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Association of Azithromycin Use With Cardiovascular Mortality

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Abstract

IMPORTANCE Azithromycin is one of the most commonly prescribed antibiotics in the US. It has been associated with an increased risk of cardiovascular death in some observational studies.

OBJECTIVE To estimate the relative and absolute risks of cardiovascular and sudden cardiac death after an outpatient azithromycin prescription compared with amoxicillin, an antibiotic not known to increase cardiovascular events.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study included 2 large, diverse, community-based integrated care delivery systems with comprehensive capture of encounters and prescriptions from January 1, 1998, to December 31, 2014. The cohort included patients aged 30 to 74 years who had at least 12 months of health-plan enrollment prior to antibiotic exposure. The exclusion criteria were absence of prescription benefits, prescription for more than 1 type of study antibiotic within 10 days, hospitalization or nursing home residence, and serious medical conditions. Risk of cardiovascular death associated with azithromycin vs amoxicillin exposure was calculated after controlling for confounding factors using a propensity score. Data were analyzed from December 1, 2016, to March 30, 2020.

EXPOSURES Outpatient prescription of azithromycin or amoxicillin.

MAIN OUTCOMES AND MEASURES The primary outcomes were cardiovascular death and sudden cardiac death. An a priori subgroup analysis quantified the effects of azithromycin exposure among patients with increased baseline cardiovascular risk. The secondary outcomes were noncardiovascular death and all-cause mortality.

RESULTS The study included 7 824 681 antibiotic exposures, including 1 736 976 azithromycin exposures (22.2%) and 6 087 705 amoxicillin exposures (77.8%), among 2 929 008 unique individuals (mean [SD] age, 50.7 [12.3] years; 1 810 127 [61.8%] women). Azithromycin was associated with a significantly increased hazard of cardiovascular death (hazard ratio [HR], 1.82; 95% CI, 1.23-2.67) but not sudden cardiac death (HR, 1.59; 95% CI, 0.90-2.81) within 5 days of exposure. No increases in risk were found 6 to 10 days after exposure. Similar results were observed in patients within the top decile of cardiovascular risk (HR, 1.71; 95% CI, 1.06-2.76). Azithromycin was also associated with an increased risk of noncardiovascular death (HR, 2.17; 95% CI, 1.44-3.26) and all-cause mortality (HR, 2.00; 95% CI, 1.51-2.63) within 5 days of exposure.

CONCLUSIONS AND RELEVANCE These findings suggest that outpatient azithromycin use was associated with an increased risk of cardiovascular death and noncardiovascular death. Causality cannot be established, particularly for noncardiovascular death, owing to the likelihood of residual confounding.

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Key Points

Question Is use of azithromycin in an outpatient setting associated with an increased short-term risk of cardiovascular death and sudden cardiac death in a diverse, community-based population?

Findings In this cohort study including 7 824 681 antibiotic exposures, after propensity score adjustment, an outpatient prescription for azithromycin was associated with a significantly increased risk of cardiovascular death within 5 days of exposure compared with amoxicillin, an antibiotic not associated with adverse cardiovascular events.

Meaning These findings suggest that prescribers should be aware of the potential association between azithromycin and cardiovascular death.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Introduction

Azithromycin, a macrolide, is one of the most commonly prescribed antibiotics in the US, with an estimated 44.9 million prescriptions dispensed to outpatients in 2016.[1] A safety concern was raised following a study by Ray et al in 2012[2] that reported an association of azithromycin use with sudden cardiac death. Prompted by concern over QT prolongation and reports of cardiac deaths, the US Food and Drug Administration made changes to the product labeling between 2011 and 2013 advising against using azithromycin in patients with known risk factors for ventricular arrhythmia.[3]

Epidemiological studies[4-9] subsequent to Ray et al[2] have produced conflicting results regarding an association between azithromycin and cardiac events. Of 6 epidemiological studies subsequently published, 3 reported an increased risk of cardiovascular deaths, serious cardiac arrhythmias, or myocardial infarction,[5,8,9] and 3 reported no such associations.[4,6,7] The conflicting results reported may, in part, be due to differences in the study populations, outcome measures, methods of confounding control, exposure risk periods, and statistical methods. In particular, studies have been limited in their ability to control for key confounders, such as indication for use.

