments to the statistical analysis plan

Two updates were made to the statistical analysis that were not previously documented in Protocol Amendment 2 (Appendix 2) nor the SAP amendment. They include:

- The 1-10 day window to assess outcomes was included as a sensitivity analysis for all analyses, in addition to the 1-5 and 6-10 day windows.
- Only ED visits not related to CV disease on index date was considered for inclusion in the PS model, since including those visits related to CV disease may result in underestimation of CV risk

These updates were documented in the SAP and in a protocol administrative change letter (PACL), dated October 24th 2019.

9.10. Quality control

Data for the study was extracted from electronic databases in the CDW of the VHA and NDI. Each data content area in the CDW was subjected to similar checks, from high level variable name/type checks, to detailed trending comparisons. For example, checks included the following:

- Consistency checks for categorical variables
- Consistency and range checks for continuous variables

Quality assurance (QA) processes occurred at multiple times throughout the study. The following are key components that were addressed by the study team:

- Project team buy-in to analysis plan: The research team was responsible for creating the analysis plan and detailed specifications of the project. The entire team reviewed the documents to make sure that all of the points outlined in the analysis plan was well understood in the same manner and that all specifications would be feasible for the study and data source
- Documentation and diagnostics applied to computer code development: The primary programmers were responsible for creating and documenting all project-specific SAS codes and including comments as to why changes were made over the course of the project. In addition to evaluating diagnostic output independently, the programmers evaluated this output with the project team before final results tables were generated
- Independent code replication: Secondary programmers were assigned to conduct independent replications of the primary programmers' results. The primary and secondary programmers worked together when any discrepancies were found to resolve them and ensure that both sets of code resulted in the same findings, in order to confirm the programming approach. Any issues identified were documented and resolved in an audit log and tracker.

- Validation of study results: The project team was responsible for validating the results tables to confirm that results were consistent across analysis tables and that the results were coherent.

- Overall QA process: The project leader was responsible for making sure that all facets of the QA process were completed and documented. All project-related materials were stored in a central location; data-related materials (e.g., raw and analytic datasets, SAS code, SAS output) were saved in a central location on the VHA servers due to restrictions of data access and file transferring.

9.11. Protection of Human Subjects

Subject Information and Consent

All parties have complied with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures included omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws. No individual-level data were transferred to Pfizer.

Informed consent was not required for this study as this is a secondary data collection study, with no patient contact. The VHA Institutional Review Board (IRB) approved the waiving of informed consent.

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

The protocol that outlined the plan for this final study report was approved by the Institutional Review Board of the Veterans Affairs Medical Center, White River Junction, VT in December 2016.

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

Table 3 presents a summary of the sample selection for this study. After applying all eligibility criteria, the final respiratory indication sample size consisted of 814,263 dispensings (641,798 azithromycin and 172,465 amoxicillin-clavulanate) and the final ENT indication sample size consisted of 354,054 dispensings (146,600 azithromycin and 207,454 amoxicillin-clavulanate). After trimming the 1st and 99th percentiles of the PS distribution to build and apply the IPTW, the final analytic samples included the following: for respiratory indication, 629,345 azithromycin dispensings and 168,429 amoxicillin-clavulanate dispensings; for ENT indication, 143,783 azithromycin dispensings and 203,142 amoxicillin-clavulanate dispensings.

Table 3. Sample selection of dispensings for azithromycin or amoxicillin-clavulanate in the Veterans Health Administration database

Inclusion criteria		Count of dispensings	% from previous step	Count of dispensings	% from previous step
Step 0	Dispensing of an outpatient prescription for azithromycin and amoxicillin-clavulanate between 2000 and 2014	6,390,237	-		
Step 1	Dispensing of an oral[1] outpatient prescription for azithromycin and amoxicillin-clavulanate between 2000 and 2014	6,372,297	99.72%		
Step 2	No other study antibiotics on or up to 60 days before index date, and no same antibiotic within 60 days prior to (not including) the index date	5,342,124	83.83%		
Step 3	No missing date of birth or gender	5,341,837	99.99%		
Step 4	Age 30-74 years on the index dispensing date	4,240,688	79.39%		
Step 5	Enrolled in VHA benefits during the 365 days prior to the index date	3,819,297	90.06%		
Step 6	Regular use of VHA medical care, defined as at least two outpatient (excluding emergency department[2]) or inpatient encounters during the 365 days prior to index antibiotic prescription dispensing	3,514,317	92.01%		
Step 7	At least 1 pharmacy dispensing (other than the index antibiotic) during the 365 days prior to the index date	3,484,413	99.15%		
Step 8	No evidence of a serious illness on or during the 365 days prior to the index date	2,285,464	65.59%		
Step 9	No hospitalization during the 30 days prior to the index date	2,184,922	95.60%		

Table 3. Sample selection of dispensings for azithromycin or amoxicillin-clavulanate in the Veterans Health Administration database

Inclusion criteria		Count of dispensings	% from previous step	Count of dispensings	% from previous step
Step 10	No residence in a nursing home or other residential institution on or during the 365 days prior to the index date, except for stays of <30 days following hospital discharge	2,177,748	99.67%		
Step 11	No evidence of death prior to patient's last index date[3]	2,177,108	99.97%		
Step 12	No dispensings of more than one type of antibiotic (any antibiotics including study antibiotics) prescribed on the index date or during the 60 days prior to the index date (i.e., wash out period)	1,928,255	88.57%		
Step 13	Dispensings with an antibiotic indication of respiratory or ENT infection on the index date	***Respiratory***		***ENT***	
	Azithromycin dispensings	641,798	33.28%	146,600	7.60%
	Amoxicillin-clavulanate dispensings	172,465	8.94%	207,454	10.76%
Final analytic sample	Trimmed the 1st and 99th percentiles of the PS distribution with and without applied IPTW	***Respiratory)***		***ENT***	
		Unweighted N	Weighted N	Unweighted N	Weighted N
	Azithromycin dispensings	629,546	629,345	143,725	143,783
	Amoxicillin-clavulanate dispensings	168,433	168,429	203,249	203,142

Abbreviations: ENT= ear-nose-throat; VHA = Veterans Health Administration; PS= propensity score; IPTW = inverse probability treatment weights.

Table 3. Sample selection of dispensings for azithromycin or amoxicillin-clavulanate in the Veterans Health Administration database

Inclusion criteria	Count of dispensings	% from previous step	Count of dispensings	% from previous step

Notes:
[1] Only oral formulations were considered (i.e., intravenous or ophthalmic formulations were excluded).
[2] Emergency department visits were excluded, as they may not be considered regular.
[3] There were 321 patients who had a date of death identified prior to last index date and were removed from the sample.

10.2. Descriptive data

10.2.1. Baseline demographic characteristics

Respiratory indication

Table 4 describes the baseline demographic characteristics of dispensings to patients who received azithromycin or amoxicillin-clavulanate for a respiratory indication, after weighting by IPTW. The standardized differences between azithromycin and amoxicillin-clavulanate were small in the unadjusted sample (largest standardized difference of 6.41% for African American race), and they became smaller after applying the IPTW. Distributions of the unadjusted baseline demographic characteristics are presented in Appendix 10.

In the IPTW-adjusted sample, the majority of dispensings to patients for azithromycin were 45 years of age or older, with the highest proportion being age 55-65 years old (40.33% for azithromycin dispensings and 40.31% for amoxicillin-clavulanate dispensings; standardized difference 0.04%). A majority of azithromycin and amoxicillin-clavulanate dispensings were to patients who were white (68.37% and 68.47%, respectively; standardized difference -0.21%) and male (89.36% and 89.29%, respectively; standardized difference 0.24%). Just over half of the sample came from the South VHA service area (50.16% among azithromycin dispensings and 50.40% among amoxicillin-clavulanate dispensings; standardized difference -0.49%). Index antibiotic prescription dispensing was relatively evenly distributed from 2000-2014 (range 3.01%-8.24% for azithromycin and 3.07%-8.26% for amoxicillin-clavulanate), with peak dispensings occurring in the winter months.

Table 4. Baseline demographic characteristics of dispensings to patients who had a respiratory indication

	IPTW-adjusted sample[1]		
	Azithromycin dispensings	**Amoxicillin-clavulanate dispensings**	**Std. Diff. (%)**
Characteristics	**N=629,345**	**N=168,429**	**Azithromycin vs. Amoxicillin-clavulanate**
Age, mean ± SD [median]	58.0 ± 9.9 [59.5]	57.9 ± 9.9 [59.5]	0.23%
<35	18,358 (2.92%)	4,886 (2.90%)	0.09%
35-<45	55,541 (8.83%)	14,868 (8.83%)	-0.01%
45-<55	136,109 (21.63%)	36,373 (21.60%)	0.08%
55-<65	253,845 (40.33%)	67,900 (40.31%)	0.04%
65-<75	165,492 (26.30%)	44,402 (26.36%)	-0.15%
Race[2], n (%)			
White	430,269 (68.37%)	115,316 (68.47%)	-0.21%
African American	113,844 (18.09%)	30,399 (18.05%)	0.11%
Hispanic	28,449 (4.52%)	7,530 (4.47%)	0.24%
Pacific Islander	7,474 (1.19%)	1,989 (1.18%)	0.06%
Native American	6,091 (0.97%)	1,616 (0.96%)	0.08%
Asian	2,969 (0.47%)	783 (0.47%)	0.10%
Unknown	40,248 (6.40%)	10,796 (6.41%)	-0.06%
Gender, n (%)			
Male	562,375 (89.36%)	150,384 (89.29%)	0.24%
Female	66,970 (10.64%)	18,045 (10.71%)	-0.24%
BMI[3] (kg/m^2), n (%)			
Underweight (15.0 to <18.5)	6,721 (1.07%)	1,791 (1.06%)	0.05%
Normal weight (18.5 to <25.0)	99,332 (15.78%)	26,605 (15.80%)	-0.03%
Overweight (25.0 to <30.0)	198,009 (31.46%)	52,995 (31.46%)	0.00%
Class I obesity (30.0 to <35.0)	171,526 (27.25%)	45,972 (27.29%)	-0.09%
Class II obesity (35.0 to <40.0)	85,664 (13.61%)	22,949 (13.63%)	-0.04%
Class III obesity (40.0 to <50.0)	45,633 (7.25%)	12,121 (7.20%)	0.21%
Unknown	22,459 (3.57%)	5,997 (3.56%)	0.04%
VHA service area - US Census Region[4], n (%)			
South	315,650 (50.16%)	84,889 (50.40%)	-0.49%
Midwest	145,506 (23.12%)	38,944 (23.12%)	0.00%
West	88,164 (14.01%)	23,161 (13.75%)	0.75%
Northeast	73,749 (11.72%)	19,797 (11.75%)	-0.11%
Other	6,276 (1.00%)	1,639 (0.97%)	0.25%
International	0 (0.00%)	0 (0.00%)	0.00%
Year of index antibiotic prescription dispensing, n (%)			
2000	18,960 (3.01%)	5,178 (3.07%)	-0.36%
2001	26,246 (4.17%)	7,132 (4.23%)	-0.32%
2002	29,184 (4.64%)	7,856 (4.66%)	-0.13%
2003	35,456 (5.63%)	9,516 (5.65%)	-0.07%
2004	37,665 (5.98%)	10,078 (5.98%)	0.01%
2005	46,377 (7.37%)	12,402 (7.36%)	0.02%
2006	42,443 (6.74%)	11,392 (6.76%)	-0.08%
2007	42,351 (6.73%)	11,387 (6.76%)	-0.12%

Table 4. Baseline demographic characteristics of dispensings to patients who had a respiratory indication

	IPTW-adjusted sample[1]		
	Azithromycin dispensings	Amoxicillin-clavulanate dispensings	Std. Diff. (%)
Characteristics	**N=629,345**	**N=168,429**	**Azithromycin vs. Amoxicillin-clavulanate**
2008	47,181 (7.50%)	12,711 (7.55%)	-0.19%
2009	49,618 (7.88%)	13,292 (7.89%)	-0.03%
2010	49,858 (7.92%)	13,281 (7.89%)	0.14%
2011	52,256 (8.30%)	13,913 (8.26%)	0.15%
2012	51,872 (8.24%)	13,759 (8.17%)	0.27%
2013	50,675 (8.05%)	13,427 (7.97%)	0.30%
2014	49,203 (7.82%)	13,105 (7.78%)	0.14%
Month of index antibiotic prescription dispensing, n (%)			
January	73,670 (11.71%)	19,736 (11.72%)	-0.04%
February	65,556 (10.42%)	17,592 (10.45%)	-0.09%
March	65,219 (10.36%)	17,486 (10.38%)	-0.06%
April	50,846 (8.08%)	13,562 (8.05%)	0.10%
May	44,272 (7.03%)	11,804 (7.01%)	0.10%
June	36,908 (5.86%)	9,847 (5.85%)	0.08%
July	30,281 (4.81%)	8,067 (4.79%)	0.10%
August	33,067 (5.25%)	8,803 (5.23%)	0.12%
September	44,617 (7.09%)	11,936 (7.09%)	0.01%
October	53,913 (8.57%)	14,421 (8.56%)	0.01%
November	57,813 (9.19%)	15,496 (9.20%)	-0.05%
December	73,183 (11.63%)	19,678 (11.68%)	-0.17%

Abbreviations: BMI = Body Mass Index; IPTW = inverse probability of treatment weight; PS = Propensity Score; SD = Standard Deviation; Std. Diff. = Standardized Difference; US = United States; VHA = Veterans Health Administration.

Notes:

[1] IPTW-adjusted for all baseline covariates. Weighted Ns of dispensings are presented.

[2] If multiple race categories were noted in the data, race was assigned based on the order of descending hierarchy as listed in the table (e.g., a patient with White and Asian races was assigned Asian), with the exception of Unknown.

[3] BMI at the time of the most recent encounter prior to date of death was included and was calculated based on patient height and weight data as dividing weight in kilograms (kg) by height in meters (m) squared. Patients with missing BMI or those with BMI <15.0 or >=50 were categorized as "Unknown".

[4] Midwest includes IL, IN, IA, KS, MI, MN, MO, NE, ND, OH, SD, WI; Northeast includes CT, ME, MA, NH, NJ, NY, PA, RI, VT; South includes AL, AR, DE, DC, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, WV; West includes AK, AZ, CA, CO, HI, ID, MT, NV, NM, OR, UT, WA, WY; Other includes Puerto Rico, Virgin Islands; International includes Philippines.

ENT indication

Table 5 describes the baseline demographic characteristics of dispensings to patients who received azithromycin or amoxicillin-clavulanate for ENT indication, after adjustment using IPTW. Gender (13.93%) and the west VHA service region (-10.34%) exceeded the 10% threshold for a standardized difference indicating imbalance. However, after IPTW adjustment, the standardized differences became negligible. Distributions of the unadjusted baseline demographic characteristics are presented in Appendix 10.

In the IPTW-weighted ENT indication group, the majority of azithromycin dispensings were to patients 45 years of age or older, with the highest proportion being age 55-65 years old (35.75% for azithromycin and 35.78% for amoxicillin-clavulanate; standardized difference -0.07%). A majority of azithromycin and amoxicillin-clavulanate dispensings were to patients who were white (66.93% and 66.94%, respectively; standardized difference -0.02%) and male (84.58% and 84.65%, respectively; standardized difference -0.21%). Just over half of the sample came from the South VHA service area (52.35% among azithromycin dispensings and 52.31% among amoxicillin-clavulanate dispensings; standardized difference 0.08%). Index antibiotic prescription dispensing showed a slight increasing trend from 2000-2014 (range 2.78%-8.32% for azithromycin and 2.79%-8.33% for amoxicillin-clavulanate), with peak dispensings occurring in the winter months.

Table 5. Baseline demographic characteristics of dispensings to patients who had an ENT indication

	IPTW-adjusted sample[1]		
	Azithromycin dispensings	**Amoxicillin-clavulanate dispensings**	**Std. Diff. (%)**
Characteristics	**N=143,783**	**N=203,142**	**Azithromycin vs. Amoxicillin-clavulanate**
Age, mean ± SD [median]	54.5 ± 10.7 [55.9]	54.5 ± 10.7 [55.9]	-0.02%
<35	8,283 (5.76%)	11,694 (5.76%)	0.02%
35-<45	21,465 (14.93%)	30,262 (14.90%)	0.09%
45-<55	38,013 (26.44%)	53,656 (26.41%)	0.06%
55-<65	51,398 (35.75%)	72,688 (35.78%)	-0.07%
65-<75	24,623 (17.13%)	34,842 (17.15%)	-0.07%
Race[2], n (%)			
White	96,239 (66.93%)	135,990 (66.94%)	-0.02%
African American	28,642 (19.92%)	40,413 (19.89%)	0.07%
Hispanic	7,376 (5.13%)	10,451 (5.14%)	-0.07%
Pacific Islander	1,695 (1.18%)	2,398 (1.18%)	-0.02%
Native American	1,470 (1.02%)	2,078 (1.02%)	-0.01%
Asian	704 (0.49%)	997 (0.49%)	-0.02%
Unknown	7,658 (5.33%)	10,815 (5.32%)	0.01%
Gender, n (%)			
Male	121,604 (84.58%)	171,958 (84.65%)	-0.21%
Female	22,178 (15.42%)	31,184 (15.35%)	0.21%
BMI[3] (kg/m^2), n (%)			
Underweight (15.0 to <18.5)	520 (0.36%)	735 (0.36%)	0.00%
Normal weight (18.5 to <25.0)	18,917 (13.16%)	26,799 (13.19%)	-0.11%
Overweight (25.0 to <30.0)	48,031 (33.40%)	67,867 (33.41%)	-0.01%
Class I obesity (30.0 to <35.0)	42,008 (29.22%)	59,264 (29.17%)	0.09%
Class II obesity (35.0 to <40.0)	19,799 (13.77%)	27,979 (13.77%)	-0.01%
Class III obesity (40.0 to <50.0)	9,759 (6.79%)	13,787 (6.79%)	0.00%
Unknown	4,749 (3.30%)	6,712 (3.30%)	-0.01%
VHA service area - US Census Region[4], n (%)			
South	75,268 (52.35%)	106,256 (52.31%)	0.08%
Midwest	31,596 (21.97%)	44,667 (21.99%)	-0.03%
West	19,954 (13.88%)	28,241 (13.90%)	-0.07%
Northeast	14,841 (10.32%)	20,967 (10.32%)	0.00%
Other	2,105 (1.46%)	2,990 (1.47%)	-0.07%
International	19 (0.01%)	22 (0.01%)	0.23%
Year of index antibiotic prescription dispensing, n (%)			
2000	3,998 (2.78%)	5,667 (2.79%)	-0.05%
2001	5,789 (4.03%)	8,182 (4.03%)	-0.01%
2002	6,560 (4.56%)	9,299 (4.58%)	-0.07%
2003	7,677 (5.34%)	10,879 (5.36%)	-0.07%
2004	8,667 (6.03%)	12,232 (6.02%)	0.03%
2005	9,884 (6.87%)	14,003 (6.89%)	-0.07%

Table 5. Baseline demographic characteristics of dispensings to patients who had an ENT indication

	IPTW-adjusted sample[1]		
	Azithromycin dispensings	Amoxicillin-clavulanate dispensings	Std. Diff. (%)
Characteristics	**N=143,783**	**N=203,142**	**Azithromycin vs. Amoxicillin-clavulanate**
2006	9,876 (6.87%)	13,930 (6.86%)	0.04%
2007	10,135 (7.05%)	14,315 (7.05%)	0.01%
2008	10,631 (7.39%)	14,997 (7.38%)	0.04%
2009	11,115 (7.73%)	15,682 (7.72%)	0.04%
2010	11,790 (8.20%)	16,608 (8.18%)	0.09%
2011	11,809 (8.21%)	16,664 (8.20%)	0.04%
2012	11,934 (8.30%)	16,861 (8.30%)	0.00%
2013	11,967 (8.32%)	16,899 (8.32%)	0.01%
2014	11,951 (8.31%)	16,924 (8.33%)	-0.07%
Month of index antibiotic prescription dispensing, n (%)			
January	15,108 (10.51%)	21,291 (10.48%)	0.09%
February	13,870 (9.65%)	19,611 (9.65%)	-0.02%
March	14,250 (9.91%)	20,113 (9.90%)	0.03%
April	11,912 (8.28%)	16,806 (8.27%)	0.04%
May	10,703 (7.44%)	15,105 (7.44%)	0.03%
June	9,611 (6.68%)	13,552 (6.67%)	0.05%
July	8,741 (6.08%)	12,345 (6.08%)	0.01%
August	9,672 (6.73%)	13,703 (6.75%)	-0.08%
September	10,726 (7.46%)	15,212 (7.49%)	-0.11%
October	11,940 (8.30%)	16,904 (8.32%)	-0.06%
November	12,441 (8.65%)	17,610 (8.67%)	-0.06%
December	14,809 (10.30%)	20,891 (10.28%)	0.05%

Abbreviations: BMI = Body Mass Index; IPTW = inverse probability of treatment weight; PS = Propensity Score; SD = Standard Deviation; Std. Diff. = Standardized Difference; US = United States; VHA = Veterans Health Administration.

Notes:

[1] IPTW-adjusted for all baseline covariates. Weighted Ns of dispensings are presented.

[2] If multiple race categories were noted in the data, race was assigned based on the order of descending hierarchy as listed in the table (e.g., a patient with White and Asian races was assigned Asian), with the exception of Unknown.

[3] BMI at the time of the most recent encounter prior to date of death was included and was calculated based on patient height and weight data as dividing weight in kilograms (kg) by height in meters (m) squared. Patients with missing BMI or those with BMI <15.0 or >=50 were categorized as "Unknown".

[4] Midwest includes IL, IN, IA, KS, MI, MN, MO, NE, ND, OH, SD, WI; Northeast includes CT, ME, MA, NH, NJ, NY, PA, RI, VT; South includes AL, AR, DE, DC, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, WV; West includes AK, AZ, CA, CO, HI, ID, MT, NV, NM, OR, UT, WA, WY; Other includes Puerto Rico, Virgin Islands; International includes Philippines.

10.2.2. Baseline clinical characteristics

Respiratory indication

Table 6 describes the baseline clinical characteristics of azithromycin or amoxicillin-clavulanate dispensings for patients with a respiratory indication, after adjustment using IPTW. In the unadjusted sample, there were some imbalances between azithromycin and amoxicillin-clavulanate dispensings for COPD comorbidity (26.96% and 32.75%, respectively; -12.68% standardized difference). Additionally, more azithromycin dispensings had a non-CV ED visit on the index date compared to the amoxicillin-clavulanate dispensings (16.78% vs. 10.62%; standardized difference 18.00%). However, after adjustment, these cohorts became balanced with respect to COPD (27.89% for azithromycin and 27.90% for amoxicillin-clavulanate; -0.04% standardized difference), non-CV ED visit on day 1 (14.81% and 14.73%; standardized difference 0.22%), and generally for all clinical characteristics. Distributions of the unadjusted baseline demographic characteristics are presented in Appendix 10.

After IPTW weighting, the mean frailty index scores for the azithromycin and amoxicillin-clavulanate dispensings were 0.110 and 0.111, respectively (standardized difference -0.37%), with similar distributions across the four frailty categories and age-related health deficits for both antibiotics. Among azithromycin dispensings, 63.88% had a respiratory comorbidity; similarly, 64.65% of amoxicillin-clavulanate dispensings had a respiratory comorbidity (standardized difference -1.61%). Just over half of the dispensings received a respiratory therapy (57.77% in azithromycin, 58.60% in amoxicillin-clavulanate; standardized difference -1.68%) and 1.86% of azithromycin and amoxicillin-clavulanate dispensings were hospitalized in the baseline period due to respiratory disease (standardized difference 0.01%).