In 2014, the Food and Drug Administration and the Pharmacovigilance Risk Assessment Committee requested the manufacturer of azithromycin conduct additional epidemiological investigations to evaluate the association of azithromycin use with cardiovascular mortality. The primary objectives of this study were to estimate the relative and absolute risks of cardiovascular death and sudden cardiac death within 5 days and within 6 to 10 days of a dispensed azithromycin prescription among individuals aged 30 to 74 years.

Methods

This study was approved by the institutional review board at Kaiser Permanente, which waived the requirement for individual written informed consent because data were deidentified and there was no patient contact. This study is reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Study Design and Population

This retrospective cohort study was designed to examine the risk of cardiovascular death and sudden cardiac death associated with azithromycin use compared with amoxicillin use in a general member population of Kaiser Permanente California. To account for potential confounding by indication (ie, need for an antibiotic), we used amoxicillin use as a relevant comparison group.

Kaiser Permanente California consists of 2 regions, Northern California and Southern California, with a combined membership of more than 8.2 million individuals. The demographic profile of the Kaiser Permanente California membership is racially, ethnically, and socioeconomically diverse and closely resembles the underlying populations of Northern and Southern California.[10,11] Kaiser Permanente is an integrated health care delivery system, and members receive almost all their care through Kaiser Permanente facilities, which include hospitals, outpatient medical offices, laboratory centers, and pharmacies. Data generated from patient encounters within the health care system are available for research purposes; information on care received at outside facilities are captured through a claims system.

Cohort Definition

Cohort inclusion criteria were an outpatient prescription for azithromycin or amoxicillin, including amoxicillin-clavulanate, between January 1, 1998, and December 31, 2013, for Southern California and December 31, 2014, for Northern California; age 30 to 74 years on the index date (ie, prescription dispense date); and health plan enrollment with prescription benefit coverage for at least 12 months prior to the index date (allowing up to 60-day gaps in membership). Exclusion criteria were lack of prescription benefit coverage on the index date, receipt of more than 1 type of study antibiotic

(azithromycin or amoxicillin) on the index date or within 10 days prior to the index date, hospitalization during the 30 days prior to the index date, or residence for more than 30 days in a nursing home in the 365 days prior to the index date. To reduce potential confounding, patients with serious underlying medical conditions prior to the index date were also excluded. Examples of these conditions include a diagnosis of cancer within 3 years prior to index or HIV at any time prior to index (eTable 1 in the Supplement).[2]

Exposure Definitions

The exposures of interest were outpatient dispensed prescriptions for oral azithromycin or amoxicillin (with or without clavulanate). Topical and injectable preparations for these products were excluded from the analysis.

Amoxicillin was chosen as the comparator antibiotic because its infectious disease indications are similar to those of azithromycin, and amoxicillin is not associated with cardiovascular death. Patients with more than 1 course of antibiotics during the study period could be entered into the cohort again if they met the inclusion and exclusion criteria; therefore, the level of analysis was set at the individual prescription.

Outcome Definitions

The primary outcomes were cardiovascular death and sudden cardiac death. Since a hypothesized mechanism of harm is potential increased risk of cardiac arrhythmia during therapy and the typical duration of use for azithromycin and amoxicillin is between 7 to 10 days, the analysis was restricted to exposure windows of 0 to 5 and 6 to 10 days after the index (prescription) date. Follow-up was censored if the patient was admitted to the hospital during the 10-day exposure window, as inpatient medications, procedures, and diagnoses may not be comprehensively captured from the inpatient setting.