Cardiovascular comorbidities were present for 86.27% of azithromycin dispensings and 86.23% of amoxicillin-clavulanate dispensings (standardized difference 0.10%), with 77.66% and 77.87% of dispensings to patients receiving cardiovascular therapy, respectively (standardized difference -0.52%). Among azithromycin dispensings, 31.24% had a comorbidity related to diabetes mellitus and 24.73% received therapy for diabetes. Similarly, among the amoxicillin-clavulanate dispensings, 31.18% had a comorbidity related to diabetes mellitus and 24.81% received therapy for diabetes. Only 6.20% and 6.21% of azithromycin and amoxicillin-clavulanate dispensings, respectively, had a psychiatric comorbidity, including schizophrenia and alcohol abuse (standardized difference -0.04%).

The most common type of medical care was an outpatient visit within 30 days prior to antibiotic dispensing (67.59% for azithromycin and 67.57% for amoxicillin-clavulanate; standardized difference 0.05%). Just over 20% had a non-CV ED visit during the baseline period (20.87% for azithromycin and 20.83% for amoxicillin-clavulanate; standardized difference 0.10%), and nearly 80% of dispensings had ten or more non-CV outpatient visits within the year prior to antibiotic dispensing (76.86% for azithromycin and 76.83% for amoxicillin-clavulanate; standardized difference 0.07%).

Table 6. Baseline clinical characteristics of dispensings to patients who had a respiratory indication

	IPTW-adjusted sample[1]		
	Azithromycin dispensings	**Amoxicillin-clavulanate dispensings**	**Std. Diff. (%)**
Characteristics[2]	**N=629,345**	**N=168,429**	**Azithromycin vs. Amoxicillin-clavulanate**
Frailty Index score[3], mean ± SD [median]	0.110 ± 0.059 [0.100]	0.111 ± 0.058 [0.100]	-0.37%
Frailty category[4]			
Fit	230,348 (36.60%)	61,106 (36.28%)	0.67%
Mild	142,876 (22.70%)	38,485 (22.85%)	-0.35%
Moderate	114,197 (18.15%)	30,730 (18.25%)	-0.26%
Severe	141,924 (22.55%)	38,107 (22.62%)	-0.18%
Select age-related health deficits[5]			
Anemia and hematinic deficiency	34,694 (5.51%)	9,149 (5.43%)	0.36%
Dizziness	25,763 (4.09%)	6,791 (4.03%)	0.31%
Dyspnea	81,804 (13.00%)	21,963 (13.04%)	-0.12%
Hearing impairment	1,018 (0.16%)	259 (0.15%)	0.20%
Hypertension	373,073 (59.28%)	100,025 (59.39%)	-0.22%
Hypotension	8,215 (1.31%)	2,069 (1.23%)	0.69%
Syncope	9,909 (1.57%)	2,537 (1.51%)	0.55%
Ischemic heart disease	121,763 (19.35%)	32,840 (19.50%)	-0.38%
Osteoporosis	9,131 (1.45%)	2,515 (1.49%)	-0.35%
Peptic ulcer	9,267 (1.47%)	2,298 (1.36%)	0.92%
Polypharmacy	297,653 (47.30%)	81,488 (48.38%)	-2.17%
Respiratory disease	605,635 (96.23%)	160,622 (95.37%)	4.32%
Sleep disturbance	87,691 (13.93%)	23,857 (14.16%)	-0.66%
Thyroid disease	38,955 (6.19%)	10,239 (6.08%)	0.46%
Visual impairment	42,218 (6.71%)	11,190 (6.64%)	0.26%
Weight loss and anorexia	8,586 (1.36%)	2,293 (1.36%)	0.03%
Respiratory			
Respiratory comorbidities, N (%)	401,999 (63.88%)	108,884 (64.65%)	-1.61%
Bronchitis	50,144 (7.97%)	13,503 (8.02%)	-0.18%
COPD	175,495 (27.89%)	46,998 (27.90%)	-0.04%
Pneumonia	31,646 (5.03%)	8,551 (5.08%)	-0.22%
Asthma	83,778 (13.31%)	22,479 (13.35%)	-0.10%
Smoking	275,862 (43.83%)	73,767 (43.80%)	0.07%
Respiratory therapies, N (%)	363,570 (57.77%)	98,699 (58.60%)	-1.68%
Nebulizer therapy			
Within 1-31 days	153,459 (24.38%)	40,751 (24.19%)	0.44%
On day 1	99,672 (15.84%)	26,438 (15.70%)	0.39%
Within 2-8 days	20,139 (3.20%)	5,390 (3.20%)	0.00%
Within 9-31 days	52,158 (8.29%)	14,016 (8.32%)	-0.12%
Within 32-365 days	187,507 (29.79%)	50,181 (29.79%)	0.00%
Beta-2-agonist therapy			

Table 6. Baseline clinical characteristics of dispensings to patients who had a respiratory indication

	IPTW-adjusted sample[1]		
	Azithromycin dispensings	**Amoxicillin-clavulanate dispensings**	**Std. Diff. (%)**
Characteristics[2]	**N=629,345**	**N=168,429**	**Azithromycin vs. Amoxicillin-clavulanate**
Within 1-31 days	154,816 (24.60%)	41,119 (24.41%)	0.43%
On day 1	99,336 (15.78%)	26,348 (15.64%)	0.39%
Within 2-8 days	21,056 (3.35%)	5,632 (3.34%)	0.01%
Within 9-31 days	54,624 (8.68%)	14,675 (8.71%)	-0.12%
Within 32-365 days	185,307 (29.44%)	49,612 (29.46%)	-0.02%
Other bronchodilator therapy			
Within 1-31 days	246,671 (39.19%)	66,708 (39.61%)	-0.84%
On day 1	189,586 (30.12%)	50,755 (30.13%)	-0.02%
Within 2-8 days	33,242 (5.28%)	8,897 (5.28%)	0.00%
Within 9-31 days	84,317 (13.40%)	22,672 (13.46%)	-0.19%
Within 32-365 days	282,599 (44.90%)	75,653 (44.92%)	-0.03%
Respiratory disease hospitalization, N (%)	11,686 (1.86%)	3,126 (1.86%)	0.01%
Cardiovascular			
Cardiovascular comorbidities, N (%)	542,931 (86.27%)	145,245 (86.23%)	0.10%
Angina pectoris	14,093 (2.24%)	3,805 (2.26%)	-0.13%
Cardiac revascularization	3,109 (0.49%)	845 (0.50%)	-0.11%
Myocardial infarction	13,931 (2.21%)	3,822 (2.27%)	-0.38%
Other coronary heart disease	113,373 (18.01%)	30,566 (18.15%)	-0.35%
Cardiac valve disease	11,281 (1.79%)	3,061 (1.82%)	-0.19%
Conduction disorder	8,533 (1.36%)	2,303 (1.37%)	-0.10%
Atrial fibrillation	20,910 (3.32%)	5,823 (3.46%)	-0.74%
Arrhythmia	42,508 (6.75%)	11,655 (6.92%)	-0.66%
Congestive heart failure	28,263 (4.49%)	7,708 (4.58%)	-0.41%
Stroke	12,496 (1.99%)	3,393 (2.01%)	-0.21%
Transient ischemic attack	6,147 (0.98%)	1,655 (0.98%)	-0.06%
Peripheral vascular disease	39,173 (6.22%)	10,502 (6.24%)	-0.05%
Obesity diagnosed, not morbid	268,714 (42.70%)	72,054 (42.78%)	-0.17%
Morbid obesity, diagnosed	146,994 (23.36%)	39,297 (23.33%)	0.06%
Hypertension	364,904 (57.98%)	97,687 (58.00%)	-0.04%
Malignant hypertension	678 (0.11%)	186 (0.11%)	-0.08%
Hyperlipidemia	336,937 (53.54%)	90,196 (53.55%)	-0.03%
Renal disease	1,972 (0.31%)	526 (0.31%)	0.02%
Other CV disease	82,485 (13.11%)	22,165 (13.16%)	-0.16%
New CV diagnosis, past 30 days	2,471 (0.39%)	663 (0.39%)	-0.02%
Cardiovascular therapies, N (%)	488,721 (77.66%)	131,158 (77.87%)	-0.52%
New CV medication, Within 1-31 days	7,653 (1.22%)	2,034 (1.21%)	0.08%
ACE inhibitor			
Within 1-31 days	81,300 (12.92%)	21,798 (12.94%)	-0.07%
On day 1	20,456 (3.25%)	5,496 (3.26%)	-0.07%

Table 6. Baseline clinical characteristics of dispensings to patients who had a respiratory indication

	IPTW-adjusted sample[1]		
	Azithromycin dispensings	Amoxicillin-clavulanate dispensings	Std. Diff. (%)
Characteristics[2]	**N=629,345**	**N=168,429**	**Azithromycin vs. Amoxicillin-clavulanate**
Within 2-8 days	14,343 (2.28%)	3,862 (2.29%)	-0.09%
Within 9-31 days	50,398 (8.01%)	13,523 (8.03%)	-0.08%
Within 32-365 days	213,639 (33.95%)	57,360 (34.06%)	-0.23%
Angiotensin receptor blocker			
Within 1-31 days	16,905 (2.69%)	4,544 (2.70%)	-0.07%
On day 1	3,934 (0.63%)	1,045 (0.62%)	0.06%
Within 2-8 days	3,244 (0.52%)	866 (0.51%)	0.02%
Within 9-31 days	10,637 (1.69%)	2,859 (1.70%)	-0.06%
Within 32-365 days	39,286 (6.24%)	10,496 (6.23%)	0.05%
Anticoagulant			
Within 1-31 days	14,700 (2.34%)	4,233 (2.51%)	-1.15%
On day 1	2,649 (0.42%)	757 (0.45%)	-0.43%
Within 2-8 days	3,172 (0.50%)	890 (0.53%)	-0.34%
Within 9-31 days	10,574 (1.68%)	3,037 (1.80%)	-0.94%
Within 32-365 days	45,477 (7.23%)	12,430 (7.38%)	-0.59%
Antiarrhythmic			
Within 1-31 days	5,286 (0.84%)	1,438 (0.85%)	-0.15%
On day 1	1,041 (0.17%)	296 (0.18%)	-0.25%
Within 2-8 days	1,044 (0.17%)	270 (0.16%)	0.14%
Within 9-31 days	3,614 (0.57%)	968 (0.57%)	0.00%
Within 32-365 days	13,366 (2.12%)	3,647 (2.17%)	-0.29%
Aspirin			
Within 1-31 days	38,592 (6.13%)	10,327 (6.13%)	0.00%
On day 1	10,053 (1.60%)	2,698 (1.60%)	-0.04%
Within 2-8 days	6,724 (1.07%)	1,799 (1.07%)	0.00%
Within 9-31 days	22,636 (3.60%)	6,058 (3.60%)	0.00%
Within 32-365 days	132,413 (21.04%)	35,499 (21.08%)	-0.09%
Beta-blocker			
Within 1-31 days	71,116 (11.30%)	19,217 (11.41%)	-0.35%
On day 1	16,510 (2.62%)	4,489 (2.67%)	-0.26%
Within 2-8 days	13,270 (2.11%)	3,559 (2.11%)	-0.03%
Within 9-31 days	44,927 (7.14%)	12,103 (7.19%)	-0.18%
Within 32-365 days	185,219 (29.43%)	49,766 (29.55%)	-0.26%
Calcium channel blocker			
Within 1-31 days	51,753 (8.22%)	13,960 (8.29%)	-0.24%
On day 1	13,422 (2.13%)	3,620 (2.15%)	-0.12%
Within 2-8 days	9,359 (1.49%)	2,524 (1.50%)	-0.09%
Within 9-31 days	31,722 (5.04%)	8,500 (5.05%)	-0.03%
Within 32-365 days	131,573 (20.91%)	35,170 (20.88%)	0.06%
Digoxin			
Within 1-31 days	5,215 (0.83%)	1,491 (0.89%)	-0.62%
On day 1	881 (0.14%)	265 (0.16%)	-0.45%

Table 6. Baseline clinical characteristics of dispensings to patients who had a respiratory indication

	IPTW-adjusted sample[1]		
	Azithromycin dispensings	Amoxicillin-clavulanate dispensings	Std. Diff. (%)
Characteristics[2]	**N=629,345**	**N=168,429**	**Azithromycin vs. Amoxicillin-clavulanate**
Within 2-8 days	1,027 (0.16%)	287 (0.17%)	-0.18%
Within 9-31 days	3,513 (0.56%)	986 (0.59%)	-0.36%
Within 32-365 days	14,719 (2.34%)	4,126 (2.45%)	-0.73%
Loop diuretic			
Within 1-31 days	24,634 (3.91%)	6,664 (3.96%)	-0.22%
On day 1	7,537 (1.20%)	2,067 (1.23%)	-0.27%
Within 2-8 days	4,261 (0.68%)	1,144 (0.68%)	-0.03%
Within 9-31 days	14,255 (2.27%)	3,871 (2.30%)	-0.22%
Within 32-365 days	62,285 (9.90%)	16,846 (10.00%)	-0.35%
Other diuretic			
Within 1-31 days	61,555 (9.78%)	16,567 (9.84%)	-0.19%
On day 1	16,798 (2.67%)	4,524 (2.69%)	-0.10%
Within 2-8 days	10,823 (1.72%)	2,914 (1.73%)	-0.08%
Within 9-31 days	36,520 (5.80%)	9,778 (5.81%)	-0.01%
Within 32-365 days	165,358 (26.27%)	44,224 (26.26%)	0.04%
Statin			
Within 1-31 days	103,901 (16.51%)	27,903 (16.57%)	-0.15%
On day 1	25,364 (4.03%)	6,839 (4.06%)	-0.15%
Within 2-8 days	18,268 (2.90%)	4,866 (2.89%)	0.08%
Within 9-31 days	64,232 (10.21%)	17,233 (10.23%)	-0.08%
Within 32-365 days	285,783 (45.41%)	76,629 (45.50%)	-0.17%
Fibrate lipid-lowering agent			
Within 1-31 days	10,857 (1.73%)	2,956 (1.76%)	-0.23%
On day 1	2,522 (0.40%)	675 (0.40%)	0.00%
Within 2-8 days	1,952 (0.31%)	530 (0.31%)	-0.08%
Within 9-31 days	6,722 (1.07%)	1,820 (1.08%)	-0.12%
Within 32-365 days	34,813 (5.53%)	9,309 (5.53%)	0.02%
Nitrate anti-anginal			
Within 1-31 days	22,918 (3.64%)	6,202 (3.68%)	-0.22%
On day 1	7,343 (1.17%)	1,987 (1.18%)	-0.12%
Within 2-8 days	4,013 (0.64%)	1,088 (0.65%)	-0.10%
Within 9-31 days	13,173 (2.09%)	3,558 (2.11%)	-0.14%
Within 32-365 days	69,217 (11.00%)	18,705 (11.11%)	-0.34%
Other antihypertensive			
Within 1-31 days	25,623 (4.07%)	6,834 (4.06%)	0.07%
On day 1	6,408 (1.02%)	1,712 (1.02%)	0.02%
Within 2-8 days	4,868 (0.77%)	1,294 (0.77%)	0.06%
Within 9-31 days	16,022 (2.55%)	4,249 (2.52%)	0.15%
Within 32-365 days	66,241 (10.53%)	17,678 (10.50%)	0.10%
Peripheral vasodilator			
Within 1-31 days	1,790 (0.28%)	487 (0.29%)	-0.09%
On day 1	464 (0.07%)	126 (0.07%)	-0.04%

Table 6. Baseline clinical characteristics of dispensings to patients who had a respiratory indication

	IPTW-adjusted sample[1]		
	Azithromycin dispensings	Amoxicillin-clavulanate dispensings	Std. Diff. (%)
Characteristics[2]	**N=629,345**	**N=168,429**	**Azithromycin vs. Amoxicillin-clavulanate**
Within 2-8 days	361 (0.06%)	93 (0.06%)	0.09%
Within 9-31 days	1,102 (0.18%)	294 (0.17%)	0.02%
Within 32-365 days	5,459 (0.87%)	1,440 (0.85%)	0.14%
Platelet inhibitor, not aspirin			
Within 1-31 days	12,429 (1.97%)	3,359 (1.99%)	-0.14%
On day 1	2,110 (0.34%)	567 (0.34%)	-0.02%
Within 2-8 days	2,533 (0.40%)	681 (0.40%)	-0.03%
Within 9-31 days	8,593 (1.37%)	2,302 (1.37%)	-0.01%
Within 32-365 days	32,775 (5.21%)	8,838 (5.25%)	-0.18%
Diabetes mellitus			
Diabetes mellitus comorbidities, N (%)	196,622 (31.24%)	52,509 (31.18%)	0.14%
Diabetes mellitus	175,699 (27.92%)	47,091 (27.96%)	-0.09%
Diabetes, neurologic complication	24,332 (3.87%)	6,498 (3.86%)	0.04%
Diabetes, skin complication	34,720 (5.52%)	9,187 (5.45%)	0.27%
Diabetes, renal complication	4,384 (0.70%)	1,172 (0.70%)	0.01%
Diabetes, other complication	11,870 (1.89%)	3,155 (1.87%)	0.10%
Diabetes, poor control noted	31,992 (5.08%)	8,595 (5.10%)	-0.09%
Diabetes mellitus therapies, N (%)	155,611 (24.73%)	41,784 (24.81%)	-0.19%
Insulin			
Within 1-31 days	29,191 (4.64%)	7,821 (4.64%)	-0.02%
On day 1	7,309 (1.16%)	1,974 (1.17%)	-0.10%
Within 2-8 days	6,143 (0.98%)	1,640 (0.97%)	0.02%
Within 9-31 days	19,593 (3.11%)	5,251 (3.12%)	-0.02%
Within 32-365 days	62,814 (9.98%)	16,812 (9.98%)	0.00%
Oral hypoglycemic			
Within 1-31 days	62,078 (9.86%)	16,583 (9.85%)	0.06%
On day 1	15,238 (2.42%)	4,067 (2.41%)	0.04%
Within 2-8 days	12,587 (2.00%)	3,368 (2.00%)	0.00%
Within 9-31 days	40,683 (6.46%)	10,863 (6.45%)	0.06%
Within 32-365 days	134,469 (21.37%)	36,022 (21.39%)	-0.05%
Psychiatric			
Psychiatric comorbidities, N (%)	39,039 (6.20%)	10,463 (6.21%)	-0.04%
Schizophrenia	19,560 (3.11%)	5,231 (3.11%)	0.01%
Alcohol abuse	20,581 (3.27%)	5,496 (3.26%)	0.04%
Psychiatric therapies, N (%)	316,864 (50.35%)	84,779 (50.34%)	0.03%
Tricyclic antidepressant			
Within 1-31 days	17,380 (2.76%)	4,629 (2.75%)	0.08%
On day 1	3,585 (0.57%)	958 (0.57%)	0.01%
Within 2-8 days	3,513 (0.56%)	944 (0.56%)	-0.03%
Within 9-31 days	11,849 (1.88%)	3,165 (1.88%)	0.03%
Within 32-365 days	43,207 (6.87%)	11,569 (6.87%)	-0.01%

Table 6. Baseline clinical characteristics of dispensings to patients who had a respiratory indication

	IPTW-adjusted sample[1]		
	Azithromycin dispensings	Amoxicillin-clavulanate dispensings	Std. Diff. (%)
Characteristics[2]	**N=629,345**	**N=168,429**	**Azithromycin vs. Amoxicillin-clavulanate**
SSRI/SNRI antidepressant			
Within 1-31 days	85,338 (13.56%)	22,861 (13.57%)	-0.04%
On day 1	14,805 (2.35%)	3,947 (2.34%)	0.06%
Within 2-8 days	18,478 (2.94%)	4,972 (2.95%)	-0.09%
Within 9-31 days	60,323 (9.59%)	16,234 (9.64%)	-0.18%
Within 32-365 days	173,768 (27.61%)	46,568 (27.65%)	-0.08%
Serotonin modulator antidepressant			
Within 1-31 days	32,036 (5.09%)	8,532 (5.07%)	0.11%
On day 1	5,816 (0.92%)	1,558 (0.93%)	-0.01%
Within 2-8 days	6,703 (1.07%)	1,795 (1.07%)	-0.01%
Within 9-31 days	22,336 (3.55%)	5,982 (3.55%)	-0.02%
Within 32-365 days	72,706 (11.55%)	19,448 (11.55%)	0.02%
Other antidepressant			
Within 1-31 days	45,892 (7.29%)	12,278 (7.29%)	0.01%
On day 1	9,108 (1.45%)	2,434 (1.45%)	0.02%
Within 2-8 days	9,753 (1.55%)	2,627 (1.56%)	-0.08%
Within 9-31 days	31,541 (5.01%)	8,441 (5.01%)	0.00%
Within 32-365 days	108,031 (17.17%)	28,884 (17.15%)	0.04%
Benzodiazepine/GABA agonist			
Within 1-31 days	66,323 (10.54%)	17,839 (10.59%)	-0.17%
On day 1	11,448 (1.82%)	3,059 (1.82%)	0.02%
Within 2-8 days	14,881 (2.36%)	4,015 (2.38%)	-0.12%
Within 9-31 days	48,854 (7.76%)	13,091 (7.77%)	-0.04%
Within 32-365 days	115,243 (18.31%)	30,947 (18.37%)	-0.16%
Antipsychotic			
Within 1-31 days	32,159 (5.11%)	8,547 (5.07%)	0.16%
On day 1	4,600 (0.73%)	1,211 (0.72%)	0.14%
Within 2-8 days	8,020 (1.27%)	2,146 (1.27%)	0.00%
Within 9-31 days	24,559 (3.90%)	6,578 (3.91%)	-0.02%
Within 32-365 days	57,118 (9.08%)	15,275 (9.07%)	0.02%
Lithium			
Within 1-31 days	3,113 (0.49%)	824 (0.49%)	0.08%
On day 1	390 (0.06%)	99 (0.06%)	0.14%
Within 2-8 days	740 (0.12%)	194 (0.11%)	0.08%
Within 9-31 days	2,334 (0.37%)	616 (0.37%)	0.08%
Within 32-365 days	6,027 (0.96%)	1,597 (0.95%)	0.10%
Mood stabilizer			
Within 1-31 days	3,089 (0.49%)	829 (0.49%)	-0.02%
On day 1	542 (0.09%)	142 (0.08%)	0.06%
Within 2-8 days	641 (0.10%)	173 (0.10%)	-0.03%
Within 9-31 days	2,186 (0.35%)	583 (0.35%)	0.02%

Table 6. Baseline clinical characteristics of dispensings to patients who had a respiratory indication