A cardiovascular death was defined as death with an underlying cardiovascular cause (eg, myocardial infarction, heart failure, arrhythmia, stroke); sudden cardiac deaths were analyzed as a subgroup of cardiovascular death. Secondary outcomes were all-cause death and noncardiovascular death. Deaths were identified using *International Classification of Diseases, Ninth Revision* (*ICD-9*)[12] and *Tenth Revision* (*ICD-10*)[13] codes from state death certificates (using underlying cause of death) except for sudden cardiac death, which used a validated algorithm based on state death certificates, radiology codes, thrombolytic drug use, and anesthesia codes (eTable 4 in the Supplement).[14]

To assess the validity of death outcome coding, cardiovascular deaths with available charts were abstracted, reviewed, and adjudicated by a panel of cardiologists. Adjudicated cardiovascular deaths were further categorized as sudden cardiac death or death due to other cardiac causes. A random sample of noncardiovascular deaths was also adjudicated to quantify the rate of false negative cardiovascular deaths (ie, miscoding of true cardiovascular deaths as noncardiovascular deaths).

Confounding and Effect Modification

Covariates included demographic information, health plan benefit data, and clinical characteristics, including indication of use, based on coded diagnoses and dispensed pharmacy prescriptions. A complete listing of variables is presented in the eAppendix in the Supplement. Given the large number of potential confounders and relatively low outcome frequencies, propensity scores were used for confounder control. Propensity scores were developed using a logistic regression model without reference to or linkage between exposures and study outcomes of interest. Variables for inclusion in the propensity score model were determined a priori and included covariates hypothesized to be associated with exposures and study outcomes and not considered mediators of the potential outcomes of interest. Variable definitions and methods, including diagnostics, are included in eTables 10-12 in the Supplement.

Two methods were used to identify the indication of use for each antibiotic exposure. Beginning in 2008, medications prescribed within the electronic medical record were directly linked to a single

diagnosis code, allowing for direct capture of indication of use. For prescriptions written prior to 2008, recent medical visit diagnostic codes were temporally linked to the antibiotic prescriptions, allowing for an indirect ascertainment of indication of use (similar to the method used by Ray et al[2]) (eTable 2 in the Supplement).

Prophylactic antibiotic prescriptions were considered as 2 separate categories. The term *immediate prophylaxis* describes a prescription that was to be started immediately to prevent an infection from developing (eg, the routine use of antibiotics before or after an elective surgical procedure). *Delayed prophylaxis* describes a prescription that is to be started at an unknown future date (eg, azithromycin for traveler's diarrhea or amoxicillin for dental prophylaxis) (eAppendix in the Supplement).

Statistical Analysis

Descriptive comparisons were made between the azithromycin and amoxicillin cohorts for all of the baseline covariates collected during 12 months prior to the index date using *t* tests and χ^2 tests. Cox regression models were used for point and interval estimations of study outcome hazard ratios (HRs) associated with azithromycin vs amoxicillin in each time interval of interest adjusted for potential confounders. The propensity score was included in all regression models as a categorical covariate, expressed in deciles.

In addition, age and sex were a priori included as model covariates, given their strong associations with study outcomes. A robust sandwich variance estimator for the Cox regression model was used to account for the effects of multiple exposures per patient. Unadjusted cumulative incidences for days 0 to 5 and 6 to 10 were calculated by means of the product limit estimator. Using the same approach as Ray et al,[2] covariate-adjusted estimates of the difference in risk between azithromycin and amoxicillin for time intervals of interest were calculated as $(HR_a - 1) \times I_O$, in which HR_a is the adjusted HR for azithromycin vs amoxicillin and I_O is the unadjusted cumulative incidence among patients prescribed amoxicillin.

Primary analyses used the exposures, outcomes, and methods for confounder adjustment as previously described. Secondary analyses examined the risk of cardiovascular death among individuals with high baseline cardiovascular risk, defined as a history of baseline cardiovascular disease or patients in the top decile of a cardiovascular risk score. Individuals with baseline cardiovascular disease were defined using inpatient or outpatient encounters with a diagnostic code for cardiovascular diseases (eTable 5 in the Supplement). High baseline cardiovascular risk was defined by generating a cardiovascular risk score, using an approach similar to that of Ray and colleagues (eTable 5 and eTable 6 in the Supplement).[2,14,15] The cardiovascular risk score variables included cardiovascular diseases, cardiovascular medications, and smoking (eTables 7-9 in the Supplement).

A sensitivity analysis was conducted that included only prescriptions associated with an infection indication of use, excluding prescriptions with prophylactic (eg, prophylaxis against endocarditis during dental procedures) or missing indications. Additional sensitivity analyses were conducted that added individual variables not adequately balanced between groups within the propensity score to the cardiovascular and noncardiovascular death models (eAppendix in the Supplement). Subgroup analyses were also performed that excluded prescription records with specific pulmonary disease variables, which were imbalanced according to antibiotic exposure. All analyses were conducted using SAS statistical software version 9.4 (SAS Institute). *P* values were 2-sided, and statistical significance was set at .05. Data were analyzed from December 1, 2016, to March 30, 2020.

Results

This cohort study included 7 824 681 antibiotic exposures, including 1 736 976 azithromycin exposures (22.2%) and 6 087 705 amoxicillin exposures, among 2 929 008 unique individuals

(mean [SD] age, 50.7 [12.3] years; 1 810 127 [61.8%] women). Among individual patients, 1 341 489 patients (45.8%) received only 1 study prescription, 622 346 patients (21.3%) received 2 prescriptions, and 964 713 patients (32.9%) received 3 or more prescriptions. The demographic and baseline clinical characteristics of the study population are presented in **Table 1**. Azithromycin exposures were dispensed more frequently during the latter part of the study period, with a mean (SD) of 2008.3 (4.4) calendar years, vs 2005.5 (4.8) calendar years for amoxicillin prescriptions. Patients receiving azithromycin prescriptions, compared with those receiving amoxicillin, had higher rates of pneumonia (242 875 patients [14.0%] vs 213 275 patients [3.5%]; $P < .001$), chronic obstructive pulmonary disease (356 871 patients [20.6%] vs 478 768 patients [7.9%]; $P < .001$), asthma (392 895 patients [22.6%] vs 635 138 patients [10.4%]; $P < .001$), and β-agonist use (706 244 patients [40.7%] vs 1 211 125 patients [19.9%]; $P < .001$) in the year prior to prescription. In addition, patients exposed to azithromycin, compared with patients exposed to amoxicillin, were more likely to receive cardioprotective medications, including angiotensin-converting enzyme inhibitors (304 134 patients [17.5%] vs 894 732 patients [14.7%]; $P < .001$), angiotensin receptor blockers (100 208 patients [5.8%] vs 205 390 patients [3.4%]; $P < .001$), statins (432 033 patients [24.9%] vs 1 194 075 patients [19.6%]; $P < .001$), and β-blockers (265 818 patients [15.3%] vs 839 572 patients [13.8%]; $P < .001$) and were more likely to have had a noncardiovascular-related emergency department encounter within 30 days prior to study antibiotic exposure (92 976 patients [5.4%] vs 125 647 patients [2.1%]; $P < .001$). Azithromycin was dispensed more frequently for an indication of pulmonary infections, whereas amoxicillin was dispensed more frequently for ear, nose, and throat infections. Indication of use data were missing for 2 155 048 amoxicillin prescriptions (35.4%) and 248 388 azithromycin prescriptions (14.3%) (eTable 3 in the Supplement). A total of 197 379 azithromycin prescriptions (11.4%) and 571 728 amoxicillin prescriptions (9.4%) were dispensed to individuals with a history of cardiovascular disease; 139 290 azithromycin prescriptions (8.0%) and 574 234 amoxicillin prescriptions (9.4%) were dispensed to patients in the top decile of the cardiovascular risk score.

A total of 485 deaths occurred within 10 days of a study antibiotic index date. Of these deaths, 256 (52.8%) were cardiovascular deaths. Among cardiovascular deaths, 112 (44%) were classified as sudden cardiac deaths. For those with available records, most (82 deaths [89.0%]) were confirmed as cardiovascular deaths after medical review. There were 229 noncardiovascular deaths during the 10-day follow-up period; the most commonly coded causes of death were lung disease (42 deaths [18.3%]), infection (34 deaths [14.8%]), cancer (37 deaths [16.2%]), and diabetes (28 deaths [12.2%]).