	IPTW-adjusted sample[1]		
	Azithromycin dispensings	**Amoxicillin-clavulanate dispensings**	**Std. Diff. (%)**
Characteristics[2]	**N=629,345**	**N=168,429**	**Azithromycin vs. Amoxicillin-clavulanate**
Within 32-365 days	7,135 (1.13%)	1,919 (1.14%)	-0.05%
Hydroxyzine			
Within 1-31 days	12,091 (1.92%)	3,268 (1.94%)	-0.14%
On day 1	2,997 (0.48%)	816 (0.48%)	-0.12%
Within 2-8 days	2,251 (0.36%)	605 (0.36%)	-0.03%
Within 9-31 days	7,683 (1.22%)	2,073 (1.23%)	-0.09%
Within 32-365 days	37,455 (5.95%)	10,057 (5.97%)	-0.08%
Psychiatric hospitalization, N (%)	6,086 (0.97%)	1,637 (0.97%)	-0.05%
Musculoskeletal and injury related			
Musculoskeletal and injury related comorbidities, N (%)	18,495 (2.94%)	4,940 (2.93%)	0.04%
Inflammatory arthropathy	8,322 (1.32%)	2,238 (1.33%)	-0.06%
Opioid poisoning	69 (0.01%)	18 (0.01%)	0.01%
Psychotropic poisoning	153 (0.02%)	41 (0.02%)	0.00%
Poisoning, unspecified medication	918 (0.15%)	245 (0.15%)	0.01%
Suicide attempt	823 (0.13%)	224 (0.13%)	-0.06%
Fall	8,855 (1.41%)	2,372 (1.41%)	-0.01%
Musculoskeletal and injury related therapies, N (%)	337,200 (53.58%)	90,366 (53.65%)	-0.15%
Morphine prescription			
Within 1-31 days	10,852 (1.72%)	2,922 (1.73%)	-0.08%
On day 1	2,092 (0.33%)	569 (0.34%)	-0.10%
Within 2-8 days	2,209 (0.35%)	582 (0.35%)	0.09%
Within 9-31 days	8,066 (1.28%)	2,140 (1.27%)	0.10%
Within 32-365 days	26,577 (4.22%)	7,099 (4.21%)	0.04%
Fentanyl prescription			
Within 1-31 days	1,737 (0.28%)	480 (0.28%)	-0.17%
On day 1	294 (0.05%)	80 (0.05%)	-0.03%
Within 2-8 days	374 (0.06%)	96 (0.06%)	0.11%
Within 9-31 days	1,310 (0.21%)	360 (0.21%)	-0.12%
Within 32-365 days	4,284 (0.68%)	1,159 (0.69%)	-0.09%
Meperidine prescription			
Within 1-31 days	200 (0.03%)	49 (0.03%)	0.15%
On day 1	71 (0.01%)	18 (0.01%)	0.05%
Within 2-8 days	25 (0.00%)	6 (0.00%)	0.05%
Within 9-31 days	122 (0.02%)	30 (0.02%)	0.13%
Within 32-365 days	2,568 (0.41%)	685 (0.41%)	0.02%
Other opioid prescription			
Within 1-31 days	135,857 (21.59%)	36,198 (21.49%)	0.23%
On day 1	80,517 (12.79%)	21,492 (12.76%)	0.10%
Within 2-8 days	18,032 (2.87%)	4,809 (2.86%)	0.06%
Within 9-31 days	55,477 (8.82%)	14,785 (8.78%)	0.13%

Table 6. Baseline clinical characteristics of dispensings to patients who had a respiratory indication

	IPTW-adjusted sample[1]		
	Azithromycin dispensings	Amoxicillin-clavulanate dispensings	Std. Diff. (%)
Characteristics[2]	**N=629,345**	**N=168,429**	**Azithromycin vs. Amoxicillin-clavulanate**
Within 32-365 days	195,214 (31.02%)	52,135 (30.95%)	0.14%
Systemic corticosteroid			
Within 1-31 days	103,626 (16.47%)	28,000 (16.62%)	-0.43%
On day 1	93,297 (14.82%)	25,182 (14.95%)	-0.36%
Within 2-8 days	4,333 (0.69%)	1,165 (0.69%)	-0.04%
Within 9-31 days	11,127 (1.77%)	3,004 (1.78%)	-0.12%
Within 32-365 days	110,436 (17.55%)	29,716 (17.64%)	-0.25%
Musculoskeletal and injury related HRU, N (%)	10,566 (1.68%)	2,804 (1.67%)	0.11%
Injury ED, 1-2 visits	3,060 (0.49%)	805 (0.48%)	0.12%
Injury ED, 3+ visits	40 (0.01%)	11 (0.01%)	0.00%
Injury outpatient, 1-2 visits	10,017 (1.59%)	2,661 (1.58%)	0.09%
Injury outpatient, 3-5 visits	471 (0.07%)	124 (0.07%)	0.04%
Injury outpatient, 6+ visits	79 (0.01%)	19 (0.01%)	0.10%
Neurologic			
Neurologic comorbidities, N (%)	8,544 (1.36%)	2,307 (1.37%)	-0.11%
Seizure disorder	4,975 (0.79%)	1,342 (0.80%)	-0.07%
Dementia	3,691 (0.59%)	995 (0.59%)	-0.05%
Neurologic therapies, N (%)	125,419 (19.93%)	33,567 (19.93%)	0.00%
Anticonvulsant			
Within 1-31 days	50,767 (8.07%)	13,715 (8.14%)	-0.28%
On day 1	10,046 (1.60%)	2,705 (1.61%)	-0.08%
Within 2-8 days	10,896 (1.73%)	2,941 (1.75%)	-0.11%
Within 9-31 days	35,536 (5.65%)	9,537 (5.66%)	-0.07%
Within 32-365 days	111,031 (17.64%)	29,736 (17.66%)	-0.03%
Parkinson's medication			
Within 1-31 days	8,063 (1.28%)	2,157 (1.28%)	0.00%
On day 1	1,468 (0.23%)	401 (0.24%)	-0.10%
Within 2-8 days	1,791 (0.28%)	474 (0.28%)	0.06%
Within 9-31 days	5,713 (0.91%)	1,534 (0.91%)	-0.03%
Within 32-365 days	16,106 (2.56%)	4,320 (2.56%)	-0.04%
Frailty			
Frailty related comorbidities, N (%)	19,344 (3.07%)	5,114 (3.04%)	0.22%
Decubitus ulcer	686 (0.11%)	164 (0.10%)	0.35%
Amputation	3,336 (0.53%)	890 (0.53%)	0.02%
Delirium	1,017 (0.16%)	267 (0.16%)	0.08%
Incontinence, urine	8,219 (1.31%)	2,195 (1.30%)	0.02%
Incontinence, fecal	810 (0.13%)	220 (0.13%)	-0.06%
Indwelling urinary catheter	218 (0.03%)	59 (0.04%)	-0.02%
Feeding/nutrition problem	2,276 (0.36%)	598 (0.36%)	0.11%
Wheelchair/walker	3,621 (0.58%)	952 (0.57%)	0.13%

Table 6. Baseline clinical characteristics of dispensings to patients who had a respiratory indication

	IPTW-adjusted sample[1]		
	Azithromycin dispensings	Amoxicillin-clavulanate dispensings	Std. Diff. (%)
Characteristics[2]	**N=629,345**	**N=168,429**	**Azithromycin vs. Amoxicillin-clavulanate**
Medical care, N (%)	629,345 (100.00%)	168,429 (100.00%)	0.00%
Any non-CV ED visit on day 1	93,216 (14.81%)	24,813 (14.73%)	0.22%
Any ED visit past 7 days	17,669 (2.81%)	4,753 (2.82%)	-0.09%
Any outpatient visit past 30 days	425,371 (67.59%)	113,799 (67.57%)	0.05%
CV inpatient visit 92-365 days before day 1	12,502 (1.99%)	3,388 (2.01%)	-0.18%
CV inpatient visit 31-91 days before day 1	2,874 (0.46%)	777 (0.46%)	-0.07%
CV hospital stay lasting >5 days	3,675 (0.58%)	991 (0.59%)	-0.06%
Non-CV hospitalization	46,488 (7.39%)	12,497 (7.42%)	-0.13%
CV ED visit	11,007 (1.75%)	2,921 (1.73%)	0.11%
Non-CV ED visit	131,357 (20.87%)	35,085 (20.83%)	0.10%
Non-CV ED visit past 30 days	28,765 (4.57%)	7,653 (4.54%)	0.13%
CV ED visit past 30 days	919 (0.15%)	244 (0.15%)	0.02%
CV outpatient visits past year: 1	42,470 (6.75%)	11,418 (6.78%)	-0.12%
CV outpatient visits past year: 2-5	34,825 (5.53%)	9,419 (5.59%)	-0.26%
CV outpatient visits past year: 6-10	2,999 (0.48%)	813 (0.48%)	-0.09%
CV outpatient visits past year: >10	609 (0.10%)	166 (0.10%)	-0.05%
Non-CV outpatient visits past year: 1	29 (0.00%)	8 (0.00%)	-0.04%
Non-CV outpatient visits past year: 2-5	39,272 (6.24%)	10,528 (6.25%)	-0.04%
Non-CV outpatient visits past year: 6-10	106,316 (16.89%)	28,487 (16.91%)	-0.05%
Non-CV outpatient visits past year: >10	483,723 (76.86%)	129,406 (76.83%)	0.07%
Other therapies, N (%)			
Any prescription dispensed within 1-31 days (not study antibiotic)	604,387 (96.03%)	162,280 (96.35%)	-1.64%
On day 1	522,193 (82.97%)	139,912 (83.07%)	-0.25%
Within 2-8 days	217,370 (34.54%)	58,281 (34.60%)	-0.13%
Within 9-31 days	428,408 (68.07%)	114,785 (68.15%)	-0.17%
Other drugs known to prolong the QT interval			
Within 1-31 days	72,890 (11.58%)	19,591 (11.63%)	-0.16%
On day 1	18,957 (3.01%)	5,096 (3.03%)	-0.08%
Within 2-8 days	13,102 (2.08%)	3,501 (2.08%)	0.02%
Within 9-31 days	43,834 (6.96%)	11,752 (6.98%)	-0.05%
Within 32-365 days	197,317 (31.35%)	52,793 (31.34%)	0.02%

Abbreviations: Std. Diff. = Standardized Difference; COPD = Chronic Obstructive Pulmonary Disease; HRU = Healthcare Resource Utilization; CV = Cardiovascular; ACE = Angiotensin-Converting-Enzyme; SSRI = Selective Serotonin Reuptake Inhibitors; SNRI = Serotonin and Norepinephrine Reuptake Inhibitors; GABA = Gamma-Aminobutyric Acid; ED = Emergency Department; IP = Inpatient; IPTW = inverse probability of

Table 6. Baseline clinical characteristics of dispensings to patients who had a respiratory indication

	IPTW-adjusted sample[1]		
	Azithromycin dispensings	**Amoxicillin-clavulanate dispensings**	**Std. Diff. (%)**
Characteristics[2]	**N=629,345**	**N=168,429**	**Azithromycin vs. Amoxicillin-clavulanate**

treatment weight; PS = Propensity Score; OP = Outpatient; CPT = Current Procedural Terminology; ICD = International Classification of Diseases.

Notes:

[1] IPTW adjusted for all baseline covariates. Weighted Ns of dispensings are presented.

[2] Disease comorbidities were identified during the 1-year baseline period prior to the index date. Medication use was identified during the 1-year baseline period and on the index date.

[3] Frailty index score was defined as the sum of age-related health deficits present per dispensing divided by the total number of age-related health deficits assessed.

[4] Frailty index scores were categorized into four groups using population quartiles: Fit (0–0.067); Mild (>0.067–0.1); Moderate (>0.1–0.134); and Severe (>0.134).

[5] Select age-related health deficits that are not shown elsewhere in the table are presented here.

ENT indication

Table 7 describes baseline clinical characteristics of azithromycin or amoxicillin-clavulanate dispensings for an ENT indication, after adjustment with IPTW. In the unadjusted sample, there were some imbalances between azithromycin and amoxicillin-clavulanate dispensings for respiratory disease, which was one of the factors used in the frailty index calculation (95.69% and 90.56%, respectively; 20.37% standardized difference). After adjusting using IPTW, balance for clinical characteristics was achieved. An imbalance in the proportion of dispensings to patients with a health deficit of respiratory disease (which was used for the calculation of frailty index) remained (95.49% and 90.70%, respectively; 18.97% standardized difference), but this was not considered to be problematic as it was only used as a component in the frailty index, which was balanced between azithromycin and amoxicillin-clavulanate dispensings. Distributions of the unadjusted baseline demographic characteristics are presented in Appendix 10.

In the adjusted sample, the mean frailty index score was 0.096 for both azithromycin and amoxicillin-clavulanate dispensings (standardized difference 0.17%), with similar distributions across the four frailty categories and age-related health deficits (with the exception of respiratory disease as previously mentioned). Among azithromycin dispensings, 44.23% had a respiratory comorbidity; similarly, 44.14% of amoxicillin-clavulanate dispensings had a respiratory comorbidity (standardized difference 0.19%). Just under half of both azithromycin and amoxicillin-clavulanate dispensings received some sort of respiratory therapy (46.97% in azithromycin, 46.95% in amoxicillin-clavulanate; standardized difference 0.04%) and 0.43% and 0.44% of azithromycin dispensings and amoxicillin-clavulanate dispensings were hospitalized during the baseline period due to respiratory disease (standardized difference -0.07%). Other respiratory comorbidities and respiratory therapies considered separately (and included in the PS model) were balanced.

Cardiovascular comorbidities were present for 84.20% of azithromycin dispensings and 83.95% of amoxicillin-clavulanate dispensings (standardized difference 0.68%), with 71.22% and 70.94% of dispensings receiving cardiovascular therapy, respectively (standardized difference 0.62%). Among azithromycin dispensings, 27.95% of had a comorbidity related to diabetes mellitus and 21.08% received therapy for diabetes. Similarly, for amoxicillin-clavulanate dispensings, 27.97% had a comorbidity related to diabetes mellitus and 21.09% received therapy for diabetes.

The most common type of medical care was any outpatient visit within 30 days prior to antibiotic dispensing (67.25% in azithromycin cohort and 67.26% in amoxicillin-clavulanate cohort; standardized difference -0.02%). Approximately 20% of dispensings had a non-CV ED visit during the baseline period (21.17% in both cohorts; standardized difference 0.01%), and a majority of dispensings had ten or more non-CV outpatient visits within the year prior to antibiotic dispensing (75.21% for azithromycin and 75.20% for amoxicillin-clavulanate; standardized difference 0.03%).

Table 7. Baseline clinical characteristics of dispensings to patients who had an ENT indication

	IPTW-adjusted sample[1]		
	Azithromycin dispensings	Amoxicillin-clavulanate dispensings	Std. Diff[2] (%)
Characteristics[3]	**N=143,783**	**N=203,142**	**Azithromycin vs. Amoxicillin-clavulanate**
Frailty Index score[4], mean ± SD [median]	0.096 ± 0.054 [0.100]	0.096 ± 0.055 [0.100]	0.17%
Frailty category[5]			
Fit	67,927 (47.24%)	96,018 (47.27%)	-0.05%
Mild	31,945 (22.22%)	44,511 (21.91%)	0.74%
Moderate	22,355 (15.55%)	31,213 (15.37%)	0.50%
Severe	21,555 (14.99%)	31,400 (15.46%)	-1.30%
Select age-related health deficits[6]			
Anemia and hematinic deficiency	6,628 (4.61%)	9,758 (4.80%)	-0.91%
Dizziness	6,927 (4.82%)	11,026 (5.43%)	-2.77%
Dyspnea	7,819 (5.44%)	12,109 (5.96%)	-2.26%
Hearing impairment	212 (0.15%)	488 (0.24%)	-2.12%
Hypertension	77,434 (53.85%)	109,642 (53.97%)	-0.24%
Hypotension	1,261 (0.88%)	1,899 (0.93%)	-0.61%
Syncope	1,789 (1.24%)	2,754 (1.36%)	-0.99%
Ischemic heart disease	18,865 (13.12%)	26,693 (13.14%)	-0.06%
Osteoporosis	1,266 (0.88%)	1,962 (0.97%)	-0.89%
Peptic ulcer	1,543 (1.07%)	2,434 (1.20%)	-1.18%
Polypharmacy	53,854 (37.45%)	77,720 (38.26%)	-1.66%
Respiratory disease	137,297 (95.49%)	184,253 (90.70%)	18.97% *
Sleep disturbance	19,964 (13.88%)	30,598 (15.06%)	-3.35%
Thyroid disease	8,947 (6.22%)	13,035 (6.42%)	-0.80%
Visual impairment	8,476 (5.90%)	12,688 (6.25%)	-1.47%
Weight loss and anorexia	1,045 (0.73%)	1,593 (0.78%)	-0.66%
Respiratory			
Respiratory comorbidities, N (%)	63,602 (44.23%)	89,673 (44.14%)	0.19%
Bronchitis	5,835 (4.06%)	8,213 (4.04%)	0.08%
COPD	10,913 (7.59%)	15,423 (7.59%)	-0.01%
Pneumonia	3,208 (2.23%)	4,523 (2.23%)	0.03%
Asthma	8,539 (5.94%)	11,992 (5.90%)	0.15%
Smoking	49,941 (34.73%)	70,435 (34.67%)	0.13%
Respiratory therapies, N (%)	67,538 (46.97%)	95,385 (46.95%)	0.04%
Nebulizer therapy			
Within 1-31 days	7,792 (5.42%)	10,866 (5.35%)	0.31%
On day 1	3,334 (2.32%)	4,615 (2.27%)	0.31%
Within 2-8 days	1,240 (0.86%)	1,734 (0.85%)	0.09%
Within 9-31 days	3,724 (2.59%)	5,264 (2.59%)	-0.01%
Within 32-365 days	19,176 (13.34%)	27,045 (13.31%)	0.07%
Beta-2-agonist therapy			
Within 1-31 days	7,164 (4.98%)	9,954 (4.90%)	0.38%
On day 1	2,770 (1.93%)	3,808 (1.87%)	0.38%
Within 2-8 days	1,219 (0.85%)	1,718 (0.85%)	0.02%

Table 7. Baseline clinical characteristics of dispensings to patients who had an ENT indication

	IPTW-adjusted sample[1]		
	Azithromycin dispensings	Amoxicillin-clavulanate dispensings	Std. Diff[2] (%)
Characteristics[3]	**N=143,783**	**N=203,142**	**Azithromycin vs. Amoxicillin-clavulanate**
Within 9-31 days	3,664 (2.55%)	5,169 (2.54%)	0.02%
Within 32-365 days	17,837 (12.41%)	25,101 (12.36%)	0.15%
Other bronchodilator therapy			
Within 1-31 days	35,247 (24.51%)	49,618 (24.43%)	0.21%
On day 1	24,724 (17.20%)	34,794 (17.13%)	0.18%
Within 2-8 days	3,611 (2.51%)	5,086 (2.50%)	0.05%
Within 9-31 days	9,962 (6.93%)	14,019 (6.90%)	0.11%
Within 32-365 days	51,201 (35.61%)	72,159 (35.52%)	0.18%
Respiratory disease hospitalization, N (%)	623 (0.43%)	890 (0.44%)	-0.07%
Cardiovascular			
Cardiovascular comorbidities, N (%)	121,070 (84.20%)	170,544 (83.95%)	0.68%
Angina pectoris	2,245 (1.56%)	3,165 (1.56%)	0.03%
Cardiac revascularization	490 (0.34%)	691 (0.34%)	0.01%
Myocardial infarction	2,145 (1.49%)	3,014 (1.48%)	0.07%
Other coronary heart disease	17,560 (12.21%)	24,794 (12.21%)	0.02%
Cardiac valve disease	1,964 (1.37%)	2,768 (1.36%)	0.03%
Conduction disorder	1,426 (0.99%)	2,024 (1.00%)	-0.05%
Atrial fibrillation	3,227 (2.24%)	4,554 (2.24%)	0.02%
Arrhythmia	7,582 (5.27%)	10,712 (5.27%)	0.00%
Congestive heart failure	2,942 (2.05%)	4,164 (2.05%)	-0.03%
Stroke	1,971 (1.37%)	2,778 (1.37%)	0.03%
Transient ischemic attack	1,081 (0.75%)	1,532 (0.75%)	-0.03%
Peripheral vascular disease	5,993 (4.17%)	8,451 (4.16%)	0.04%
Obesity diagnosed, not morbid	63,600 (44.23%)	89,776 (44.19%)	0.08%
Morbid obesity, diagnosed	32,873 (22.86%)	46,435 (22.86%)	0.01%
Hypertension	75,697 (52.65%)	106,972 (52.66%)	-0.02%
Malignant hypertension	139 (0.10%)	195 (0.10%)	0.01%
Hyperlipidemia	74,347 (51.71%)	105,006 (51.69%)	0.03%
Renal disease	364 (0.25%)	517 (0.25%)	-0.02%
Other CV disease	15,926 (11.08%)	22,481 (11.07%)	0.03%
New CV diagnosis, past 30 days	545 (0.38%)	779 (0.38%)	-0.07%
Cardiovascular therapies, N (%)	102,409 (71.22%)	144,113 (70.94%)	0.62%
New CV medication, Within 1-31 days	1,878 (1.31%)	2,650 (1.30%)	0.02%
ACE inhibitor			
Within 1-31 days	15,825 (11.01%)	22,369 (11.01%)	-0.02%
On day 1	4,009 (2.79%)	5,655 (2.78%)	0.03%
Within 2-8 days	2,864 (1.99%)	4,051 (1.99%)	-0.02%
Within 9-31 days	9,723 (6.76%)	13,733 (6.76%)	0.01%
Within 32-365 days	41,881 (29.13%)	59,189 (29.14%)	-0.02%
Angiotensin receptor blocker			

Table 7. Baseline clinical characteristics of dispensings to patients who had an ENT indication

	IPTW-adjusted sample[1]		
	Azithromycin dispensings	Amoxicillin-clavulanate dispensings	Std. Diff[2] (%)
Characteristics[3]	**N=143,783**	**N=203,142**	**Azithromycin vs. Amoxicillin-clavulanate**
Within 1-31 days	3,009 (2.09%)	4,236 (2.09%)	0.05%
On day 1	642 (0.45%)	905 (0.45%)	0.02%
Within 2-8 days	571 (0.40%)	806 (0.40%)	0.01%
Within 9-31 days	1,959 (1.36%)	2,743 (1.35%)	0.10%
Within 32-365 days	7,201 (5.01%)	10,169 (5.01%)	0.01%
Anticoagulant			
Within 1-31 days	2,465 (1.71%)	3,467 (1.71%)	0.06%
On day 1	410 (0.28%)	586 (0.29%)	-0.06%
Within 2-8 days	542 (0.38%)	766 (0.38%)	0.00%
Within 9-31 days	1,860 (1.29%)	2,621 (1.29%)	0.02%
Within 32-365 days	7,083 (4.93%)	10,026 (4.94%)	-0.04%
Antiarrhythmic			
Within 1-31 days	913 (0.63%)	1,286 (0.63%)	0.02%
On day 1	172 (0.12%)	240 (0.12%)	0.06%
Within 2-8 days	195 (0.14%)	270 (0.13%)	0.07%
Within 9-31 days	615 (0.43%)	875 (0.43%)	-0.04%
Within 32-365 days	2,254 (1.57%)	3,194 (1.57%)	-0.04%
Aspirin			
Within 1-31 days	6,437 (4.48%)	9,063 (4.46%)	0.08%
On day 1	1,507 (1.05%)	2,126 (1.05%)	0.02%
Within 2-8 days	1,134 (0.79%)	1,609 (0.79%)	-0.04%
Within 9-31 days	3,917 (2.72%)	5,511 (2.71%)	0.07%
Within 32-365 days	23,256 (16.17%)	32,850 (16.17%)	0.01%
Beta-blocker			
Within 1-31 days	13,334 (9.27%)	18,869 (9.29%)	-0.05%
On day 1	3,060 (2.13%)	4,313 (2.12%)	0.04%
Within 2-8 days	2,523 (1.75%)	3,569 (1.76%)	-0.02%
Within 9-31 days	8,417 (5.85%)	11,870 (5.84%)	0.04%
Within 32-365 days	35,312 (24.56%)	49,876 (24.55%)	0.02%
Calcium channel blocker			
Within 1-31 days	9,750 (6.78%)	13,809 (6.80%)	-0.07%
On day 1	2,489 (1.73%)	3,504 (1.72%)	0.05%
Within 2-8 days	1,790 (1.24%)	2,528 (1.24%)	0.01%
Within 9-31 days	5,965 (4.15%)	8,454 (4.16%)	-0.06%
Within 32-365 days	24,990 (17.38%)	35,335 (17.39%)	-0.04%
Digoxin			
Within 1-31 days	663 (0.46%)	935 (0.46%)	0.01%
On day 1	111 (0.08%)	153 (0.08%)	0.07%
Within 2-8 days	134 (0.09%)	188 (0.09%)	0.01%
Within 9-31 days	443 (0.31%)	628 (0.31%)	-0.03%
Within 32-365 days	1,826 (1.27%)	2,590 (1.28%)	-0.04%
Loop diuretic			

Table 7. Baseline clinical characteristics of dispensings to patients who had an ENT indication

	IPTW-adjusted sample[1]		
	Azithromycin dispensings	Amoxicillin-clavulanate dispensings	Std. Diff[2] (%)
Characteristics[3]	**N=143,783**	**N=203,142**	**Azithromycin vs. Amoxicillin-clavulanate**
Within 1-31 days	2,627 (1.83%)	3,724 (1.83%)	-0.04%
On day 1	597 (0.41%)	833 (0.41%)	0.08%
Within 2-8 days	498 (0.35%)	710 (0.35%)	-0.05%
Within 9-31 days	1,670 (1.16%)	2,346 (1.15%)	0.06%
Within 32-365 days	7,708 (5.36%)	10,852 (5.34%)	0.08%
Other diuretic			
Within 1-31 days	13,214 (9.19%)	18,659 (9.19%)	0.02%
On day 1	3,623 (2.52%)	5,086 (2.50%)	0.11%
Within 2-8 days	2,356 (1.64%)	3,317 (1.63%)	0.05%
Within 9-31 days	7,787 (5.42%)	11,002 (5.42%)	0.00%
Within 32-365 days	35,067 (24.39%)	49,460 (24.35%)	0.10%
Statin			
Within 1-31 days	20,763 (14.44%)	29,236 (14.39%)	0.14%
On day 1	5,055 (3.52%)	7,131 (3.51%)	0.03%
Within 2-8 days	3,710 (2.58%)	5,252 (2.59%)	-0.03%
Within 9-31 days	12,722 (8.85%)	17,939 (8.83%)	0.06%
Within 32-365 days	57,842 (40.23%)	81,725 (40.23%)	0.00%
Fibrate lipid-lowering agent			
Within 1-31 days	2,438 (1.70%)	3,403 (1.68%)	0.16%
On day 1	565 (0.39%)	804 (0.40%)	-0.05%
Within 2-8 days	437 (0.30%)	608 (0.30%)	0.09%
Within 9-31 days	1,490 (1.04%)	2,109 (1.04%)	-0.02%
Within 32-365 days	7,885 (5.48%)	11,149 (5.49%)	-0.02%
Nitrate anti-anginal			
Within 1-31 days	2,955 (2.06%)	4,158 (2.05%)	0.06%
On day 1	829 (0.58%)	1,171 (0.58%)	0.00%
Within 2-8 days	518 (0.36%)	733 (0.36%)	-0.01%
Within 9-31 days	1,767 (1.23%)	2,495 (1.23%)	0.01%
Within 32-365 days	10,397 (7.23%)	14,684 (7.23%)	0.01%
Other antihypertensive			
Within 1-31 days	5,540 (3.85%)	7,819 (3.85%)	0.02%
On day 1	1,383 (0.96%)	1,951 (0.96%)	0.01%
Within 2-8 days	1,063 (0.74%)	1,495 (0.74%)	0.04%
Within 9-31 days	3,457 (2.40%)	4,875 (2.40%)	0.03%
Within 32-365 days	14,235 (9.90%)	20,074 (9.88%)	0.06%
Peripheral vasodilator			
Within 1-31 days	290 (0.20%)	395 (0.19%)	0.17%
On day 1	69 (0.05%)	96 (0.05%)	0.02%
Within 2-8 days	61 (0.04%)	87 (0.04%)	-0.02%
Within 9-31 days	176 (0.12%)	243 (0.12%)	0.08%
Within 32-365 days	893 (0.62%)	1,263 (0.62%)	0.00%
Platelet inhibitor, not aspirin			

Table 7. Baseline clinical characteristics of dispensings to patients who had an ENT indication

	IPTW-adjusted sample[1]		
	Azithromycin dispensings	Amoxicillin-clavulanate dispensings	Std. Diff[2] (%)
Characteristics[3]	**N=143,783**	**N=203,142**	**Azithromycin vs. Amoxicillin-clavulanate**
Within 1-31 days	1,859 (1.29%)	2,632 (1.30%)	-0.02%
On day 1	320 (0.22%)	450 (0.22%)	0.03%
Within 2-8 days	365 (0.25%)	519 (0.26%)	-0.04%
Within 9-31 days	1,288 (0.90%)	1,814 (0.89%)	0.03%
Within 32-365 days	5,161 (3.59%)	7,274 (3.58%)	0.04%
Diabetes mellitus			
Diabetes mellitus comorbidities, N (%)	40,183 (27.95%)	56,811 (27.97%)	-0.04%
Diabetes mellitus	34,844 (24.23%)	49,246 (24.24%)	-0.02%
Diabetes, neurologic complication	4,555 (3.17%)	6,435 (3.17%)	0.00%
Diabetes, skin complication	8,082 (5.62%)	11,406 (5.62%)	0.03%
Diabetes, renal complication	779 (0.54%)	1,098 (0.54%)	0.02%
Diabetes, other complication	2,252 (1.57%)	3,180 (1.57%)	0.01%
Diabetes, poor control noted	6,317 (4.39%)	8,907 (4.38%)	0.04%
Diabetes mellitus therapies, N (%)	30,306 (21.08%)	42,850 (21.09%)	-0.04%
Insulin			
Within 1-31 days	5,342 (3.72%)	7,589 (3.74%)	-0.11%
On day 1	1,283 (0.89%)	1,813 (0.89%)	0.00%
Within 2-8 days	1,140 (0.79%)	1,622 (0.80%)	-0.06%
Within 9-31 days	3,644 (2.53%)	5,150 (2.54%)	0.00%
Within 32-365 days	11,266 (7.84%)	15,940 (7.85%)	-0.04%
Oral hypoglycemic			
Within 1-31 days	12,274 (8.54%)	17,325 (8.53%)	0.03%
On day 1	3,010 (2.09%)	4,252 (2.09%)	0.00%
Within 2-8 days	2,532 (1.76%)	3,597 (1.77%)	-0.07%
Within 9-31 days	8,030 (5.58%)	11,336 (5.58%)	0.02%
Within 32-365 days	26,661 (18.54%)	37,642 (18.53%)	0.03%
Psychiatric			
Psychiatric comorbidities, N (%)	7,076 (4.92%)	10,036 (4.94%)	-0.09%
Schizophrenia	3,405 (2.37%)	4,827 (2.38%)	-0.05%
Alcohol abuse	3,838 (2.67%)	5,442 (2.68%)	-0.06%
Psychiatric therapies, N (%)	71,882 (49.99%)	101,152 (49.79%)	0.40%
Tricyclic antidepressant			
Within 1-31 days	3,918 (2.73%)	5,561 (2.74%)	-0.08%
On day 1	826 (0.57%)	1,168 (0.58%)	0.00%
Within 2-8 days	805 (0.56%)	1,133 (0.56%)	0.02%
Within 9-31 days	2,654 (1.85%)	3,751 (1.85%)	0.00%
Within 32-365 days	10,371 (7.21%)	14,674 (7.22%)	-0.04%
SSRI/SNRI antidepressant			
Within 1-31 days	19,990 (13.90%)	28,370 (13.97%)	-0.18%
On day 1	3,489 (2.43%)	4,931 (2.43%)	-0.01%
Within 2-8 days	4,432 (3.08%)	6,246 (3.07%)	0.04%

Table 7. Baseline clinical characteristics of dispensings to patients who had an ENT indication

	IPTW-adjusted sample[1]		
	Azithromycin dispensings	Amoxicillin-clavulanate dispensings	Std. Diff[2] (%)
Characteristics[3]	**N=143,783**	**N=203,142**	**Azithromycin vs. Amoxicillin-clavulanate**
Within 9-31 days	14,085 (9.80%)	19,910 (9.80%)	-0.02%
Within 32-365 days	40,856 (28.41%)	57,622 (28.37%)	0.11%
Serotonin modulator antidepressant			
Within 1-31 days	6,903 (4.80%)	9,855 (4.85%)	-0.23%
On day 1	1,236 (0.86%)	1,745 (0.86%)	0.00%
Within 2-8 days	1,501 (1.04%)	2,131 (1.05%)	-0.05%
Within 9-31 days	4,813 (3.35%)	6,802 (3.35%)	-0.01%
Within 32-365 days	16,441 (11.43%)	23,186 (11.41%)	0.06%
Other antidepressant			
Within 1-31 days	10,345 (7.20%)	14,676 (7.22%)	-0.11%
On day 1	1,937 (1.35%)	2,741 (1.35%)	-0.01%
Within 2-8 days	2,286 (1.59%)	3,217 (1.58%)	0.05%
Within 9-31 days	7,191 (5.00%)	10,152 (5.00%)	0.02%
Within 32-365 days	24,949 (17.35%)	35,205 (17.33%)	0.06%
Benzodiazepine/GABA agonist			
Within 1-31 days	13,981 (9.72%)	19,674 (9.68%)	0.13%
On day 1	2,299 (1.60%)	3,231 (1.59%)	0.07%
Within 2-8 days	3,239 (2.25%)	4,585 (2.26%)	-0.03%
Within 9-31 days	10,187 (7.08%)	14,356 (7.07%)	0.07%
Within 32-365 days	25,279 (17.58%)	35,637 (17.54%)	0.10%
Antipsychotic			
Within 1-31 days	6,286 (4.37%)	8,882 (4.37%)	0.00%
On day 1	900 (0.63%)	1,277 (0.63%)	-0.04%
Within 2-8 days	1,561 (1.09%)	2,183 (1.07%)	0.11%
Within 9-31 days	4,735 (3.29%)	6,666 (3.28%)	0.07%
Within 32-365 days	11,808 (8.21%)	16,652 (8.20%)	0.05%
Lithium			
Within 1-31 days	681 (0.47%)	972 (0.48%)	-0.07%
On day 1	87 (0.06%)	123 (0.06%)	0.01%
Within 2-8 days	168 (0.12%)	234 (0.12%)	0.04%
Within 9-31 days	507 (0.35%)	725 (0.36%)	-0.07%
Within 32-365 days	1,368 (0.95%)	1,957 (0.96%)	-0.13%
Mood stabilizer			
Within 1-31 days	688 (0.48%)	952 (0.47%)	0.15%
On day 1	116 (0.08%)	166 (0.08%)	-0.04%
Within 2-8 days	152 (0.11%)	208 (0.10%)	0.11%
Within 9-31 days	479 (0.33%)	668 (0.33%)	0.07%
Within 32-365 days	1,572 (1.09%)	2,198 (1.08%)	0.11%
Hydroxyzine			
Within 1-31 days	2,639 (1.84%)	3,694 (1.82%)	0.13%
On day 1	684 (0.48%)	960 (0.47%)	0.04%
Within 2-8 days	490 (0.34%)	682 (0.34%)	0.09%

Table 7. Baseline clinical characteristics of dispensings to patients who had an ENT indication

	IPTW-adjusted sample[1]		
	Azithromycin dispensings	**Amoxicillin-clavulanate dispensings**	**Std. Diff[2] (%)**
Characteristics[3]	**N=143,783**	**N=203,142**	**Azithromycin vs. Amoxicillin-clavulanate**
Within 9-31 days	1,639 (1.14%)	2,316 (1.14%)	0.00%
Within 32-365 days	8,468 (5.89%)	11,896 (5.86%)	0.14%
Psychiatric hospitalization, N (%)	1,293 (0.90%)	1,840 (0.91%)	-0.07%
Musculoskeletal and injury related			
Musculoskeletal and injury related comorbidities, N (%)	3,990 (2.77%)	5,580 (2.75%)	0.17%
Inflammatory arthropathy	1,832 (1.27%)	2,560 (1.26%)	0.13%
Opioid poisoning	10 (0.01%)	15 (0.01%)	-0.05%
Psychotropic poisoning	29 (0.02%)	38 (0.02%)	0.11%
Poisoning, unspecified medication	167 (0.12%)	238 (0.12%)	-0.02%
Suicide attempt	179 (0.12%)	251 (0.12%)	0.02%
Fall	1,900 (1.32%)	2,662 (1.31%)	0.10%
Musculoskeletal and injury related therapies, N (%)	60,858 (42.33%)	86,422 (42.54%)	-0.44%
Morphine prescription			
Within 1-31 days	2,213 (1.54%)	3,150 (1.55%)	-0.09%
On day 1	425 (0.30%)	598 (0.29%)	0.02%
Within 2-8 days	460 (0.32%)	655 (0.32%)	-0.04%
Within 9-31 days	1,642 (1.14%)	2,307 (1.14%)	0.06%
Within 32-365 days	5,479 (3.81%)	7,741 (3.81%)	0.00%
Fentanyl prescription			
Within 1-31 days	368 (0.26%)	502 (0.25%)	0.17%
On day 1	65 (0.04%)	91 (0.04%)	0.01%
Within 2-8 days	78 (0.05%)	115 (0.06%)	-0.10%
Within 9-31 days	264 (0.18%)	368 (0.18%)	0.05%
Within 32-365 days	821 (0.57%)	1,171 (0.58%)	-0.07%
Meperidine prescription			
Within 1-31 days	62 (0.04%)	89 (0.04%)	-0.03%
On day 1	28 (0.02%)	38 (0.02%)	0.04%
Within 2-8 days	7 (0.01%)	15 (0.01%)	-0.28%
Within 9-31 days	28 (0.02%)	39 (0.02%)	-0.02%
Within 32-365 days	591 (0.41%)	826 (0.41%)	0.08%
Other opioid prescription			
Within 1-31 days	23,128 (16.09%)	32,847 (16.17%)	-0.23%
On day 1	10,866 (7.56%)	15,315 (7.54%)	0.07%
Within 2-8 days	3,635 (2.53%)	5,141 (2.53%)	-0.02%
Within 9-31 days	11,722 (8.15%)	16,528 (8.14%)	0.06%
Within 32-365 days	43,536 (30.28%)	61,470 (30.26%)	0.04%
Systemic corticosteroid			
Within 1-31 days	7,570 (5.26%)	10,644 (5.24%)	0.11%
On day 1	6,111 (4.25%)	8,586 (4.23%)	0.12%
Within 2-8 days	365 (0.25%)	500 (0.25%)	0.15%

Table 7. Baseline clinical characteristics of dispensings to patients who had an ENT indication

	IPTW-adjusted sample[1]		
	Azithromycin dispensings	Amoxicillin-clavulanate dispensings	Std. Diff[2] (%)
Characteristics[3]	**N=143,783**	**N=203,142**	**Azithromycin vs. Amoxicillin-clavulanate**
Within 9-31 days	1,286 (0.89%)	1,802 (0.89%)	0.08%
Within 32-365 days	16,396 (11.40%)	23,077 (11.36%)	0.14%
Musculoskeletal and injury related HRU, N (%)	2,347 (1.63%)	3,325 (1.64%)	-0.04%
Injury ED, 1-2 visits	710 (0.49%)	1,014 (0.50%)	-0.08%
Injury ED, 3+ visits	6 (0.00%)	4 (0.00%)	0.37%
Injury outpatient, 1-2 visits	2,254 (1.57%)	3,202 (1.58%)	-0.07%
Injury outpatient, 3-5 visits	86 (0.06%)	121 (0.06%)	0.02%
Injury outpatient, 6+ visits	6 (0.00%)	3 (0.00%)	0.58%
Neurologic			
Neurologic comorbidities, N (%)	1,592 (1.11%)	2,259 (1.11%)	-0.05%
Seizure disorder	1,063 (0.74%)	1,509 (0.74%)	-0.04%
Dementia	541 (0.38%)	764 (0.38%)	0.00%
Neurologic therapies, N (%)	27,859 (19.38%)	39,340 (19.37%)	0.02%
Anticonvulsant			
Within 1-31 days	11,215 (7.80%)	15,846 (7.80%)	0.00%
On day 1	2,258 (1.57%)	3,170 (1.56%)	0.08%
Within 2-8 days	2,484 (1.73%)	3,495 (1.72%)	0.06%
Within 9-31 days	7,737 (5.38%)	10,947 (5.39%)	-0.03%
Within 32-365 days	25,061 (17.43%)	35,335 (17.39%)	0.09%
Parkinson's medication			
Within 1-31 days	1,332 (0.93%)	1,879 (0.93%)	0.01%
On day 1	209 (0.15%)	297 (0.15%)	-0.02%
Within 2-8 days	297 (0.21%)	416 (0.20%)	0.04%
Within 9-31 days	959 (0.67%)	1,337 (0.66%)	0.11%
Within 32-365 days	2,941 (2.05%)	4,140 (2.04%)	0.05%
Frailty			
Frailty related comorbidities, N (%)	4,231 (2.94%)	6,003 (2.96%)	-0.08%
Decubitus ulcer	124 (0.09%)	173 (0.09%)	0.03%
Amputation	626 (0.44%)	883 (0.43%)	0.01%
Delirium	157 (0.11%)	222 (0.11%)	0.00%
Incontinence, urine	1,866 (1.30%)	2,608 (1.28%)	0.13%
Incontinence, fecal	173 (0.12%)	252 (0.12%)	-0.10%
Indwelling urinary catheter	36 (0.02%)	51 (0.03%)	-0.02%
Feeding/nutrition problem	680 (0.47%)	959 (0.47%)	0.02%
Wheelchair/walker	732 (0.51%)	1,044 (0.51%)	-0.06%
Medical care, N (%)	143,783 (100.00%)	203,142 (100.00%)	0.00%
Any non-CV ED visit on day 1	21,639 (15.05%)	30,559 (15.04%)	0.02%
Any ED visit past 7 days	3,897 (2.71%)	5,483 (2.70%)	0.07%
Any outpatient visit past 30 days	96,689 (67.25%)	136,624 (67.26%)	-0.02%
CV inpatient visit 92-365 days before day 1	1,869 (1.30%)	2,630 (1.29%)	0.05%

Table 7. Baseline clinical characteristics of dispensings to patients who had an ENT indication

	IPTW-adjusted sample[1]		
	Azithromycin dispensings	Amoxicillin-clavulanate dispensings	Std. Diff[2] (%)
Characteristics[3]	**N=143,783**	**N=203,142**	**Azithromycin vs. Amoxicillin-clavulanate**
CV inpatient visit 31-91 days before day 1	406 (0.28%)	567 (0.28%)	0.06%
CV hospital stay lasting >5 days	474 (0.33%)	663 (0.33%)	0.06%
Non-CV hospitalization	7,951 (5.53%)	11,265 (5.55%)	-0.07%
CV ED visit	2,188 (1.52%)	3,074 (1.51%)	0.07%
Non-CV ED visit	30,441 (21.17%)	43,002 (21.17%)	0.01%
Non-CV ED visit past 30 days	6,359 (4.42%)	8,955 (4.41%)	0.07%
CV ED visit past 30 days	170 (0.12%)	245 (0.12%)	-0.06%
CV outpatient visits past year: 1	7,291 (5.07%)	10,308 (5.07%)	-0.02%
CV outpatient visits past year: 2-5	5,654 (3.93%)	7,962 (3.92%)	0.07%
CV outpatient visits past year: 6-10	421 (0.29%)	599 (0.29%)	-0.03%
CV outpatient visits past year: >10	71 (0.05%)	106 (0.05%)	-0.11%
Non-CV outpatient visits past year: 1	5 (0.00%)	6 (0.00%)	-0.01%
Non-CV outpatient visits past year: 2-5	9,956 (6.92%)	14,071 (6.93%)	-0.01%
Non-CV outpatient visits past year: 6-10	25,686 (17.86%)	36,308 (17.87%)	-0.02%
Non-CV outpatient visits past year: >10	108,136 (75.21%)	152,756 (75.20%)	0.03%
Other therapies, N (%)			
Any prescription dispensed within 1-31 days (not study antibiotic)	133,309 (92.72%)	188,957 (93.02%)	-1.17%
On day 1	107,611 (74.84%)	151,930 (74.79%)	0.12%
Within 2-8 days	44,199 (30.74%)	62,478 (30.76%)	-0.03%
Within 9-31 days	90,445 (62.90%)	127,737 (62.88%)	0.05%
Other drugs known to prolong the QT interval			
Within 1-31 days	15,405 (10.71%)	21,683 (10.67%)	0.13%
On day 1	3,933 (2.74%)	5,535 (2.72%)	0.07%
Within 2-8 days	2,736 (1.90%)	3,875 (1.91%)	-0.03%
Within 9-31 days	9,315 (6.48%)	13,114 (6.46%)	0.09%
Within 32-365 days	42,969 (29.88%)	60,597 (29.83%)	0.12%

Abbreviations: Std. Diff. = Standardized Difference; COPD = Chronic Obstructive Pulmonary Disease; HRU = Healthcare Resource Utilization; CV = Cardiovascular; ACE = Angiotensin-Converting-Enzyme; SSRI = Selective Serotonin Reuptake Inhibitors; SNRI = Serotonin and Norepinephrine Reuptake Inhibitors; GABA = Gamma-Aminobutyric Acid; ED = Emergency Department; IP = Inpatient; IPTW = inverse probability of treatment weight; PS = Propensity Score; OP = Outpatient; CPT = Current Procedural Terminology; ICD = International Classification of Diseases.

Notes:

[1] IPTW adjusted for all baseline covariates. Weighted Ns of dispensings are presented.

[2] Variables with a standardized difference ≥10% were denoted with "*".

Table 7. Baseline clinical characteristics of dispensings to patients who had an ENT indication

	IPTW-adjusted sample[1]		
	Azithromycin dispensings	**Amoxicillin-clavulanate dispensings**	**Std. Diff[2] (%)**
Characteristics[3]	**N=143,783**	**N=203,142**	**Azithromycin vs. Amoxicillin-clavulanate**

[3] Disease comorbidities were identified during the 1-year baseline period prior to the index date. Medication use was identified during the 1-year baseline period and on the index date.
[4] Frailty index score was defined as the sum of age-related health deficits present per dispensing divided by the total number of age-related health deficits assessed. Disease comorbidities included in the frailty index score were identified during the 1-year baseline period and on the index date. Medication use included in the frailty index score was assessed during the 30 days prior to the index date and on the index date.
[5] Frailty index scores were categorized into four groups using population quartiles: Fit (0–0.067); Mild (>0.067–0.1); Moderate (>0.1–0.134); and Severe (>0.134).
[6] Select age-related health deficits that are not shown elsewhere in the table are presented here.