Primary and Secondary Analyses

Compared with amoxicillin, patients receiving azithromycin were at significantly higher risk of cardiovascular death (HR, 1.82; 95% CI, 1.23-2.67) but not sudden cardiac death (HR, 1.59; 95% CI, 0.90-2.81) within 5 days of the index date (**Table 2**). The results were not significant within 6 to 10 days after the index date. The adjusted risk difference for cardiovascular death for azithromycin within 5 days of the index date was 12.79 (95% CI, 3.66-26.21) per 1 000 000 prescriptions. There was an increased risk of cardiovascular death within 5 days for those in the top decile of the cardiovascular risk score (HR, 1.71; 95% CI, 1.06-2.76) (**Table 3**). Azithromycin was also associated with an increased hazard of all-cause death within 5 days (HR, 2.17; 95% CI, 1.44-3.26) and noncardiovascular death within 5 days (HR, 2.00; 95% CI, 1.51-2.63) but not 6-10 days after exposure (**Table 4**).

Sensitivity Analyses

Among prescriptions with a coded infection indication of use, the results were similar to those observed in the primary analysis within 5 days of exposure (HR for cardiovascular death, 1.62; 95% CI, 1.06-2.49; adjusted risk difference, 10.21; 95% CI, 0.92-24.49). The addition of individual variables not adequately balanced between groups within the propensity score to the model did not

Table 1. Demographic and Clinical Characteristics of the Study Population

Characteristic	No. (%)		*P* value[a]
	Azithromycin (n = 1 736 976)	Amoxicillin (n = 6 087 705)	
Age, mean (SD), y	51.7 (12.0)	50.4 (11.7)	<.001
Prescriptions, No. (% of total)			
KP Northern California	1 093 980 (63.0)	2 856 689 (46.9)	<.001
KP Southern California	642 996 (37.0)	3 231 016 (53.1)	<.001
Women	1 104 417 (63.6)	3 733 583 (61.3)	<.001
Calendar year of prescriptions, mean (SD)	2008.3 (4.4)	2005.5 (4.8)	<.001
Race/ethnicity			
Hispanic	339 685 (19.6)	1 393 493 (22.9)	<.001
Black	147 448 (8.5)	602 716 (9.9)	
Hawaiian or Pacific Islander	15 688 (0.9)	47 693 (0.8)	
Asian	222 723 (12.8)	603 639 (9.9)	
Native American	7865 (0.5)	22 691 (0.4)	
White	915 575 (52.7)	2 978 294 (48.9)	
Missing or other	87 992 (5.1)	439 179 (7.2)	
Dose			
Azithromycin			
250 mg (2 tabs typically taken on the 1st day)	1 686 423 (97.1)	NA	NA
500 mg	43 181 (2.5)	NA	
Other	7372 (0.4)	NA	
Amoxicillin			
Trihydrate 500 mg	NA	4 912 019 (80.7)	NA
Amoxicillin-clavulanate 875-125 mg	NA	750 312 (12.3)	
Trihydrate, 250 mg	NA	231 917 (3.8)	
Clavulanate, 500-125 mg	NA	182 254 (3.0)	
Other	NA	11 203 (0.2)	
Supply, d			
Mean (SD)	5.0 (5.8)	9.9 (5.8)	<.001
<3	57 639 (3.3)	NA	NA
3	711 700 (41.0)	NA	
4-5	712 138 (41.0)	NA	
<7	NA	534 020 (8.8)	
7	NA	1 061 860 (17.4)	
6-10	217 816 (12.5)	NA	
8-10	NA	3 851 110 (63.3)	
>10	37 683 (2.2)	NA	
11-14	NA	345 265 (5.7)	
>14	NA	295 450 (4.9)	
Current or 1-y past use of medications			
ACE inhibitor	304 134 (17.5)	894 732 (14.7)	<.001
Angiotensin receptor blocker	100 208 (5.8)	205 390 (3.4)	<.001
Anticoagulant	50 679 (2.9)	200 079 (3.3)	<.001
Antiarrhythmic	14 414 (0.8)	60 286 (1.0)	<.001
β-agonist	706 244 (40.7)	1 211 125 (19.9)	<.001
β-blocker	265 818 (15.3)	839, 572 (13.8)	<.001
Calcium-channel blocker	157 840 (9.1)	443 543 (7.3)	<.001
Digoxin	11 171 (0.6)	59 383 (1.0)	<.001
Insulin	61 473 (3.5)	161 260 (2.7)	<.001
Loop diuretic	58 889 (3.4)	141 423 (2.3)	<.001
Other diuretic	303 124 (17.5)	874 343 (14.4)	<.001
Nitrate	60 212 (3.5)	184 332 (3.0)	<.001
Oral hypoglycemic	176 914 (10.2)	514 486 (8.5)	<.001
Platelet inhibitor	21 064 (1.2)	56 372 (0.9)	<.001
Statin	432 033 (24.9)	1 194 075 (19.6)	<.001
Systemic glucocorticoid	421 811 (24.3)	869 807 (14.3)	<.001