10.3. Outcome data

10.3.1. Number of CV, non-CV, and cardiac deaths

Respiratory indication

Table 8 summarizes the number of CV, non-CV, and cardiac deaths within 1-5, 6-10, and 1-10 days of the index dates (the latter as a sensitivity analysis), among all dispensings to patients with a respiratory indication, as well as azithromycin and amoxicillin-clavulanate dispensings, separately. The values are summarized for the full sample and for all subgroups and sensitivity analyses. Cumulative incidences are also reported for CV death among all dispensings to patients with a respiratory indication.

Within 1-5 days of the index date, there were a total of 79 CV deaths, 64 among azithromycin dispensings and 15 among amoxicillin-clavulanate dispensings. This resulted in an overall cumulative incidence of CV death of 107 (95% CI: 86, 134) per million dispensings. The cumulative incidence of CV death for azithromycin during this time period was 110 (95% CI: 86, 140) per million dispensings, while the cumulative incidence of CV death for amoxicillin-clavulanate was 98 (95% CI: 58, 164).

Within 6-10 days of the index date, there were a total of 56 CV deaths, 40 among azithromycin dispensings and 16 among amoxicillin-clavulanate dispensings. This resulted in an overall cumulative incidence of CV death of 81 (95% CI: 62, 104) per million dispensings. The cumulative incidence of CV death for azithromycin during this time period was 72 (95% CI: 53, 98) per million dispensings, while the cumulative incidence of CV death for amoxicillin-clavulanate was 112 (95% CI: 68, 182).

Within 1-10 days of the index date (i.e., the sensitivity analysis), there were a total of 135 CV deaths, 104 among azithromycin dispensings and 31 among amoxicillin-clavulanate dispensings. This resulted in an overall cumulative incidence of CV death of 188 (95% CI: 158, 222) per million dispensings. The cumulative incidence of CV death for azithromycin during this time period was 182 (95% CI: 150, 220) per million dispensings, while the cumulative incidence of CV death for amoxicillin-clavulanate was 209 (95% CI: 147, 299).

The incidence of non-CV death was slightly higher in the overall sample compared to CV death. Within the 1-5 day period, there were 80 and 20 non-CV deaths, respectively, in the azithromycin cohort and amoxicillin-clavulanate cohort. Within 6-10 days, there were 54 non-CV deaths among azithromycin dispensings and 16 non-CV deaths among amoxicillin-clavulanate dispensings. Within 1-10 days of the index date, there were a total of 170 non-CV deaths, with 134 among azithromycin dispensings and 36 among amoxicillin-clavulanate dispensings.

As a subset of CV death, cardiac death (as a sensitivity analysis) was slightly less frequent in the overall sample. Within the 1-5 day period, there were 58 and 14 cardiac deaths, respectively, among azithromycin dispensings and amoxicillin-clavulanate dispensings. Within 6-10 days, there were 36 cardiac deaths among azithromycin dispensings and 14 cardiac deaths among amoxicillin-clavulanate dispensings. Within 1-10 days of the index

date, there were a total of 122 cardiac deaths, with 94 among azithromycin dispensings and 28 among amoxicillin-clavulanate dispensings.

Table 8. CV, non-CV, and cardiac deaths within 1-5, 6-10, and 1-10 days of antibiotic dispensing, identified from the VHA CDW from 2000-2014, among dispensings to patients who had a respiratory indication[1-4]

	Within 1-5 days			Within 6-10 days			Within 1-10 days		
	Azithromycin	Amoxicillin-clavulanate	Total	Azithromycin	Amoxicillin-clavulanate	Total	Azithromycin	Amoxicillin-clavulanate	Total
CV death									
All dispensings, N	629,546	168,433	797,979	573,583	154,639	728,222	629,546	168,433	797,979
Number of events, N	64	15	79	40	16	56	104	31	135
Cumulative incidence (95% CI), per million dispensings	109.50 (85.63, 140.03)	97.59 (58.18, 163.68)	106.98 (85.66, 133.60)	72.21 (53.12, 98.15)	111.71 (68.40, 182.44)	80.57 (62.14, 104.46)	181.70 (149.97, 220.15)	209.29 (146.61, 298.76)	187.53 (158.39, 222.03)
Subgroup with CV disease at baseline, N	184,856	54,720	239,576	168,709	50,345	219,054	184,856	54,720	239,576
Number of events, N	30	8	38	25	6	31	55	14	69
Subgroup in top decile of CV mortality risk score, N	59,892	19,932	79,824	54,514	18,321	72,835	59,892	19,932	79,824
Number of events, N	16	5	21	15	6	21	31	11	42
Sensitivity 1: PS as continuous covariate, N	629,546	168,433	797,979	573,583	154,639	728,222	629,546	168,433	797,979
Number of events, N	64	15	79	40	16	56	104	31	135
Sensitivity 3a: High CV mortality risk category, N	59,892	19,932	79,824	54,514	18,321	72,835	59,892	19,932	79,824
Number of events, N	16	5	21	15	6	21	31	11	42
Sensitivity 3b: Medium CV mortality risk category, N	252,670	68,397	321,067	230,029	62,725	292,754	252,670	68,397	321,067
Number of events, N	29	7	36	18	2	20	47	9	56
Sensitivity 3c: Low CV mortality risk category, N	317,034	80,056	397,090	289,070	73,526	362,596	317,034	80,056	397,090
Number of events, N	21	3	24	8	8	16	29	11	40

Table 8. CV, non-CV, and cardiac deaths within 1-5, 6-10, and 1-10 days of antibiotic dispensing, identified from the VHA CDW from 2000-2014, among dispensings to patients who had a respiratory indication[1-4]

	Within 1-5 days			Within 6-10 days			Within 1-10 days		
	Azithromycin	Amoxicillin-clavulanate	Total	Azithromycin	Amoxicillin-clavulanate	Total	Azithromycin	Amoxicillin-clavulanate	Total
Sensitivity 4: Priority 1, N	177,337	48,151	225,488	166,917	45,590	212,507	177,337	48,151	225,488
Number of events, N	18	4	22	11	3	14	29	7	36
Sensitivity 5: Patients < 65 years of age, N	464,290	123,050	587,340	422,951	112,976	535,927	464,290	123,050	587,340
Number of events, N	35	7	42	30	13	43	65	20	85
Non-CV death									
All dispensings, N	629,546	168,433	797,979	573,583	154,639	728,222	629,546	168,433	797,979
Number of events, N	80	20	100	54	16	70	134	36	170
Subgroup with CV disease at baseline, N	184,856	54,720	239,576	168,709	50,345	219,054	184,856	54,720	239,576
Number of events, N	32	11	43	27	6	33	59	17	76
Subgroup in top decile of CV mortality risk score, N	59,892	19,932	79,824	54,514	18,321	72,835	59,892	19,932	79,824
Number of events, N	19	7	26	16	1	17	35	8	43
Cardiac death									
Sensitivity 2: All dispensings, N	629,546	168,433	797,979	573,583	154,639	728,222	629,546	168,433	797,979
Number of events, N	58	14	72	36	14	50	94	28	122

Abbreviations: CDW = Corporate Data Warehouse; CI = confidence interval; CV = cardiovascular; VHA = Veterans Health Administration.

Notes:

[1] Cumulative incidence were estimated using IPTW-weighted Cox regression models with a robust sandwich variance estimator to account for multiple dispensings for the same patient. Ties in failure time were handled using the Breslow method.

[2] After the study-eligible antibiotic dispensing, observations were censored based on the earliest date of: outpatient dispensing of a subsequent study antibiotic, hospitalization, nursing home admission, disenrollment from VHA benefits, death due to cause other than that for analysis objective, end of risk interval of interest, and end of study (December 31, 2014).

[3] CV deaths and cardiac deaths were identified by ICD-10-CM encoded cause of death from the NDI. Cause of death information is not available in the VA Vital Status Mini File. Therefore, dates of death identified in the VA Vital Status Mini File were assigned a missing cause of death and did not contribute to the number of CV deaths or cardiac deaths.

Table 8. CV, non-CV, and cardiac deaths within 1-5, 6-10, and 1-10 days of antibiotic dispensing, identified from the VHA CDW from 2000-2014, among dispensings to patients who had a respiratory indication[1-4]

	Within 1-5 days			Within 6-10 days			Within 1-10 days		
	Azithromycin	Amoxicillin-clavulanate	Total	Azithromycin	Amoxicillin-clavulanate	Total	Azithromycin	Amoxicillin-clavulanate	Total

[4] Unweighted Ns of dispensings are presented.

ENT indication

Table 9 summarizes the number of CV, non-CV, and cardiac deaths within 1-5, 6-10, and 1-10 days of the index dates (i.e., the latter as a sensitivity analysis), among all dispensings to patients with an ENT indication, as well as stratified by azithromycin and amoxicillin-clavulanate dispensings. The values are summarized for the full sample and for all subgroups and sensitivities that were outlined in the methods section. Cumulative incidences are also reported for CV death among all dispensings to patients with an ENT indication.

Within 1-5 days of the index date, there were a total of 8 CV deaths, 2 among azithromycin dispensings and 6 among amoxicillin-clavulanate dispensings. This resulted in a total cumulative incidence of 25 (95% CI: 12, 50) CV deaths per million dispensings. The cumulative incidence of CV death for azithromycin during this time period was 15 (95% CI: 4, 61) per million dispensings, while the cumulative incidence of CV death for amoxicillin-clavulanate was 32 (95% CI: 14, 71).

Within 6-10 days of the index date, there were a total of 13 CV deaths, 4 among azithromycin dispensings and 9 among amoxicillin-clavulanate dispensings. This resulted in a total cumulative incidence of CV death 42 (95% CI: 25, 72) per million dispensings. The cumulative incidence of CV death for azithromycin during this time period was 34 (95% CI: 13, 87) per million dispensings, while the cumulative incidence of CV death for amoxicillin-clavulanate was 48 (95% CI: 25, 93).

Within 1-10 days of the index date (i.e., the sensitivity analysis), there were a total of 21 CV deaths, 6 among azithromycin dispensings and 15 among amoxicillin-clavulanate dispensings. This resulted in a total cumulative incidence of 67 (95% CI: 44, 103) CV deaths per million dispensings. The cumulative incidence of CV death for azithromycin during this time period was 48 (95% CI: 22, 106) per million dispensings, while the cumulative incidence of CV death for amoxicillin-clavulanate was 80 (95% CI: 48, 133).

Non-CV death occurred less frequently in the overall sample compared to CV death. Within the 1-5 day period, there were 3 and 2 non-CV deaths, respectively, among azithromycin dispensings and amoxicillin-clavulanate dispensings. Within 6-10 days, there were 3 non-CV deaths among azithromycin dispensings and 4 non-CV deaths among amoxicillin-clavulanate dispensings. Within 1-10 days, there were a total of 12 non-CV deaths, with 6 among azithromycin dispensings and 6 among amoxicillin-clavulanate dispensings.

As a subset of CV death, cardiac death (as a sensitivity analysis) was slightly less frequent in the overall sample. Within the 1-5 day period, there were 2 and 6 cardiac deaths, respectively, among azithromycin and amoxicillin-clavulanate dispensings. Within 6-10 days, there were 4 cardiac deaths among azithromycin dispensings and 6 cardiac deaths among amoxicillin-clavulanate dispensings. Within 1-10 days, there were a total of 18 cardiac deaths, with 6 among azithromycin dispensings and 12 among amoxicillin-clavulanate dispensings.

Table 9. CV, non-CV, and cardiac deaths within 1-5, 6-10, and 1-10 days of antibiotic dispensing, identified from the VHA CDW from 2000-2014, among dispensings to patients who had an ENT indication[1-4]

	Within 1-5 days			Within 6-10 days			Within 1-10 days		
	Azithromycin	Amoxicillin-clavulanate	Total	Azithromycin	Amoxicillin-clavulanate	Total	Azithromycin	Amoxicillin-clavulanate	Total
CV death									
All dispensings, N	143,725	203,249	346,974	132,008	187,264	319,272	143,725	203,249	346,974
Number of events, N	2	6	8	4	9	13	6	15	21
Cumulative incidence (95% CI), per million dispensings	14.62 (3.53, 60.58)	31.67 (14.16, 70.84)	24.61 (12.20, 49.62)	33.82 (13.16, 86.90)	48.15 (24.90, 93.12)	42.23 (24.59, 72.52)	48.44 (22.07, 106.33)	79.82 (47.92, 132.95)	66.83 (43.55, 102.57)
Subgroup with CV disease at baseline, N	29,985	43,866	73,851	27,671	40,643	68,314	29,985	43,866	73,851
Number of events, N	2	2	4	3	4	7	5	6	11
Subgroup in top decile of CV mortality risk score, N	14,191	20,647	34,838	13,090	19,134	32,224	14,191	20,647	34,838
Number of events, N	1	1	2	2	5	7	3	6	9
Sensitivity 1: PS as continuous covariate, N	143,725	203,249	346,974	132,008	187,264	319,272	143,725	203,249	346,974
Number of events, N	2	6	8	4	9	13	6	15	21
Sensitivity 3a: High CV mortality risk category, N	14,191	20,647	34,838	13,090	19,134	32,224	14,191	20,647	34,838
Number of events, N	1	1	2	2	5	7	3	6	9
Sensitivity 3b: Medium CV mortality risk category, N	57,193	81,987	139,180	52,461	75,611	128,072	57,193	81,987	139,180
Number of events, N	1	5	6	1	2	3	2	7	9
Sensitivity 3c: Low CV mortality risk category, N	72,302	100,656	172,958	66,434	92,555	158,989	72,302	100,656	172,958
Number of events, N	0	0	0	1	2	3	1	2	3
Sensitivity 4: Priority 1, N	44,484	62,374	106,858	42,088	59,246	101,334	44,484	62,374	106,858

Table 9. CV, non-CV, and cardiac deaths within 1-5, 6-10, and 1-10 days of antibiotic dispensing, identified from the VHA CDW from 2000-2014, among dispensings to patients who had an ENT indication[1-4]

	Within 1-5 days			Within 6-10 days			Within 1-10 days		
	Azithromycin	Amoxicillin-clavulanate	Total	Azithromycin	Amoxicillin-clavulanate	Total	Azithromycin	Amoxicillin-clavulanate	Total
Number of events, N	0	2	2	1	2	3	1	4	5
Sensitivity 5: Patients < 65 years of age, N	119,610	168,114	287,724	109,826	154,729	264,555	119,610	168,114	287,724
Number of events, N	2	4	6	2	5	7	4	9	13
Non-CV death									
All dispensings, N	143,725	203,249	346,974	132,008	187,264	319,272	143,725	203,249	346,974
Number of events, N	3	2	5	3	4	7	6	6	12
Subgroup with CV disease at baseline, N	29,985	43,866	73,851	27,671	40,643	68,314	29,985	43,866	73,851
Number of events, N	0	1	1	0	0	0	0	1	1
Subgroup in top decile of CV mortality risk score, N	14,191	20,647	34,838	13,090	19,134	32,224	14,191	20,647	34,838
Number of events, N	0	1	1	0	0	0	0	1	1
Cardiac death									
Sensitivity 2: All dispensings, N	143,725	203,249	346,974	132,008	187,264	319,272	143,725	203,249	346,974
Number of events, N	2	6	8	4	6	10	6	12	18

Abbreviations: CDW = Corporate Data Warehouse; CI = confidence interval; CV = cardiovascular; VHA = Veterans Health Administration.

Notes:

[1] Cumulative incidence were estimated using IPTW-weighted Cox regression models with a robust sandwich variance estimator to account for multiple dispensings for the same patient. Ties in failure time were handled using the Breslow method.

[2] After the study-eligible antibiotic dispensing, patients were censored based on the earliest date of: outpatient dispensing of a subsequent study antibiotic, hospitalization, nursing home admission, disenrollment from VHA benefits, death due to cause other than that for analysis objective, end of risk interval of interest, and end of study (December 31, 2014).

[3] CV deaths and cardiac deaths were identified by ICD-10-CM encoded cause of death from the NDI. Cause of death information is not available in the VA Vital Status Mini File. Therefore, dates of death identified in the VA Vital Status Mini File were assigned a missing cause of death and did not contribute to the number of CV deaths or cardiac deaths.

[4] Unweighted Ns of dispensings are presented.

10.4. Main results

10.4.1. HRs for primary and secondary outcomes

Respiratory indication

Table 10 reports the HRs of CV and non-CV deaths within 1-5, 6-10, and 1-10 days of antibiotic dispensing among dispensings for a respiratory indication. Results of the 1-10 day sensitivity analysis are included in these results because azithromycin's persistence in tissue a week after last dose[29,30,31] means that the drug effect might be expected to extend for 10 days following treatment initiation and a five-day course. Overall, the HR estimates for CV and non-CV death remained close to the null of 1.00, with all 95% CIs overlapping 1.00, indicating no statistically significant difference in risk of death between azithromycin and amoxicillin-clavulanate.

For all dispensings for a respiratory indication, the HR of CV death for azithromycin compared to amoxicillin-clavulanate was 1.12 (95% CI: 0.63, 2.00) within 1-5 days, 0.65 (95% CI: 0.36, 1.16) within 6-10 days, and 0.87 (95% CI: 0.58, 1.31) within 1-10 days. Among the subgroup with CV disease at baseline, the HR of CV death for azithromycin compared to amoxicillin-clavulanate was 1.03 (95% CI: 0.46, 2.32) within 1-5 days, 1.04 (95% CI: 0.42, 2.57) within 6-10 days, and 1.04 (95% CI: 0.57, 1.89) within 1-10 days. Finally, among the subgroup in the top decile of CV mortality risk, the HR of CV death for azithromycin compared to amoxicillin-clavulanate was 1.12 (95% CI: 0.40, 3.14) within 1-5 days, 0.68 (95% CI: 0.26, 1.77) within 6-10 days, and 0.85 (95% CI: 0.42, 1.72) within 1-10 days.

For all dispensings for a respiratory indication, the HR of non-CV death for azithromycin compared to amoxicillin-clavulanate was 1.26 (95% CI: 0.77, 2.07) within 1-5 days, 1.05 (95% CI: 0.60, 1.86) within 6-10 days, and 1.17 (95% CI: 0.80, 1.70) within 1-10 days. Among the subgroup with CV disease at baseline, the HR of non-CV death for azithromycin compared to amoxicillin-clavulanate was 1.04 (95% CI: 0.52, 2.08) within 1-5 days, 1.54 (95% CI: 0.62, 3.84) within 6-10 days, and 1.23 (95% CI: 0.71, 2.13) within 1-10 days. Finally, among the subgroup of dispensings to patients who were in the top decile of CV mortality risk, the HR of non-CV death for azithromycin compared to amoxicillin-clavulanate was 1.12 (95% CI: 0.46, 2.70) within 1-5 days, 6.60 (95% CI: 0.88, 49.77) within 6-10 days, and 1.84 (95% CI: 0.84, 4.03) within 1-10 days. Although the estimate for the HR of non-CV death within 6-10 days for this subgroup is relatively large compared to the other estimates, it is based on a very small number of deaths during this time period (as indicated by the very wide CI).

Table 10. HR of CV and non-CV deaths within 1-5, 6-10, and 1-10 days of antibiotic dispensing, identified from the VHA CDW from 2000-2014, among dispensings to patients who had a respiratory indication[1-3]

		HR (95% CI)	
	Within 1-5 days	**Within 6-10 days**	**Within 1-10 days**
CV death			
All dispensings, N	*797,979*	*728,222*	*797,979*
Number of events	*79*	*56*	*135*
Azithromycin (ref: amoxicillin-clavulanate)	1.12 (0.63, 2.00)	0.65 (0.36, 1.16)	0.87 (0.58, 1.31)
Subgroup with CV disease at baseline, N	*239,576*	*219,054*	*239,576*
Number of events	*38*	*31*	*69*
Azithromycin (ref: amoxicillin-clavulanate)	1.03 (0.46, 2.32)	1.04 (0.42, 2.57)	1.04 (0.57, 1.89)
Subgroup in top decile of CV mortality risk score, N	*79,824*	*72,835*	*79,824*
Number of events	*21*	*21*	*42*
Azithromycin (ref: amoxicillin-clavulanate)	1.12 (0.40, 3.14)	0.68 (0.26, 1.77)	0.85 (0.42, 1.72)
Non-CV death			
All dispensings, N	*797,979*	*728,222*	*797,979*
Number of events	*100*	*70*	*170*
Azithromycin (ref: amoxicillin-clavulanate)	1.26 (0.77, 2.07)	1.05 (0.60, 1.86)	1.17 (0.80, 1.70)
Subgroup with CV disease at baseline, N	*239,576*	*219,054*	*239,576*
Number of events	*43*	*33*	*76*
Azithromycin (ref: amoxicillin-clavulanate)	1.04 (0.52, 2.08)	1.54 (0.62, 3.84)	1.23 (0.71, 2.13)
Subgroup in top decile of CV mortality risk score, N	*79,824*	*72,835*	*79,824*
Number of events	*26*	*17*	*43*
Azithromycin (ref: amoxicillin-clavulanate)	1.12 (0.46, 2.70)	6.60 (0.88, 49.77)	1.84 (0.84, 4.03)

Abbreviations: CDW = Corporate Data Warehouse; CI = confidence interval; CV = cardiovascular; ED = emergency department; HR = hazard ratio; IPTW= inverse probability of treatment weighting; VHA = Veterans Health Administration.

Notes:
[1] HR were estimated using IPTW-weighted Cox regression models with a robust sandwich variance estimator to account for multiple dispensings for the same patient. Ties in failure time were handled using the Breslow method.

Table 10. HR of CV and non-CV deaths within 1-5, 6-10, and 1-10 days of antibiotic dispensing, identified from the VHA CDW from 2000-2014, among dispensings to patients who had a respiratory indication[1-3]

		HR (95% CI)	
	Within 1-5 days	**Within 6-10 days**	**Within 1-10 days**

[2] After the study-eligible antibiotic dispensing, observations were censored based on the earliest date of: outpatient dispensing of a subsequent study antibiotic, hospitalization, nursing home admission, disenrollment from VHA benefits, death due to cause other than that for analysis objective, end of risk interval of interest, and end of study (December 31, 2014).
[3] Unweighted Ns of dispensings are presented

ENT indication

Table 11 reports the HR of CV and non-CV deaths within 1-5, 6-10, and 1-10 days of antibiotic dispensing to patients with an ENT indication. Results of the 1-10 day sensitivity analysis are included in these results for contextualization of the main analyses. Overall, the number of events were quite small. The HR estimates for CV and non-CV death remained close to 1.00, with all CIs overlapping 1.00.

For all dispensings with ENT indication, the HR of CV death for azithromycin compared to amoxicillin-clavulanate was 0.46 (95% CI: 0.09, 2.30) within 1-5 days, 0.70 (95% CI: 0.22, 2.29) within 6-10 days, and 0.60 (95% CI: 0.23, 1.57) within 1-10 days. Among the subgroup with CV disease at baseline, the HR of CV death for azithromycin compared to amoxicillin-clavulanate was 1.38 (95% CI: 0.19, 9.95) within 1-5 days, 1.30 (95% CI: 0.29, 5.83) within 6-10 days, and 1.33 (95% CI: 0.40, 4.38) within 1-10 days. Finally, among the subgroup in the top decile of CV mortality risk, the HR of CV death for azithromycin compared to amoxicillin-clavulanate was 1.54 (95% CI: 0.10, 24.60) within 1-5 days, 0.63 (95% CI: 0.12, 3.28) within 6-10 days, and 0.78 (95% CI: 0.19, 3.14) within 1-10 days.