(continued)

Table 1. Demographic and Clinical Characteristics of the Study Population (continued)

Characteristic	No. (%)		P value[a]
	Azithromycin (n = 1 736 976)	Amoxicillin (n = 6 087 705)	
Cardiovascular comorbidity			
Arrhythmia	53 459 (3.1)	170 411 (2.8)	<.001
Cardiac valve disease	16 790 (1.0)	86 979 (1.4)	<.001
Myocardial infarction	30 149 (1.7)	83 613 (1.4)	<.001
Cardiac revascularization	6768 (0.4)	25 879 (0.4)	<.001
Other coronary heart disease	61 410 (3.5)	179 895 (3.0)	<.001
Heart failure	27 686 (1.6)	76 906 (1.3)	<.001
Peripheral vascular disease	68 682 (4.0)	160 425 (2.6)	<.001
Stroke	4186 (0.2)	10 562 (0.2)	<.001
TIA	8812 (0.5)	25 773 (0.4)	<.001
Noncardiovascular comorbidity			
Asthma	392 895 (22.6)	635 138 (10.4)	<.001
Chronic obstructive pulmonary disease	356 871 (20.6)	478 768 (7.9)	<.001
Prior pneumonia	242 875 (14.0)	213 275 (3.5)	<.001
Diabetes	233 531 (13.4)	691 758 (11.4)	<.001
Complications of diabetes	100 425 (5.8)	255 582 (4.2)	<.001
Smoking	736 700 (42.4)	2 163 908 (35.6)	<.001
Renal disease	63 643 (3.7)	134 488 (2.2)	<.001
Incontinence of urine or feces	58 791 (3.4)	145 508 (2.4)	<.001
Use of wheelchair or walker	1613 (0.1)	4272 (0.1)	<.001
Health care utilization			<.001
ED visit for cardiovascular disease			
Within 31-365 d	17 204 (1.0)	54 422 (0.9)	<.001
Within 30 d	2408 (0.1)	4866 (0.1)	<.001
ED visit for noncardiovascular disease			
Within 31-365 d	263 682 (15.2)	730 229 (12.0)	<.001
Within 30 d	92 976 (5.4)	125 647 (2.1)	<.001
Cardiovascular disease hospitalization			
Within 91-365 d	7801 (0.5)	30 776 (0.5)	<.001
Within 30-90 d	1703 (0.1)	6715 (0.1)	<.001
Noncardiovascular disease hospitalization within 365 d	51 497 (3.0)	202 146 (3.3)	<.001
Use of a study antibiotic within the past 30 d	72 486 (4.2)	281 661 (4.6)	<.001
Use of any other antibiotic within the past 30 d	118 005 (6.8)	259 457 (4.3)	<.001
Cardiovascular risk score			
Mean (SD)	8.78 (5.97)	9.45 (5.64)	<.001
Median (IQR)	9 (3-14)	9 (5-14)	

Abbreviations: ACE, angeiotensin-conveting enzyme; ED, emergency department; IQR, interquartile range; KP, Kaiser Permanente; NA, not applicable; TIA, transient ischemic attack.

[a] Comparisons made using *t* tests and χ^2 tests.

substantially change the HR point estimates for cardiovascular or noncardiovascular death (eAppendix in the Supplement). The exclusion of records with specific pulmonary disease variables (eg, asthma, chronic obstructive pulmonary disease, history of pneumonia, β-agonist use, glucocorticoid use, smoking) also did not substantially change the point estimates for cardiovascular death. While there were some statistically significant interactions between these variables and noncardiovascular death, the direction of the associations did not change.

Discussion

In this cohort study of more than 7.8 million antibiotic exposures, there was a statistically significantly increased relative risk and absolute risk of cardiovascular death associated with azithromycin exposure compared with amoxicillin within 5 days of index date but not within 6 to 10 days after index date. This study also found an increased risk of noncardiovascular and all-cause death within 5

days of exposure among individuals prescribed azithromycin. While the risk of cardiovascular death is consistent with proposed mechanisms, an increased risk of noncardiovascular mortality is not.

Reports of an association of erythromycin, one of the first macrolide antibiotics, with QT interval prolongation and cardiac arrhythmias first appeared more than 20 years ago.[16-19] Subsequently, cardiac arrhythmias have been reported for clarithromycin and azithromycin, and macrolide antibiotics, as a class, are now known to cause QT prolongation in some at-risk populations.[20] In most of the case reports of macrolide antibiotic use and cardiac arrhythmias, patients had other factors that put them at an increased risk for cardiac arrhythmias, including underlying cardiac disease (ie, bradycardia, congestive heart failure, baseline QT prolongation, cardiomyopathy, atrial fibrillation, and myocardial ischemia), metabolic anomalies that increase the risk of arrhythmia (ie, hypokalemia, hypocalcemia, hypomagnesemia, and hypoxia), or concomitant use of other medications known to prolong the QT interval.[21]

Our observed association of azithromycin with cardiovascular death is similar to that reported by Ray et al[2] in a Tennessee Medicaid population but differs from the findings reported by Svanstrom et al[4] in a Danish general population sample. When examining the findings across these studies, it is

Table 2. Cardiovascular Death and Sudden Cardiac Death After Azithromycin and Amoxicillin Exposure

	Azithromycin (n = 1 736 976)		Amoxicillin (n = 6 087 705)		Adjusted	
Mortality	Deaths, No.	Cumulative incidence[a]	Deaths, No.	Cumulative incidence[a]	Risk difference (95% CI)[a,b]	Hazard ratio (95% CI)[b]
Cardiovascular, d						
0-5	62	35.91	95	15.68	12.79 (3.66 to 26.21)	1.82 (1.23 to 2.67)
6-10	31	18.34	68	11.41	3.15 (−2.31 to 11.91)	1.28 (0.80 to 2.04)
Sudden cardiac, d						
0-5	21	12.17	39	6.44	3.83 (−0.63 to 11.70)	1.59 (0.90 to 2.81)
6-10	16	9.47	36	6.04	4.04 (−3.82 to 19.04)	1.32 (0.69 to 2.52)

[a] Per 1 000 000 prescriptions.

[b] Adjusted for propensity score decile, age, and sex.

Table 3. Cardiovascular Death in High Cardiovascular Risk Subgroups After Azithromycin and Amoxicillin Exposure

	Azithromycin			Amoxicillin			Adjusted[b]	
	No.			No.				
Subgroup	Prescriptions	Deaths	Cumulative Incidence[a]	Prescriptions	Deaths	Cumulative incidence[a]	Risk difference (95% CI)	Hazard ratio (95% CI)
Prior CV disease	197 379	47	NA	571 728	81	NA	NA	NA
0-5 d	NA	30	153.13	NA	50	88.01	51.47 (−8.73 to 157.40)	1.58 (0.90 to 2.79)
6-10 d	NA	17	89.57	NA	31	55.82	25.69 (−14.10 to 103.43)	1.46 (0.75 to 2.85)
Top decile CVRS	139 290	57	NA	574 234	120	NA	NA	NA
0-5 d	NA	37	268.33	NA	69	120.91	85.48 (6.80 to 212.66)	1.71 (1.06 to 2.76)
6-10 d	NA	20	149.83	NA	51	91.20	24.00 (−25.79 to 111.68)	1.26 (0.72 to 2.22)

Abbreviations: CV, cardiovascular; CVRS, cardiovascular risk score; NA, not applicable.

[a] Per 1 000 000 prescriptions.

[b] Adjusted for propensity score decile, age, and sex.