For all dispensings with ENT indication, the HR of non-CV death for azithromycin compared to amoxicillin-clavulanate was 2.18 (95% CI: 0.36, 13.14) within 1-5 days, 1.24 (95% CI: 0.27, 5.64) within 6-10 days, and 1.55 (95% CI: 0.49, 4.86) within 1-10 days. Because there was 0 or 1 non-CV death for the subgroup with CV disease at baseline and the subgroup in the top decile of CV mortality risk, HRs could not be estimated.

Table 11. HR of CV and non-CV deaths within 1-5, 6-10, and 1-10 days of antibiotic dispensing, identified from the VHA CDW from 2000-2014, among dispensings to patients who had an ENT indication[1-3]

		HR (95% CI)	
	Within 1-5 days	**Within 6-10 days**	**Within 1-10 days**
CV death			
All dispensings, N	*346,974*	*319,272*	*346,974*
Number of events	*8*	*13*	*21*
Azithromycin (ref: amoxicillin-clavulanate)	0.46 (0.09, 2.30)	0.70 (0.22, 2.29)	0.60 (0.23, 1.57)
Subgroup with CV disease at baseline, N	*73,851*	*68,314*	*73,851*
Number of events	*4*	*7*	*11*
Azithromycin (ref: amoxicillin-clavulanate)	1.38 (0.19, 9.95)	1.30 (0.29, 5.83)	1.33 (0.40, 4.38)
Subgroup in top decile of CV mortality risk score, N	*34,838*	*32,224*	*34,838*
Number of events	*2*	*7*	*9*
Azithromycin (ref: amoxicillin-clavulanate)	1.54 (0.10, 24.60)	0.63 (0.12, 3.28)	0.78 (0.19, 3.14)
Non-CV death			
All dispensings, N	*346,974*	*319,272*	*346,974*
Number of events	*5*	*7*	*12*
Azithromycin (ref: amoxicillin-clavulanate)	2.18 (0.36, 13.14)	1.24 (0.27, 5.64)	1.55 (0.49, 4.86)
Subgroup with CV disease at baseline, N	*73,851*	*68,314*	*73,851*
Number of events	*1*	*0*	*1*
Azithromycin (ref: amoxicillin-clavulanate)[4]	-	-	-
Subgroup in top decile of CV mortality risk score, N	*34,838*	*32,224*	*34,838*
Number of events	*1*	*0*	*1*
Azithromycin (ref: amoxicillin-clavulanate)[4]	-	-	-

Abbreviations: CDW = Corporate Data Warehouse; CI = confidence interval; CV = cardiovascular; ENT = ear-nose-throat; HR = hazard ratio; IPTW= inverse probability of treatment weighting; VHA = Veterans Health Administration.

Notes:
[1] HR were estimated using IPTW-weighted Cox regression models with a robust sandwich variance estimator to account for multiple dispensings for the same patient. Ties in failure time were handled using the Breslow method.

Table 11. HR of CV and non-CV deaths within 1-5, 6-10, and 1-10 days of antibiotic dispensing, identified from the VHA CDW from 2000-2014, among dispensings to patients who had an ENT indication[1-3]

		HR (95% CI)	
	Within 1-5 days	**Within 6-10 days**	**Within 1-10 days**

[2] After the study-eligible antibiotic dispensing, observations were censored based on the earliest date of: outpatient dispensing of a subsequent study antibiotic, hospitalization, nursing home admission, disenrollment from VHA benefits, death due to cause other than that for analysis objective, end of risk interval of interest, and end of study (December 31, 2014).
[3] Unweighted Ns of dispensings are presented.
[4] HRs were unavailable due to the small number of events.

Pooled analysis across indications - Meta-analysis using random effects model

Table 12 reports pooled primary and secondary results across both indication groups for the HR of CV and non-CV deaths within 1-5, 6-10, and 1-10 days of antibiotic dispensing. Generally, the HRs were close to 1.00, with 95% CIs overlapping 1.00. The I^2 statistic for heterogeneity remained low across each meta-analysis, and there were no statistically significant p-values associated with high heterogeneity between respiratory and ENT indications.

Among all dispensings, the HR of CV death for azithromycin compared to amoxicillin-clavulanate, using meta-analysis to pool ENT and respiratory indications, was 1.00 (95% CI: 0.55, 1.81) within 1-5 days, 0.66 (95% CI: 0.39, 1.11) within 6-10 days, and 0.82 (95% CI: 0.57, 1.20) within 1-10 days. Among the subgroup with CV disease at baseline, the pooled HR of CV death was 1.08 (95% CI: 0.51, 2.28) within 1-5 days, 1.10 (95% CI: 0.51, 2.39) within 6-10 days, and 1.09 (95% CI: 0.64, 1.87) within 1-10 days. Among the subgroup in the top decile of CV mortality risk, the pooled HR of CV death was 1.16 (95% CI: 0.44, 3.06) within 1-5 days, 0.67 (95% CI: 0.29, 1.53) within 6-10 days, and 0.83 (95% CI: 0.44, 1.57) within 1-10 days.

Among all dispensings, the pooled HR of non-CV death for azithromycin compared to amoxicillin-clavulanate was 1.31 (95% CI: 0.81, 2.12) within 1-5 days, 1.07 (95% CI: 0.63, 1.83) within 6-10 days, and 1.20 (95% CI: 0.84, 1.71) within 1-10 days. Because there was a very small number of non-CV deaths in the subgroups of interest, pooled HRs were unable to be generated using meta-analysis.

Table 12. Meta-analysis of HR of CV deaths and non-CV deaths within 1-5, 6-10, and 1-10 days of antibiotic dispensing, identified from the VHA CDW from 2000-2014, among dispensings to patients who had a respiratory or ENT indication - main analyses[1-3]

	HR (95% CI)		
	Within 1-5 days	**Within 6-10 days**	**Within 1-10 days**
CV death			
All dispensings, N	*1,144,953*	*1,047,494*	*1,144,953*
Azithromycin (ref: amoxicillin-clavulanate)	1.00 (0.55, 1.81)	0.66 (0.39, 1.11)	0.82 (0.57, 1.20)
I^2 statistic for heterogeneity	*4.8%*	*0.0%*	*0.0%*
P-value[4]	*0.305*	*0.904*	*0.487*
Subgroup with CV disease at baseline, N	*313,427*	*287,368*	*313,427*
Azithromycin (ref: amoxicillin-clavulanate)	1.08 (0.51, 2.28)	1.10 (0.51, 2.39)	1.09 (0.64, 1.87)
I^2 statistic for heterogeneity	*0.0%*	*0.0%*	*0.0%*
P-value[4]	*0.788*	*0.805*	*0.718*
Subgroup in top decile of CV mortality risk score, N	*114,662*	*105,059*	*114,662*
Azithromycin (ref: amoxicillin-clavulanate)	1.16 (0.44, 3.06)	0.67 (0.29, 1.53)	0.83 (0.44, 1.57)
I^2 statistic for heterogeneity	*0.0%*	*0.0%*	*0.0%*
P-value[4]	*0.832*	*0.945*	*0.919*
Non-CV death			
All dispensings, N	*1,144,953*	*1,047,494*	*1,144,953*
Azithromycin (ref: amoxicillin-clavulanate)	1.31 (0.81, 2.12)	1.07 (0.63, 1.83)	1.20 (0.84, 1.71)
I^2 statistic for heterogeneity	*0.0%*	*0.0%*	*0.0%*
P-value[4]	*0.565*	*0.846*	*0.646*
Subgroup with CV disease at baseline, N	*313,427*	*287,368*	*313,427*
Azithromycin (ref: amoxicillin-clavulanate)[5]	-	-	-
I^2 statistic for heterogeneity	-	-	-
P-value[4]	-	-	-
Subgroup in top decile of CV mortality risk score, N	*114,662*	*105,059*	*114,662*
Azithromycin (ref: amoxicillin-clavulanate)[5]	-	-	-
I^2 statistic for heterogeneity	-	-	-

Table 12. Meta-analysis of HR of CV deaths and non-CV deaths within 1-5, 6-10, and 1-10 days of antibiotic dispensing, identified from the VHA CDW from 2000-2014, among dispensings to patients who had a respiratory or ENT indication - main analyses[1-3]

		HR (95% CI)	
	Within 1-5 days	**Within 6-10 days**	**Within 1-10 days**
P-value[4]	-	-	-

Abbreviations: CDW = Corporate Data Warehouse; CI = confidence interval; CV = cardiovascular; ED = emergency department; HR = hazard ratio; IPTW = inverse probability of treatment weighting; VHA = Veterans Health Administration.

Notes:
[1] Pooled HRs were estimated by a random effects meta-analysis model following the methodology of DerSimonian and Laird.
[2] After the study-eligible antibiotic dispensing, observations were censored based on the earliest date of: outpatient dispensing of a subsequent study antibiotic, hospitalization, nursing home admission, disenrollment from VHA benefits, death due to cause other than that for analysis objective, end of risk interval of interest, and end of study (December 31, 2014).
[3] Unweighted Ns of dispensings are presented.
[4] The Cochran's Q test p-values were reported.
[5] Pooled HRs were unavailable due to the small number of events.

Pooled analysis across indications - Cox proportional hazards model with random effect

Table 13 reports results from regression analyses combining the respiratory and ENT indication groups to obtain pooled results for HRs of CV and non-CV deaths within 1-5, 6-10, and 1-10 days of antibiotic dispensing. Results from these analyses were consistent with pooled results from the meta-analyses described above and did not indicate an association between risk of CV death and azithromycin as compared to amoxicillin-clavulanate.

Across dispensings with respiratory or ENT indication, the HR of CV death for azithromycin compared to amoxicillin-clavulanate was 1.07 (95% CI: 0.64, 1.80) within 1-5 days, 0.67 (95% CI: 0.40, 1.13) within 6-10 days, and 0.85 (95% CI: 0.59, 1.23) within 1-10 days. Among the subgroup with CV disease at baseline, the HR of CV death was 1.12 (95% CI: 0.53, 2.36) within 1-5 days, 1.02 (95% CI: 0.48, 2.19) within 6-10 days, and 1.07 (95% CI: 0.63, 1.82) within 1-10 days. Among the subgroup in the top decile of CV mortality risk, the HR of CV death was 1.15 (95% CI: 0.44, 3.04) within 1-5 days, and 0.65 (95% CI: 0.29, 1.47) within 6-10 days, and 0.82 (95% CI: 0.44, 1.53) within 1-10 days.

The HR of non-CV death for azithromycin compared to amoxicillin-clavulanate, combining the ENT and respiratory indications, was 1.26 (95% CI: 0.79, 2.00) within 1-5 days, 1.07 (95% CI: 0.63, 1.82) within 6-10 days, and 1.17 (95% CI: 0.83, 1.66) within 1-10 days. Among the subgroup with CV disease at baseline, the HR of non-CV death was 0.97 (95% CI: 0.51, 1.85) within 1-5 days, 1.57 (95% CI: 0.64, 3.86) within 6-10 days, and 1.18 (95% CI: 0.70, 1.98) within 1-10 days. Among the subgroup in the top decile of CV mortality risk, the HR of non-CV death was 0.91 (95% CI: 0.40, 2.06) within 1-5 days, 6.04 (95% CI: 0.80, 45.54) within 6-10 days, and 1.52 (95% CI: 0.74, 3.13) within 1-10 days.

Table 13. Pooled HR of CV and non-CV deaths within 1-5, 6-10, and 1-10 days of antibiotic dispensing, identified from the VHA CDW from 2000-2014, among dispensings to patients who had a respiratory or ENT indication[1-3]

		HR (95% CI)	
	Within 1-5 days	**Within 6-10 days**	**Within 1-10 days**
CV deaths			
All dispensings, N	*1,144,951*	*1,047,517*	*1,144,951*
Number of events	*88*	*70*	*158*
Azithromycin (ref: amoxicillin-clavulanate)	1.07 (0.64, 1.80)	0.67 (0.40, 1.13)	0.85 (0.59, 1.23)
Subgroup with CV disease at baseline, N	*313,425*	*287,361*	*313,425*
Number of events	*43*	*39*	*82*
Azithromycin (ref: amoxicillin-clavulanate)	1.12 (0.53, 2.36)	1.02 (0.48, 2.19)	1.07 (0.63, 1.82)
Subgroup in top decile of CV mortality risk score, N	*114,660*	*105,049*	*114,660*
Number of events	*23*	*28*	*51*
Azithromycin (ref: amoxicillin-clavulanate)	1.15 (0.44, 3.04)	0.65 (0.29, 1.47)	0.82 (0.44, 1.53)
Non-CV deaths			
All dispensings, N	*1,144,951*	*1,047,517*	*1,144,951*
Number of events	*109*	*77*	*186*
Azithromycin (ref: amoxicillin-clavulanate)	1.26 (0.79, 2.00)	1.07 (0.63, 1.82)	1.17 (0.83, 1.66)
Subgroup with CV disease at baseline, N	*313,425*	*287,361*	*313,425*
Number of events	*47*	*34*	*81*
Azithromycin (ref: amoxicillin-clavulanate)	0.97 (0.51, 1.85)	1.57 (0.64, 3.86)	1.18 (0.70, 1.98)
Subgroup in top decile of CV mortality risk score, N	*114,660*	*105,049*	*114,660*
Number of events	*28*	*17*	*45*
Azithromycin (ref: amoxicillin-clavulanate)	0.91 (0.40, 2.06)	6.04 (0.80, 45.54)	1.52 (0.74, 3.13)

Abbreviations: CDW = Corporate Data Warehouse; CI = confidence interval; CV = cardiovascular; ED = emergency department; ENT = ear-nose-throat; HR = hazard ratio; IPTW= inverse probability of treatment weighting; VHA = Veterans Health Administration.

Notes:
[1] HRs were estimated using IPTW-weighted Cox regression models with a robust sandwich variance estimator to account for multiple dispensings for the same patient and clustering by indication. Ties in failure time were handled using the Breslow method.

Table 13. Pooled HR of CV and non-CV deaths within 1-5, 6-10, and 1-10 days of antibiotic dispensing, identified from the VHA CDW from 2000-2014, among dispensings to patients who had a respiratory or ENT indication[1-3]

		HR (95% CI)	
	Within 1-5 days	**Within 6-10 days**	**Within 1-10 days**

[2] After the study-eligible antibiotic dispensing, observations were censored based on the earliest date of: outpatient dispensing of a subsequent study antibiotic, hospitalization, nursing home admission, disenrollment from VHA benefits, death due to cause other than that for analysis objective, end of risk interval of interest, and end of study (December 31, 2014).
[3] Unweighted Ns of dispensings are presented.

10.4.2. RDs for primary and secondary outcomes

Respiratory indication

Table 14 reports the RD per million dispensings of CV and non-CV deaths within 1-5, 6-10, 1-10 days, among dispensings to patients with a respiratory indication for azithromycin and amoxicillin-clavulanate. Overall, the RD estimates for CV and non-CV death remained close to zero, with all 95% CIs overlapping zero.

The RD for CV death comparing azithromycin to amoxicillin-clavulanate was 11 (95% CI: -43, 64) within 1-5 days, -39 (95% CI: -98, 20) within 6-10 days, and -25 (95% CI: -101, 51) within 1-10 days. Among the subgroup with CV disease at baseline, the RD for CV death comparing azithromycin to amoxicillin-clavulanate was 4 (95% CI: -122, 131) within 1-5 days, 6 (95% CI: -126, 138) within 6-10 days, and 9 (95% CI: -166, 185) within 1-10 days. Finally, among the subgroup in the top decile of CV mortality risk, the RD for CV death among dispensings of azithromycin compared to amoxicillin-clavulanate was 26 (95% CI: -226, 278) within 1-5 days, -132 (95% CI: -495, 231) within 6-10 days, and -97 (95% CI: -514, 321) within 1-10 days.

The RD for non-CV death comparing azithromycin to amoxicillin-clavulanate was 26 (95% CI: -27, 80) within 1-5 days, 5 (95% CI: -47, 57) within 6-10 days, and 30 (95% CI: -42, 102) within 1-10 days. Among the subgroup with CV disease at baseline, the RD for non-CV death comparing azithromycin to amoxicillin-clavulanate was 5 (95% CI: -111, 122) within 1-5 days, 58 (95% CI: -50, 166) within 6-10 days, and 58 (95% CI: -95, 211) within 1-10 days. Finally, among the subgroup in the top decile of CV mortality risk, the RD for non-CV death comparing azithromycin to amoxicillin-clavulanate was 30 (95% CI: -221, 281) within 1-5 days, 258 (95% CI: 83, 432) within 6-10 days, and 264 (95% CI: -33, 561) within 1-10 days.

Table 14. RD (per million dispensings) of CV deaths and non-CV deaths within 1-5, 6-10, and 1-10 days of antibiotic dispensing from the VHA CDW from 2000-2014, among dispensings to patients who a had respiratory indication[1-3]

	RD (95% CI)		
	Within 1-5 days	**Within 6-10 days**	**Within 1-10 days**
CV death			
All dispensings, N	*797,979*	*728,222*	*797,979*
Number of events	*79*	*56*	*135*
Azithromycin (ref: amoxicillin-clavulanate)	10.68 (-42.84, 64.20)	-38.78 (-97.89, 20.32)	-25.13 (-101.22, 50.97)
Subgroup with CV disease at baseline, N	*239,576*	*219,054*	*239,576*
Number of events	*38*	*31*	*69*
Azithromycin (ref: amoxicillin-clavulanate)	4.36 (-122.38, 131.10)	6.04 (-126.29, 138.38)	9.18 (-166.29, 184.65)
Subgroup in top decile of CV mortality risk score, N	*79,824*	*72,835*	*79,824*
Number of events	*21*	*21*	*42*
Azithromycin (ref: amoxicillin-clavulanate)	26.17 (-225.97, 278.30)	-131.81 (-494.64, 231.03)	-96.78 (-514.15, 320.59)
Non-CV death			
All dispensings, N	*797,979*	*728,222*	*797,979*
Number of events	*100*	*70*	*170*
Azithromycin (ref: amoxicillin-clavulanate)	26.09 (-27.45, 79.63)	4.88 (-47.40, 57.16)	30.17 (-41.62, 101.95)
Subgroup with CV disease at baseline, N	*239,576*	*219,054*	*239,576*
Number of events	*43*	*33*	*76*
Azithromycin (ref: amoxicillin-clavulanate)	5.47 (-111.36, 122.29)	57.91 (-49.82, 165.64)	57.84 (-95.11, 210.79)
Subgroup in top decile of CV mortality risk score, N	*79,824*	*72,835*	*79,824*
Number of events	*26*	*17*	*43*
Azithromycin (ref: amoxicillin-clavulanate)	29.94 (-221.14, 281.01)	257.53 (83.20, 431.87)	264.21 (-33.01, 561.42)

Abbreviations: CDW = Corporate Data Warehouse; CI = confidence interval; CV = cardiovascular; ED = emergency department; RD = risk difference; IPTW= inverse probability of treatment weighting; VHA = Veterans Health Administration.

Notes:

[1] RD was estimated using IPTW-weighted binomial regression models by generalized estimating equations with an identity link and a sandwich variance estimator to account for multiple dispensings for the same patient.

Table 14. RD (per million dispensings) of CV deaths and non-CV deaths within 1-5, 6-10, and 1-10 days of antibiotic dispensing from the VHA CDW from 2000-2014, among dispensings to patients who a had respiratory indication[1-3]

	RD (95% CI)		
	Within 1-5 days	**Within 6-10 days**	**Within 1-10 days**

[2] After the study-eligible antibiotic dispensing, observations were censored based on the earliest date of: outpatient dispensing of a subsequent study antibiotic, hospitalization, nursing home admission, disenrollment from VHA benefits, death due to cause other than that for analysis objective, end of risk interval of interest, and end of study (December 31, 2014).
[3] Unweighted Ns of dispensings are presented

ENT indication

Table 15 reports the RD per million dispensings of CV and non-CV deaths within 1-5, 6-10, and 1-10 days among dispensings to patients with an ENT indication for azithromycin and amoxicillin-clavulanate. Overall the number of events were quite small; the RD estimates for CV and non-CV death remained close to zero, with all 95% CIs overlapping zero.

For all dispensings, the RD for CV death among dispensings of azithromycin compared to those receiving amoxicillin-clavulanate was -16 (95% CI: -46, 14) within 1-5 days, -14 (95% CI: -60, 31) within 6-10 days, and -29 (95% CI: -81, 22) within 1-10 days. Among the subgroup with CV disease at baseline, the RD for CV death comparing azithromycin to amoxicillin-clavulanate was 18 (95% CI: -93, 128) within 1-5 days, 28 (95% CI: -141, 197) within 6-10 days, and 43 (95% CI: -148, 235) within 1-10 days. Finally, among the subgroup in the top decile of CV mortality risk, the RD for CV death comparing azithromycin to amoxicillin-clavulanate was 24 (95% CI: -138, 187) within 1-5 days, -91 (95% CI: -400, 218) within 6-10 days, and -61 (95% CI: -389, 268) within 1-10 days.

For all dispensings, the RD for non-CV death comparing azithromycin to amoxicillin-clavulanate was 11 (95% CI: -16, 39) within 1-5 days, 5 (95% CI: -32, 41) within 6-10 days, and 16 (95% CI: -28, 59) within 1-10 days. Among the subgroup with CV disease at baseline, the RD for non-CV death comparing azithromycin to amoxicillin-clavulanate was -20 (95% CI: unable to be computed) within 1-5 days and within 1-10 days. Finally, among the subgroup in the top decile of CV mortality risk, the RD for non-CV death among azithromycin dispensings compared to amoxicillin-clavulanate was -51 (95% CI: unable to be computed) within 1-5 days and within 1-10 days. Because there were no non-CV deaths in these two subgroups within the 6-10 days period, RDs and 95% CIs were unable to be calculated.

Table 15. RD (per million dispensings) of CV deaths and non-CV deaths within 1-5, 6-10, and 1-10 days of antibiotic dispensing, identified from the VHA CDW from 2000-2014, among dispensings to patients who had an ENT indication[1-3]

	RD (95% CI)		
	Within 1-5 days	**Within 6-10 days**	**Within 1-10 days**
CV death			
All dispensings, N	*346,974*	*319,272*	*346,974*
Number of events	*8*	*13*	*21*
Azithromycin (ref: amoxicillin-clavulanate)	-15.95 (-46.22, 14.31)	-14.29 (-59.70, 31.12)	-29.19 (-80.77, 22.39)
Subgroup with CV disease at baseline, N	*73,851*	*68,314*	*73,851*
Number of events	*4*	*7*	*11*
Azithromycin (ref: amoxicillin-clavulanate)	17.73 (-92.60, 128.07)	28.14 (-140.85, 197.12)	43.49 (-147.75, 234.73)
Subgroup in top decile of CV mortality risk score, N	*34,838*	*32,224*	*34,838*
Number of events	*2*	*7*	*9*
Azithromycin (ref: amoxicillin-clavulanate)	24.24 (-138.01, 186.50)	-91.27 (-400.20, 217.65)	-60.83 (-389.34, 267.69)
Non-CV death			
All dispensings, N	*346,974*	*319,272*	*346,974*
Number of events	*5*	*7*	*12*
Azithromycin (ref: amoxicillin-clavulanate)	11.34 (-16.04, 38.72)	4.92 (-31.65, 41.49)	15.81 (-27.56, 59.18)
Subgroup with CV disease at baseline, N[4]	*73,851*	*68,314*	*73,851*
Number of events	*1*	*0*	*1*
Azithromycin (ref: amoxicillin-clavulanate)	-20.49 (-)	-	-20.49 (-)
Subgroup in top decile of CV mortality risk score, N[4]	*34,838*	*32,224*	*34,838*
Number of events	*1*	*0*	*1*
Azithromycin (ref: amoxicillin-clavulanate)	-50.72 (-)	-	-50.72 (-)

Abbreviations: CDW = Corporate Data Warehouse; CI = confidence interval; CV = cardiovascular; ENT = ear-nose-throat; RD = risk difference; IPTW= inverse probability of treatment weighting; VHA = Veterans Health Administration.