Table 4. Noncardiovascular Death and All-Cause Death After Azithromycin and Amoxicillin Exposure

	Azithromycin (n = 1 736 976)		Amoxicillin (n = 6 087 705)		Adjusted	
Mortality	Deaths, No.	Cumulative incidence[a]	Deaths, No.	Cumulative incidence[a]	Risk difference (95% CI)[a,b]	Hazard ratio (95% CI)[b]
Noncardiovascular, d						
0-5 d	83	48.06	68	11.22	13.13 (4.99-25.37)	2.17 (1.44-3.26)
6-10 d	35	20.71	43	7.22	3.29 (-0.89-10.21)	1.46 (0.88-2.41)
All-cause, d						
0-5 d	145	83.97	163	26.90	26.77 (13.74-43.97)	2.00 (1.51-2.63)
6-10 d	66	39.05	111	18.63	6.37 (-0.89-16.59)	1.34 (0.95-1.89)

[a] Per 1 000 000 prescriptions.

[b] Adjusted for propensity score decile, age, and sex.

important to note key differences between populations. The incidence of cardiovascular death at Kaiser Permanente was 35.9 deaths per 1 000 000 azithromycin exposures, which was lower than the incidence found by Ray et al (85.2 deaths per 1 000 000 azithromycin exposures)[2] yet higher than the incidence found by Svanstrom et al (15.4 deaths per 1 000 000 azithromycin exposures).[4] These differences may largely be explained by baseline differences in population characteristics, although there also may have been differences in detection and classification of cardiovascular deaths.

Limitations and Strengths

Several limitations need to be considered when evaluating the results of this observational study. Although several strategies were used to decrease the potential for confounding by indication of use, severity of infection, and underlying comorbidities, there is the potential for residual confounding. First, although indication of use was included in the propensity score, full control of this confounder was not possible because 31% of the records had a missing indication of use; however, a sensitivity analysis restricted to patients with an infection indication produced similar results to the primary analysis. Second, varying disease severity within the specific indication for antibiotic use may be associated with both choice of antibiotic and risk of cardiovascular death. To mitigate the potential for confounding by unmeasured infection severity, this study only included outpatient prescriptions; patients with severe infections are generally hospitalized. Third, comorbid conditions may be important if patients with other comorbid diseases are more likely to receive azithromycin, even for the same antibiotic indication, and to have an increased risk of cardiovascular or noncardiovascular death.[22] Consistent with this, azithromycin was associated with an increased risk for noncardiovascular mortality from causes unlikely to be related to recent antibiotic exposures, such as lung disease and cancer. However, additional sensitivity analyses that added individual variables not adequately balanced between groups within the propensity score to the model did not change the HR point estimates for cardiovascular or noncardiovascular death. Serious underlying illnesses and all clinical characteristics captured in the propensity score were assessed in the 12 months prior to the index date. Underlying health status within the prior year is likely correlated with but may not fully reflect the health of the person at the time of the infection. Fourth, temporal changes may influence disease risk and prescribing patterns. During the time period for this study (1998-2014), there was a significant decline in the rate of cardiovascular events within the study population[23] and increased use of azithromycin. The influence of this was addressed by including prescription year within the propensity score. Fifth, misclassification of study outcomes (ie, cardiovascular vs noncardiovascular death) is possible given the potential for errors in the *ICD* codes used to define the outcomes. However, adjudication of the cardiovascular deaths showed a high confirmation rate for coded cardiovascular deaths.

This study also has many strengths, including its large sample of patients prescribed antibiotics; detailed pharmacy data that included date, dose, duration, and indication of use (beginning in 2008); high-quality electronic data; availability of written records for manual validation; a diverse community-based population that is comparable to the region's underlying census distribution by multiple demographic factors; and the extensive efforts that were made to address confounding. The adjudication process was also able to provide a degree of reassurance about the validity of the coded outcomes.

Conclusions

This cohort study found an approximately 2-fold increased risk of cardiovascular death and noncardiovascular death after outpatient azithromycin use compared with use of amoxicillin within a 5-day window after dispensing. Although these analyses cannot establish causality, prescribers should be aware of this potential association.

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SUPPLEMENT.

eAppendix. Supplementary Methods
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