Notes:

[1] RD was estimated using IPTW-weighted binomial regression models by generalized estimating equations with an identity link and a sandwich variance estimator to account for multiple dispensings for the same patient.

Table 15. RD (per million dispensings) of CV deaths and non-CV deaths within 1-5, 6-10, and 1-10 days of antibiotic dispensing, identified from the VHA CDW from 2000-2014, among dispensings to patients who had an ENT indication[1-3]

	RD (95% CI)		
	Within 1-5 days	**Within 6-10 days**	**Within 1-10 days**

[2] After the study-eligible antibiotic dispensing, observations were censored based on the earliest date of: outpatient dispensing of a subsequent study antibiotic, hospitalization, nursing home admission, disenrollment from VHA benefits, death due to cause other than that for analysis objective, end of risk interval of interest, and end of study (December 31, 2014).
[3] Unweighted Ns of dispensings are presented.
[4] Only one non-CV death occurred within 1-5 days and within 1-10 days for the subgroup with CV disease at baseline and for the subgroup in top decile of CV mortality risk score, therefore 95% CI was not reported for these time frames. No non-CV death occurred within 6-10 days and thus no estimate was reported.

Pooled analysis across indications - Meta-analysis using random effects model

Table 16 reports the primary and secondary outcome meta-analysis for the RD for CV and non-CV deaths within 1-5, 6-10, and 1-10 days of antibiotic dispensing among all dispensings to patients with a respiratory or ENT indication. Generally, the RDs were close to zero, with CIs overlapping zero. The I^2 statistic for heterogeneity remained low across each meta-analysis, and there were no statistically significant p-values associated with high heterogeneity between respiratory and ENT indications.

Among all dispensings, the RD for CV death comparing azithromycin to amoxicillin-clavulanate, using meta-analysis to pool ENT and respiratory cohorts, was -10 (95% CI: -36, 17) within 1-5 days, -23 (95% CI: -59, 13) within 6-10 days, and -28 (95% CI: -71, 15) within 1-10 days. Among the subgroup with CV disease at baseline, the RD for CV death was 12 (-71, 95) within 1-5 days, 14 (95% CI: -90, 119) within 6-10 days, and 25 (95% CI: -104, 154) within 1-10 days. Among the subgroup in the top decile of CV mortality risk, the RD for CV death was 25 (95% CI: -112, 161) within 1-5 days, -108 (95% CI: -344, 127) within 6-10 days, and -75 (95% CI: -333, 184) within 1-10 days.

Among all dispensings, the RD for non-CV death comparing azithromycin to amoxicillin-clavulanate, using meta-analysis to pool ENT and respiratory cohorts, was 14 (95% CI: -10, 39) within 1-5 days, 5 (95% CI: -25, 35) within 6-10 days, and 20 (95% CI: -17, 57) within 1-10 days. Because there were a very small number of non-CV deaths, pooled RDs for subgroups could not be estimated using meta-analysis.

Table 16. Meta-analysis of RD of CV deaths and non-CV deaths within 1-5, 6-10, and 1-10 days of antibiotic dispensing, identified from the VHA CDW from 2000-2014, among dispensings to patients who had a respiratory or ENT indication - main analyses[1-3]

	RD (95% CI)		
	Within 1-5 days	**Within 6-10 days**	**Within 1-10 days**
CV death			
All dispensings, N	*1,144,953*	*1,047,494*	*1,144,953*
Azithromycin (ref: amoxicillin-clavulanate)	-9.50 (-35.84, 16.85)	-23.38 (-59.39, 12.63)	-27.91 (-70.61, 14.78)
I^2 statistic for heterogeneity	*0.0%*	*0.0%*	*0.0%*
P-value[4]	*0.396*	*0.520*	*0.931*
Subgroup with CV disease at baseline, N	*313,427*	*287,368*	*313,427*
Azithromycin (ref: amoxicillin-clavulanate)	11.97 (-71.25, 95.19)	14.44 (-89.75, 118.63)	24.86 (-104.43, 154.15)
I^2 statistic for heterogeneity	*0.0%*	*0.0%*	*0.0%*
P-value[4]	*0.876*	*0.840*	*0.796*
Subgroup in top decile of CV mortality risk score, N	*114,662*	*105,059*	*114,662*
Azithromycin (ref: amoxicillin-clavulanate)	24.81 (-111.63, 161.25)	-108.31 (-343.53, 126.91)	-74.58 (-332.72, 183.56)
I^2 statistic for heterogeneity	*0.0%*	*0.0%*	*0.0%*
P-value[4]	*0.990*	*0.868*	*0.894*
Non-CV death			
All dispensings, N	*1,144,953*	*1,047,494*	*1,144,953*
Azithromycin (ref: amoxicillin-clavulanate)	14.40 (-9.98, 38.77)	4.91 (-25.06, 34.87)	19.65 (-17.47, 56.77)
I^2 statistic for heterogeneity	*0.0%*	*0.0%*	*0.0%*
P-value[4]	*0.631*	*0.999*	*0.737*
Subgroup with CV disease at baseline, N	*313,427*	*287,368*	*313,427*
Azithromycin (ref: amoxicillin-clavulanate)[5]	-	-	-
I^2 statistic for heterogeneity	-	-	-
P-value[4]	-	-	-
Subgroup in top decile of CV mortality risk score, N	*114,662*	*105,059*	*114,662*
Azithromycin (ref: amoxicillin-clavulanate)[5]	-	-	-
I^2 statistic for heterogeneity	-	-	-

Table 16. Meta-analysis of RD of CV deaths and non-CV deaths within 1-5, 6-10, and 1-10 days of antibiotic dispensing, identified from the VHA CDW from 2000-2014, among dispensings to patients who had a respiratory or ENT indication - main analyses[1-3]

	RD (95% CI)		
	Within 1-5 days	**Within 6-10 days**	**Within 1-10 days**
P-value[4]	-	-	-

Abbreviations: CDW = Corporate Data Warehouse; CI = confidence interval; CV = cardiovascular; ED = emergency department; RD = risk difference; IPTW= inverse probability of treatment weighting; VHA = Veterans Health Administration.

Notes:
[1] Pooled RDs were estimated by a random effects meta-analysis model following the methodology of DerSimonian and Laird.
[2] After the study-eligible antibiotic dispensing, observations were censored based on the earliest date of: outpatient dispensing of a subsequent study antibiotic, hospitalization, nursing home admission, disenrollment from VHA benefits, death due to cause other than that for analysis objective, end of risk interval of interest, and end of study (December 31, 2014).
[3] Unweighted Ns of dispensings are presented.
[4] The Cochran's Q test p-values were reported.
[5] Pooled RDs were unavailable due to the small number of events.

Pooled analysis across indications - GEE model with indicator term for indication

Table 17 reports the pooled data analyses of primary and secondary outcomes for the RD for CV and non-CV deaths within 1-5, 6-10, and 1-10 days of antibiotic dispensing among all dispensings to patients with a respiratory or ENT indication. Generally, the RDs were close to zero, with 95% CIs overlapping zero. Additionally, these results remained consistent with the indication-specific primary and secondary results, as well as results from the meta-analysis.

Among all dispensings, the RD for CV death comparing azithromycin to amoxicillin-clavulanate, after pooling ENT and respiratory cohorts, was 5 (95% CI: -33, 43) within 1-5 days, -30 (95% CI: -73, 13) within 6-10 days, and -23 (95% CI: -78, 32) within 1-10 days. Among the subgroup with CV disease at baseline, the RD for CV death was 14 (95% CI: -84, 113) within 1-5 days, 3 (95% CI: -103, 110) within 6-10 days, and 17 (95% CI: -122, 155) within 1-10 days. Among the subgroup in the top decile of CV mortality risk, the RD for CV death was 26 (95% CI: -154, 207) within 1-5 days, -129 (95% CI: -393, 136) within 6-10 days, and -93 (95% CI: -397, 210) within 1-10 days.

Among all dispensings, the RD for non-CV death comparing azithromycin to amoxicillin-clavulanate, after pooling ENT and respiratory cohorts, was 20 (95% CI: -19, 59) within 1-5 days, 5 (95% CI: -33, 43) within 6-10 days, and 24 (95% CI: -28, 76) within 1-10 days. Among the subgroup with CV disease at baseline, the RD for CV death was -5 (95% CI: -99, 89) within 1-5 days, 48 (95% CI: -35, 131) within 6-10 days, and 38 (-83, 159) within 1-10 days. Among the subgroup in the top decile of CV mortality risk, the RD for CV death was -23 (95% CI: -210, 165) within 1-5 days, 175 (95% CI: 51, 298) within 6-10 days, and 137 (95% CI: -82, 356) within 1-10 days.

Table 17. Pooled RD of CV deaths and non-CV deaths within 1-5, 6-10, and 1-10 days of antibiotic dispensing, identified from the VHA CDW from 2000-2014, among dispensings to patients who had a respiratory or ENT indication[1-3]

	RD (95% CI)		
	Within 1-5 days	**Within 6-10 days**	**Within 1-10 days**
CV death			
All dispensings, N	*1,144,951*	*1,047,517*	*1,144,951*
Number of events	*88*	*70*	*158*
Azithromycin (ref: amoxicillin-clavulanate)	4.88 (-33.02, 42.79)	-30.22 (-73.34, 12.91)	-23.07 (-77.85, 31.71)
Subgroup with CV disease at baseline, N	*313,425*	*287,361*	*313,425*
Number of events	*43*	*39*	*82*
Azithromycin (ref: amoxicillin-clavulanate)	14.48 (-83.54, 112.50)	3.21 (-103.36, 109.79)	16.81 (-121.75, 155.36)
Subgroup in top decile of CV mortality risk score, N	*114,660*	*105,049*	*114,660*
Number of events	*23*	*28*	*51*
Azithromycin (ref: amoxicillin-clavulanate)	26.26 (-154.23, 206.76)	-128.56 (-393.49, 136.37)	-93.49 (-396.60, 209.63)
Non-CV death			
All dispensings, N	*1,144,951*	*1,047,517*	*1,144,951*
Number of events	*109*	*77*	*186*
Azithromycin (ref: amoxicillin-clavulanate)	19.96 (-19.02, 58.95)	4.79 (-33.26, 42.84)	24.08 (-28.23, 76.39)
Subgroup with CV disease at baseline, N	*313,425*	*287,361*	*313,425*
Number of events	*47*	*34*	*81*
Azithromycin (ref: amoxicillin-clavulanate)	-5.20 (-99.14, 88.74)	47.60 (-35.48, 130.67)	38.02 (-83.00, 159.05)
Subgroup in top decile of CV mortality risk score, N	*114,660*	*105,049*	*114,660*
Number of events	*28*	*17*	*45*
Azithromycin (ref: amoxicillin-clavulanate)	-22.50 (-209.92, 164.92)	174.67 (51.45, 297.88)	137.04 (-81.75, 355.82)

Abbreviations: CDW = Corporate Data Warehouse; CI = confidence interval; CV = cardiovascular; ED = emergency department; RD = risk difference; IPTW= inverse probability of treatment weighting; VHA = Veterans Health Administration.

Notes:

[1] RDs were estimated by a GEE model that includes an indicator term for each indication stratum to obtain the overall risk difference and its sandwich-variance-derived estimator.

Table 17. Pooled RD of CV deaths and non-CV deaths within 1-5, 6-10, and 1-10 days of antibiotic dispensing, identified from the VHA CDW from 2000-2014, among dispensings to patients who had a respiratory or ENT indication[1-3]

	RD (95% CI)		
	Within 1-5 days	**Within 6-10 days**	**Within 1-10 days**

[2] After the study-eligible antibiotic dispensing, patients were censored based on the earliest date of: outpatient dispensing of a subsequent study antibiotic, hospitalization, nursing home admission, disenrollment from VHA benefits, death due to cause other than that for analysis objective, end of risk interval of interest, and end of study (December 31, 2014).
[3] Unweighted Ns of dispensings are presented.

10.5. Other analyses

10.5.1. Sensitivity analyses

Respiratory indication

Appendix 11 Table S1.1 reports findings from the sensitivity analyses for the HR of CV death (i.e., the primary endpoint) within 1-5, 6-10, and 1-10 days of antibiotic dispensings to patients with a respiratory indication. Results for cardiac death (a sensitivity endpoint) are also presented. Generally, the sensitivity analyses are consistent with the results for the primary and secondary analyses.

Sensitivity 1: PS included as a continuous covariate in the model

This resulted in a HR of 1.13 (95% CI: 0.64, 1.99) within 1-5 days, 0.70 (95% CI: 0.38, 1.29) within 6-10 days, and 0.91 (95% CI: 0.60, 1.37) within 1-10 days when comparing azithromycin to amoxicillin-clavulanate.

Sensitivity 2: Cardiac death as endpoint

This resulted in a HR of cardiac death comparing azithromycin to amoxicillin-clavulanate of 1.15 (95% CI: 0.63, 2.08) within 1-5 days, 0.68 (95% CI: 0.36, 1.26) within 6-10 days, and 0.90 (95% CI: 0.59, 1.39) within 1-10 days.

Sensitivity 3: CV death among those in the high, medium, and low CV mortality risk categories

Among dispensings in the high risk category, the HR of CV death for azithromycin compared to amoxicillin-clavulanate was 1.12 (95% CI: 0.40, 3.14) within 1-5 days, 0.68 (95% CI: 0.26, 1.77) within 6-10 days, and 0.85 (95% CI: 0.42, 1.72) within 1-10 days. For those in the medium risk category, the HR of CV death was 0.96 (95% CI: 0.41, 2.25) within 1-5 days, 2.74 (95% CI: 0.63, 11.84) within 6-10 days, and 1.29 (95% CI: 0.62, 2.69) within 1-10 days. Finally, among those in the low risk category, the HR of CV death was 1.92 (95% CI: 0.57, 6.43) within 1-5 days, 0.25 (95% CI: 0.09, 0.68) within 6-10 days, and 0.68 (95% CI: 0.34, 1.37) within 1-10 days.

Sensitivity 4: CV death in VHA Priority Group 1

This resulted in a HR of 1.11 (95% CI: 0.36, 3.40) within 1-5 days, 0.94 (95% CI: 0.26, 3.39) within 6-10 days, and 1.04 (95% CI: 0.45, 2.41) within 1-10 days.

Sensitivity 5: CV death among those who were <65 years of age

This resulted in a HR of 1.24 (95% CI: 0.53, 2.88) within 1-5 days, 0.60 (95% CI: 0.31, 1.16) within 6-10 days, and 0.83 (95% CI: 0.50, 1.38) within 1-10 days.

ENT indication

Appendix 11 Table S1.2 reports findings from the sensitivity analyses for the HR of CV and cardiac death within 1-5, 6-10, and 1-10 days of antibiotic dispensings to patients with an ENT indication. Generally, the sensitivity analyses are consistent with the results for the primary and secondary objectives.

Sensitivity 1: PS included as a continuous covariate in the model

This resulted in a HR for CV death comparing to amoxicillin-clavulanate of 0.46 (95% CI: 0.09, 2.29) within 1-5 days, 0.67 (95% CI: 0.20, 2.30) within 6-10 days, and 0.59 (95% CI: 0.22, 1.55) within 1-10 days.

Sensitivity 2: Cardiac death as endpoint

This resulted in a HR of 0.46 (95% CI: 0.09, 2.30) within 1-5 days, 1.05 (95% CI: 0.29, 3.73) within 6-10 days, and 0.75 (95% CI: 0.28, 2.02) within 1-10 days.

Sensitivity 3: CV death among those in the high, medium, and low CV mortality risk categories

Among those in the high risk category, the HR of CV death comparing azithromycin to amoxicillin-clavulanate was 1.54 (95% CI: 0.10, 24.60) within 1-5 days, 0.63 (95% CI: 0.12, 3.28) within 6-10 days, and 0.78 (95% CI: 0.19, 3.14) within 1-10 days. For those in the medium risk category, the HR was 0.24 (95% CI: 0.03, 2.07) within 1-5 days, 0.81 (95% CI: 0.07, 8.96) within 6-10 days, and 0.40 (95% CI: 0.08, 1.98) within 1-10 days. Finally, among those in the low risk category, the HR was 0.75 (95% CI: 0.07, 8.25) within 6-10 days and within 1-10 days. Because there were very few CV deaths in the 1-5 day period among those with low CV mortality risk, HRs were unable to be calculated.

Sensitivity 4: CV death in VHA Priority Group 1

This resulted in a HR of 0.80 (95% CI: 0.07, 8.86) within 6-10 days and 0.40 (95% CI: 0.04, 3.59) within 1-10 days. Because there were very few CV deaths in the 1-5 day period among those with Priority Group 1 status, HRs were unable to be calculated.

Sensitivity 5: CV death among those who were <65 years of age

This resulted in a HR of 0.70 (95% CI: 0.13, 3.85), within 1-5 days 0.65 (95% CI: 0.13, 3.38) within 6-10 days, and 0.67 (95% CI: 0.21, 2.20) within 1-10 days.

Pooled analysis - Meta-analysis using random effects model

Appendix 11 Table S1.3 reports the sensitivity meta-analyses for the HR of CV and cardiac deaths within 1-5, 6-10, and 1-10 days of antibiotic dispensing among all dispensings with a respiratory or ENT indication. Generally, the HRs remained consistent with the primary and secondary outcome results presented in Table 12. All HRs were near 1.00, with all 95% CIs

overlapping 1.00. The I^2 statistic for heterogeneity remained low across each meta-analysis, and there were no statistically significant p-values associated with high heterogeneity between respiratory and ENT indications.

Sensitivity 1: PS included as a continuous covariate in the model

The pooled HR of CV death for azithromycin compared to amoxicillin-clavulanate was 1.00 (95% CI: 0.55, 1.82) within 1-5 days, 0.70 (95% CI: 0.40, 1.20) within 6-10 days, and 0.85 (95% CI: 0.58, 1.24) within 1-10 days.

Sensitivity 2: Cardiac death as endpoint

The pooled HR of cardiac death for azithromycin compared to amoxicillin-clavulanate was 1.00 (95% CI: 0.52, 1.90) within 1-5 days, 0.74 (95% CI: 0.42, 1.29) within 6-10 days, and 0.88 (95% CI: 0.59, 1.30) within 1-10 days.

Sensitivity 3: CV death among those in the high, medium, and low CV mortality risk categories

In the high CV mortality risk category, the pooled HR of CV death for azithromycin compared to amoxicillin-clavulanate was 1.16 (95% CI: 0.44, 3.06) within 1-5 days, 0.67 (95% CI: 0.29, 1.53) within 6-10 days, and 0.83 (95% CI: 0.44, 1.57) within 1-10 days. In the medium CV mortality risk category, the pooled HR of CV death was 0.70 (95% CI: 0.22, 2.19) within 1-5 days, 1.97 (95% CI: 0.56, 6.88) within 6-10 days, and 0.90 (95% CI: 0.31, 2.59) within 1-10 days. In the low CV mortality risk category, the pooled HR of CV death was 0.30 (95% CI: 0.12, 0.74) within 6-10 days and 0.69 (95% CI: 0.35, 1.35) within 1-10 days. Because there were a very small number of CV deaths within 1-5 days for this subgroup, pooled HRs were unable to be generated using meta-analysis to pool.

Sensitivity 4: CV death in VHA Priority Group 1

The pooled HR of CV death for azithromycin compared to amoxicillin-clavulanate was 0.92 (95% CI: 0.42, 2.01) within 1-10 days and 0.91 (95% CI: 0.29, 2.81) within 6-10 days. Because there were a very small number of CV deaths within 1-5 days for this subgroup, pooled HRs were unable to be generated using meta-analysis to pool.

Sensitivity 5: CV death among those who were <65 years of age

The pooled HR of CV death for azithromycin compared to amoxicillin-clavulanate was 1.11 (95% CI: 0.52, 2.36) within 1-5 days, 0.61 (95% CI: 0.33, 1.12) within 6-10 days, and 0.80 (0.50, 1.28) within 1-10 days.

Pooled analysis - Cox proportional hazards model with random effect

Appendix 11 Table S1.4 reports the pooled sensitivity analyses for the HR of CV and cardiac deaths within 1-5, 6-10, and 1-10 days of antibiotic dispensing among all dispensings with a

respiratory or ENT indication. Generally, the HRs remained consistent with the pooled primary and secondary outcome results presented in Table 11. All HRs were near 1.00, with 95% CIs overlapping 1.00. Additionally, these results remained consistent with the pooled meta-analysis.

Sensitivity 1: PS included as a continuous covariate in the model

The pooled HR of CV death for azithromycin compared to amoxicillin-clavulanate was 1.06 (95% CI: 0.64, 1.75) within 1-5 days, 0.70 (95% CI: 0.41, 1.21) within 6-10 days, and 0.87 (95% CI: 0.61, 1.26) within 1-10 days.

Sensitivity 2: Cardiac death as endpoint

The pooled HR of cardiac death for azithromycin compared to amoxicillin-clavulanate was 1.07 (95% CI: 0.63, 1.83) within 1-5 days, 0.73 (95% CI: 0.41, 1.29) within 6-10 days, and 0.90 (95% CI: 0.61, 1.32) within 1-10 days.

Sensitivity 3: CV death among those in the high, medium, and low CV mortality risk categories

In the high CV mortality risk category, the pooled HR of CV death for azithromycin compared to amoxicillin-clavulanate was 1.15 (95% CI: 0.44, 3.04) within 1-5 days, 0.65 (95% CI: 0.29, 1.47) within 6-10 days, and 0.82 (95% CI: 0.44, 1.53) within 1-10 days. In the medium CV mortality risk category, the pooled HR of CV death was 0.84 (95% CI: 0.41, 1.73) within 1-5 days, 2.24 (95% CI: 0.69, 7.26) within 6-10 days, and 1.13 (95% CI: 0.61, 2.09) within 1-10 days. In the low CV mortality risk category, the pooled HR of CV death was 1.79 (95% CI: 0.53, 6.01) within 1-5 days, 0.29 (95% CI: 0.11, 0.73) within 6-10 days, and 0.67 (95% CI: 0.34, 1.31) within 1-10 days.

Sensitivity 4: CV death in VHA Priority Group 1

The pooled HR of CV death for azithromycin compared to amoxicillin-clavulanate was 0.98 (95% CI: 0.36, 2.63) within 1-5 days, 0.89 (95% CI: 0.30, 2.59) within 6-10 days, and 0.93 (95% CI: 0.45, 1.93) within 1-10 days.

Sensitivity 5: CV death among those who were <65 years of age

The pooled HR of CV death for azithromycin compared to amoxicillin-clavulanate was 1.21 (95% CI: 0.58, 2.52) within 1-5 days, 0.58 (95% CI: 0.32, 1.07) within 6-10 days, and 0.81 (95% CI: 0.51, 1.28) within 1-10 days.

11. DISCUSSION

11.1. Key results

This study of over 1 million dispensings of azithromycin and amoxicillin-clavulanate for respiratory and ENT indications demonstrated no evidence for an increased risk of CV death,

non-CV death, or cardiac death within 1-5 and 6-10 days of antibiotic dispensings associated with azithromycin as compared with amoxicillin-clavulanate. This conclusion persists in subgroups with higher risk of baseline CV death (those with history of CV disease and high CV mortality risk score) and across multiple sensitivity analyses, including when the entire 1-10 day outcome window following treatment initiation was assessed.

11.1.1. Primary objectives

CV death

While analyses were conducted separately for the respiratory and ENT indication groups, pooled analyses were also performed in order to provide a single estimate for the study objectives. For the primary analysis, the HR of CV death for azithromycin compared to amoxicillin-clavulanate, using meta-analysis, was 1.00 (95% CI: 0.55, 1.81) within 1-5 days, 0.66 (95% CI: 0.39, 1.11) within 6-10 days, and 0.82 (95% CI: 0.57, 1.20) within 1-10 days. Results from the pooled regression analyses were similar. These findings confirm those from the individual indication groups and support the conclusion that there is no statistically significant increased risk of CV death with azithromycin as compared to amoxicillin-clavulanate. Specifically, in both the respiratory indication group and the ENT indication group, the HRs for the primary outcome of CV death assessed in all outcome assessment windows (or risk periods) were near the null of 1.00 and the narrow 95% CIs included 1.00. Similarly, the RD estimates for the primary outcome were near the null value of 0 and 95% CIs all included the null value of 0 for the respiratory and ENT indication groups. For the respiratory indication of use, the HR was 1.12 (95% CI: 0.63, 2.00) within 1-5 days, 0.65 (95% CI: 0.36, 1.16) within 6-10 days, and 0.87 (95% CI: 0.58, 1.31) within 1-10 days. Following the same pattern, the RD for CV death per million dispensings was 10.68 (95% CI: -42.84, 64.20) within 1-5 days, -38.78 (95% CI: -97.89, 20.32) within 6-10 days, and -25.13 (95% CI: -101.22, 50.97) within 1-10 days. For the ENT indication of use, the HR of CV death was 0.46 (95% CI: 0.09, 2.30) within 1-5 days, 0.70 (95% CI: 0.22, 2.29) within 6-10 days, and 0.60 (95% CI: 0.23, 1.57) within 1-10 days. The RD for CV death per million dispensings was -15.96 (95% CI: -46.22, 14.31) within 1-5 days, -14.29 (95% CI: -59.70, 31.12) within 6-10 days, and -29.19 (95% CI: -80.77, 22.39) within 1-10 days.

Results from subgroup analyses of dispensings to patients with high baseline CV risk (i.e., history of baseline CV disease and high baseline CV mortality risk) were also consistent with results from the primary analyses with regard to point estimates, and 95% CIs of HRs for CV death overlapped with 1.00 and 95% CIs for RDs overlapped with 0, indicating no excess risk associated with azithromycin. Similar results were seen across the other subgroups with similar point estimates and 95% CIs for each subgroup largely overlapping with each other as well as null values.

While findings from this study are consistent with those reported by Svanström et al. (2013), the results are notably different than those presented by Ray et al. (2012), who found a statistically significant increased risk for azithromycin compared to amoxicillin for both 5 day and 10 day CV death: HR of 2.49 (95% CI: 1.38, 4.50) and 1.87 (95% CI: 1.16, 3.01), respectively. In the current study, the upper confidence limits for the HR of CV death within

5 and 10 days were 1.81 and 1.20 from pooled meta-analyses across indications. Therefore, a relative risk in the magnitude of results found by Ray et al's study is highly unlikely and incompatible with this study.

The current study made many improvements to the methodology employed by Ray et al. (2012), including omitting dispensings with ambiguous or missing indications. The importance of maintaining control over indication is clear in Table 4 and Table 5, which show that the odds of using azithromycin are approximately four-fold higher in the respiratory than in the ENT indication group, and in Table 8 and Table 9, from which it is apparent that the respiratory indication carries almost five times higher risk of CV mortality than the ENT group during days 1-5. Serious respiratory infections in patients with COPD, asthma, or bronchitis are treated with multiple therapies in addition to antibiotics, most notably beta-agonists that have been demonstrated to carry a significant adverse CV risk). In Ray et al. (2012)'s study[1], indication was missing for 30% of the study population which may have contributed to a large extent of residual confounding. Ray reported that the cumulative incidence of CV death within 5 days was 85.2 per million courses. The current study found 109 per million dispensings in the respiratory indication group and 15 per million in the ENT indication group. The large difference in risk across indications in the current study demonstrates that indication strongly predicts CV death, and that confounding by indication may explain the results such as those reported by Ray et al. (2012), in which patients with uncertain indication are included. This appears to be true especially since indication is associated with the type of antibiotic a patient receives (as reflected by the differences in distribution of azithromycin across indication groups in the current study: 79% in the respiratory indication group vs. 41% in the ENT indication group). The feasibility assessment that was conducted as part of this study (see Appendix 12 for more information) also found that indication was a major contributor to poor overlap in PS distributions, and that balance in baseline characteristics was poor between antibiotic cohorts when indication groups were combined. Therefore, without identifying indication and conducting analyses stratified by indication, confounding by indication would bias comparisons due to differences in baseline risk. This was also observed in Chou et al. (2015)[6], where azithromycin was not associated with a higher risk of death compared to amoxicillin-clavulanate in a stratified analysis considering respiratory infections separately (OR=1.76; 95% CI: 0.94, 3.29) though an association was found in the overall study population (OR=2.62; 95% CI: 1.69, 4.06).

In addition, the current study used amoxicillin-clavulanate as a comparator to azithromycin rather than amoxicillin (with and without clavulanate), which was used by Ray et al. (2012)[1]. Amoxicillin (without clavulanate) is often prescribed by physicians for minor upper respiratory illnesses thereby skewing the population treated with amoxicillin to a population with lesser intrinsic risk of morbidity and mortality. Amoxicillin with clavulanate is reserved for more serious infections; thus, using this comparator resulted in larger overlap of PS distributions for the comparators in the current study, while Appendix Table 5 of Ray et al. (2012) indicates that overlap of the PS for the azithromycin and amoxicillin cohorts may not have been as large (e.g., wide variation in the 25th, 50th, and 75th percentiles between the cohorts). This is consistent with the study conducted by Chou et al. (2015)[6], in which amoxicillin-clavulanate was used as the comparator to azithromycin instead of amoxicillin in

order to increase comparability of infection severity between treatment groups. Ray et al. (2012) did not assess amoxicillin-clavulanate separately from amoxicillin to determine whether it would be a more appropriate comparator to azithromycin and did not allow for a washout period prior to each antibiotic dispensing to ensure that carryover effects from a prior dispensing did not impact results. In addition, Ray et al. (2012) assessed baseline covariates in a fixed 365 day window prior to initiation of the antibiotic only. This is a limitation of their analysis since values of key confounding variables (in addition to antibiotic exposure) may change rapidly over time and accounting for shorter-term risk factors (or covariates) is important in this setting. The current study addressed this by comprehensively assessing baseline characteristics from the distant past (31-365 days prior), recent past (1-7 and 8-30 days prior), and concurrent time of the antibiotic dispensing (on index date), in order to capture (and adjust for) for medical therapies and care from the patient's medical history that may impact study outcomes.

Sensitivity analyses

Sensitivity analyses were conducted to ensure the robustness of results from the primary analyses by considering various scenarios that aimed to increase the internal validity of these analyses. Pooled results for the combined indication groups and results for each indication group separately supported the conclusion that there is no association between azithromycin and CV death. Thus, the conclusion that there is no association between azithromycin and CV death from the primary analysis is robust to: confounding adjustment using the PS as a continuous covariate as opposed to IPTW; consideration of cardiac death as opposed to CV death; subgroups defined by high, medium, and low CV mortality risk; dispensings to Priority Group 1 veterans, who receive the majority of their care at the VHA, thus ensuring complete data availability; and dispensings to younger patients (age <65 years) to exclude older patients who become eligible for Medicare and may seek care elsewhere and to allow for a more homogeneous group with respect to comorbidities, concomitant medications, and frailty (as compared to older patients among whom there may be greater variation in such characteristics).

11.1.2. Secondary objectives

Non-CV death

The secondary outcome of non-CV death served as a "negative-control endpoint" since no known underlying clinical mechanism is expected to increase the risk of non-CV death (such as cancer) in patients treated with azithromycin vs. amoxicillin-clavulanate. Therefore, in the absence of a causal hypothesis linking use of any of the study antibiotics to non-CV death, observed associations were interpreted as indicators of residual confounding posited, for example, by Rao et al. (2014)[3]. Similar to results for CV death, there was no evidence of a clear increased risk of non-CV death for azithromycin as compared to amoxicillin-clavulanate in analyses stratified by indication and pooled analysis. In the respiratory indication group, the HR for non-CV death was 1.26 (95% CI: 0.77, 2.07) within 1-5 days, 1.05 (95% CI: 0.60, 1.86) within 6-10 days, and 1.17 (95% CI: 0.80, 1.70) within 1-10 days. The RD for non-CV death per million dispensings was 26 (95% CI: -27, 80) within 1-5 days,

5 (95% CI: -47, 57) within 6-10 days, and 30 (95% CI: -42, 102) within 1-10 days. For the ENT indication group, the HR of non-CV death was 2.18 (95% CI: 0.36, 13.14) within 1-5 days, 1.24 (95% CI: 0.27, 5.64) within 6-10 days, and 1.55 (95% CI: 0.49, 4.86) within 1-10 days. The RD was 11 (95% CI: -16, 39) per million dispensings within 1-5 days, 5 (95% CI: -32, 41) within 6-10 days, and 16 (95% CI: -28, 59) within 1-10 days. Results from the meta-analysis of indication-specific estimates found an HR of 1.31 (95% CI: 0.81, 2.12) within 1-5 days, 1.07 (95% CI: 0.63, 1.83) within 6-10 days, and 1.20 (95% CI: 0.84, 1.71) within 1-10 days.

Conclusions from subgroup analyses of non-CV death in the respiratory and ENT indications were consistent with overall results. Even though the point estimate for non-CV death was greater than 1, wide confidence intervals for the point estimates indicated a higher degree of uncertainty regarding these point estimates and thus these findings do not indicate a higher risk of non-CV death associated with azithromycin as compared to amoxicillin -clavulanate. These were largely driven by the small number of events occurring in the ENT indication. Similarly, because there was only 1, or 0, non-CV death events for the subgroups considered, 95% CIs could not be generated.

While Ray et al. (2012)[1] considered deaths due to other causes as an endpoint for comparing azithromycin use vs. no antibiotic use, no results for this endpoint were presented comparing azithromycin to amoxicillin. Within a 5-day course, azithromycin was found to be associated with increased risk of death from any cause, as compared to amoxicillin, with a HR of 2.02 (95% CI: 1.24, 3.30). However, this may be attributable to the reported relationship between azithromycin and CV death. CV deaths comprise a larger proportion of total deaths as compared to other causes of death, and thus it is expected that the HR for all-cause death would be closer to that for CV death than other causes of death. Since all-cause death combines non-CV death and CV death into a single aggregate outcome that combines the different underlying clinical mechanisms that cause CV death and non-CV death, considering both of these together as a combined endpoint results in uninterpretable outcomes.

11.2. Limitations

This study focused on dispensings to patients treated with azithromycin or amoxicillin-clavulanate and on respiratory or ENT indications for which azithromycin is most commonly used. Prior to the analyses, extensive feasibility analyses were conducted to identify the most appropriate antibiotic comparator for azithromycin and to ensure the internal validity and interpretability of study findings (see Appendix 12). Amoxicillin-clavulanate was selected based on an assessment of the PS distribution overlap and comparability of baseline characteristics, which indicated greater similarity between amoxicillin-clavulanate and azithromycin, as compared to amoxicillin (with and without clavulanate). Additionally, indication was determined to be an important contributing factor to imbalances in baseline characteristics. The dispensings included in the study are restricted to those for respiratory and ENT indications (i.e., as part of the inclusion/exclusion criteria), which were found to be the largest indication groups in the study population (42% and 19%, respectively). Therefore, this analysis comparing amoxicillin-clavulanate to azithromycin within respiratory and ENT indications strengthens the internal validity of the study though the

generalizability to patients treated for other indications is limited. There was no evidence of heterogeneity of effect across indication, though it is noted that given fewer events associated with use for ENT indication, conclusions of the pooled analyses may be more applicable to respiratory indication.

Although the VHA CDW has many strengths in its comprehensive structure, large number of variables, and electronic accessibility, there may be gaps in the data since veterans may receive health care services outside of the VHA, and these services are not recorded in the CDW. For example, veterans with secondary insurance or veterans who are 65 years of age or older who have Medicare may have received health care services outside of VHA facilities. The Sponsor attempted to address this by examining sensitivity analyses of dispensings to Priority Group 1 veterans (i.e., those with the highest level of disability who receive all their care within the VHA) and dispensings to veterans <65 years of age (i.e., those ineligible for Medicare); results of these sensitivities confirmed the primary analysis, indicating that this limitation may be appropriately addressed. Veterans may also have elected to fill prescriptions outside of the VHA, especially if the medications are inexpensive, such as the generic antibiotics studied in the analysis. Any medications or care that patients receive outside of VHA facilities were not captured in the VHA EMR system. To address this concern and ensure that the patient was receiving most care at the VHA, one of the study inclusion criteria required that eligible dispensings be to patients who have at least two inpatient or outpatient (except ED) encounters and at least one dispensing of a medication other than amoxicillin-clavulanate or azithromycin recorded in the database during the year preceding the index antibiotic dispensing date. In this way, the patients included were better assured to regularly use VHA services. In addition, while dispensing data are available from the VHA database, there is no information on whether patients actually used the antibiotics as prescribed. This limitation is applicable to all analyses of prescription or dispensing data from secondary data sources.

In some cases, small numbers of death events were observed in subgroup and sensitivity analyses conducted in this study (e.g., for the ENT indication group the subgroup analyses for non-CV death and the sensitivities of low CV mortality risk and Priority Group 1 status). In such instances, estimates could not be generated. However, the remaining analyses support the same finding that there is no evidence indicating that azithromycin is associated with an increased risk of death (CV or non-CV) as compared to amoxicillin-clavulanate, and therefore, this small number of incomplete results may be negligible. CIs generated in some of the analyses may also be unstable to due small numbers of death events observed, as the estimation of the CIs relies on the assumption of normally distributed data, which may not hold in such cases. For instance, a high HR of 6.60 (95% CI: 0.88, 49.77) was observed for non-CV death within 6-10 days for the respiratory indication among dispensings to patients in the top decile of the CV mortality risk score, this was because only 1 death occurred in the amoxicillin-clavulanate group as compared to 16 non-CV deaths in the azithromycin group. The large CI indicates that the HR is statistically unstable.

The possibility of diagnostic bias, whereby CV death was more accurately identified for azithromycin than for amoxicillin cannot be excluded. However, this scenario is unlikely for the following reasons: 1) the individual completing the death certificate is unlikely to be the same person who prescribed the azithromycin, particularly since sudden cardiac deaths are

likely to occur outside the healthcare setting 2) the individual completing the death certificate would be unlikely to consider azithromycin as a cause of death, and 3) individual completing the death certificate (assuming they did not prescribe the azithromycin) would unlikely have access to data confirming the patient's use of azithromycin.

This study relied on NDI-coded cause of death, rather than adjudicated cause of death. As part of the pilot adjudication it was determined that adjudication would be feasible for only a very low proportion of medical records. Of 100 CV deaths adjudicated in the pilot study, only 28 had sufficient clinical information for adjudicators to determine and agree upon a CV or non-CV cause of death. This may be due, in part, to the fact that sudden cardiac deaths are most likely to occur outside of healthcare settings. Additionally, it is unlikely that deaths with sufficient clinical information to determine an adjudicable cause of death are representative of those without sufficient clinical information, so that considering the sample of adjudicable deaths only may be difficult to interpret. Further, during the pilot study adjudicators agreed with National Death Index [NDI]-coded CV deaths in 27 of 28 (96.4%) adjudicable outcomes. For these reasons we believe that reliance of NDI-coded deaths is a valid method of outcome ascertainment in this study.

Lastly, residual confounding is always a remaining concern for observational studies. The Sponsor addressed concerns for sources of bias via study design and statistical methods. Specifically, the distribution of the propensity score was examined carefully, and weighted exposure groups were compared to assess balance of covariates between azithromycin and amoxicillin dispensings. The null findings for non-CV death further confirm that residual confounding is unlikely to have impacted our results.

11.3. Interpretation

This study demonstrates that there is no evidence for an increased risk of CV death, non-CV death, and cardiac death with azithromycin compared to amoxicillin-clavulanate. The study was prompted by findings from Ray et al. (2012)[1] who reported a small absolute increase in CV deaths during 5 days of azithromycin therapy. Though Ray et al. (2012) hypothesized that azithromycin may increase the risk of CV death, potentially due to QT prolongation resulting in ventricular arrhythmia and SCD, their data could not establish a specific causal mechanism for this finding. Findings from the current study remained consistent in several subgroup and sensitivity analyses, and no heterogeneity of effect for the respiratory and ENT indication groups were found, allowing for the pooling of results using meta-analytic techniques. Given the inconclusive and inconsistent evidence presented in the literature on this topic, this study makes a valuable contribution by selecting more appropriate comparator antibiotics, focusing on indications that are commonly treated with these antibiotics, and ensuring robust confounding control.

Taken together, the body of literature on this topic suggests that indication is an important confounding factor that should be controlled for in such analyses. While Ray et al. (2012) [1] and Rao et al. (2014)[3] found an association between azithromycin use and CV or mortality endpoints, both studies were missing data on indication for a third of patients. Rao et al. (2014) specifically indicated that confounding by indication may impact their results that azithromycin was associated with an increased risk of all-cause death (HR: 1.47; 95% CI:

1.05, 2.09) and serious arrhythmia (HR: 1.77; 95% CI: 1.20, 2.62) within the first 5 days of drug dispensing. Mortensen et al. (2014)[4] found a protective effect of azithromycin on 30- and 90-day all-cause mortality (OR: 0.77; 95% CI: 0.73, 0.81 and OR: 0.73; 95% CI: 0.70, 0.76), though their study did not appropriately control for confounding by indication either. Conversely, the current study, which involved stratified analyses by indication that were later pooled to obtain an estimate across indications and the analysis of patients with respiratory infections by Chou et al. (2015) report no evidence of an association between azithromycin and death. Therefore, residual confounding may have impacted previously reported findings.

While this study considered risk periods of 1-5 days, 6-10 days, and 1-10 days (like Ray et al. (2012)), the period considering 1-10 days may be more appropriate to consider from a clinical perspective given the pharmacokinetic properties of azithromycin (see Appendix 12). This is because the half-life of azithromycin is 68 hours and azithromycin is found in lung tissue within a week after the last dose (a 5-day course is usually given), and since the course of amoxicillin-clavulanate is typically 7-10 days. As expected, findings for the 1-5 day period and the 1-10 day period were consistent with each other in our analysis. A larger number of events were observed during the 1-10 day period, contributing to greater power for the analysis.

Findings from our study were consistent with several other previous studies. Trifirò et al. (2017)[5] assessed population-based health care databases in European countries to investigate the relationship between azithromycin use and ventricular arrhythmia, and found no increased risk associated with azithromycin as compared to amoxicillin (OR: 0.90; 95% CI: 0.48-1.71). Svanström et al. (2013)[2] also concluded that Danish patients receiving azithromycin did not have an increased risk of CV death when compared with those taking penicillin V (HR: 0.93; 95% CI: 0.56–1.55).

Several meta-analyses have examined the association between macrolide use more broadly and increased risk of CV events. For example, Cheng et al. (2015) found that the use of macrolides (as compared to no use of macrolides) was associated with increased risk of CV death with a RR of 1.31 (95% CI: 1.06, 1.62).[32] Looking at azithromycin more specifically, the authors found an RR associated with SCD or ventricular arrhythmias of 3.40 (95% CI: 1.68, 6.90) and an RR for cardiovascular death of 1.54 (95% CI: 1.24, 1.90). While the authors did not distinguish between study design in reporting of antibiotic-stratified results, the above-described limitations (e.g. residual confounding by indication and other factors, including lack of adjustment for covariates occurring close to the index antibiotic dispensing, and conflation of effects by patients' use of multiple antibiotics in short periods of time) of the specific observational studies on this topic must be considered when interpreting these results. Additionally, Wong et al. (2017)[33] systematically reviewed 41 studies, including RCTs, case-control studies, and cohort studies, on macrolide use and CV risk; analyses were conducted separately by study design. Though their study found an increased short-term (within 30 days) risk of the primary outcome in observational studies, an RR of 0.99 (95% CI: 0.74, 1.34) was reported for RCTs. The authors concluded that while observational studies might indicate an increase in short-term risk of CV events, no risk was found in RCTs, and that more studies should be conducted to investigate short-term CV outcomes

with different types of macrolides. While the results of the present study cannot be generalized beyond azithromycin and amoxicillin-clavulanate, learnings from this study with regard to bias control can be implemented for future studies on CV outcomes associated with different types of macrolides.

Key strengths of the design and analysis of the present study are: (1) empirical choice for the antibiotic comparator of amoxicillin-clavulanate; (2) restriction of the study population to dispensings with respiratory and ENT indication; (3) application of an antibiotic washout period of 60 days prior to index to minimize conflation of effects from other antibiotics; (4) use of NDI-coded CV death as the study outcome; (5) validation of the algorithm used to identify antibiotic indication; (6) stratification by baseline risk for CV death based on history of CV disease and a CV mortality risk score; (7) inclusion of concurrent, recent past, and distant past measures of baseline characteristics; (8) inclusion of a frailty index; and (9) use of IPTW for confounder control.

The results of this study are consistent with some, and contrast with other, published observational studies that have examined similar research questions. However, the rigorous design and statistical analysis implemented in this study allow the current study to present strong evidence that there is no statistically significant difference in risk of CV death between azithromycin and amoxicillin-clavulanate, as demonstrated by null results and narrow confidence intervals.

11.4. Generalizability

The VHA population analyzed in this study is largely male and is restricted to patients 30-74 years of age (chosen to closely match the population of Ray's study). Therefore, this population may not be generalizable beyond populations like the veterans served by the VHA. In addition, findings from this study may not be generalizable to patients treated with azithromycin or amoxicillin-clavulanate for other indications besides respiratory and ENT. However, there is no underlying mechanism of these study drugs that would cause gender, age or indication of use to modify the risk of azithromycin on CV death relative to amoxicillin-clavulanate. Lastly, the results of this study are not generalizable beyond the specific antibiotics assessed (i.e., azithromycin and amoxicillin-clavulanate), and findings should not be interpreted at the macrolide class level.

12. OTHER INFORMATION

Not applicable.

13. CONCLUSIONS

In this study, there is no evidence that azithromycin is associated with an increased risk of CV death as compared to amoxicillin-clavulanate among patients who are treated for respiratory or ENT indications. The benefit-risk balance of azithromycin remains favorable.

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15. LIST OF SOURCE TABLES AND FIGURES

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