ORIGINAL ARTICLE

Azithromycin and the Risk of Cardiovascular Death

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ABSTRACT

BACKGROUND

Although several macrolide antibiotics are proarrhythmic and associated with an increased risk of sudden cardiac death, azithromycin is thought to have minimal cardiotoxicity. However, published reports of arrhythmias suggest that azithromycin may increase the risk of cardiovascular death.

METHODS

We studied a Tennessee Medicaid cohort designed to detect an increased risk of death related to short-term cardiac effects of medication, excluding patients with serious noncardiovascular illness and person-time during and shortly after hospitalization. The cohort included patients who took azithromycin (347,795 prescriptions), propensity-score–matched persons who took no antibiotics (1,391,180 control periods), and patients who took amoxicillin (1,348,672 prescriptions), ciprofloxacin (264,626 prescriptions), or levofloxacin (193,906 prescriptions).

RESULTS

During 5 days of therapy, patients taking azithromycin, as compared with those who took no antibiotics, had an increased risk of cardiovascular death (hazard ratio, 2.88; 95% confidence interval [CI], 1.79 to 4.63; P<0.001) and death from any cause (hazard ratio, 1.85; 95% CI, 1.25 to 2.75; P=0.002). Patients who took amoxicillin had no increase in the risk of death during this period. Relative to amoxicillin, azithromycin was associated with an increased risk of cardiovascular death (hazard ratio, 2.49; 95% CI, 1.38 to 4.50; P=0.002) and death from any cause (hazard ratio, 2.02; 95% CI, 1.24 to 3.30; P=0.005), with an estimated 47 additional cardiovascular deaths per 1 million courses; patients in the highest decile of risk for cardiovascular disease had an estimated 245 additional cardiovascular deaths per 1 million courses. The risk of cardiovascular death was significantly greater with azithromycin than with ciprofloxacin but did not differ significantly from that with levofloxacin.

CONCLUSIONS

During 5 days of azithromycin therapy, there was a small absolute increase in cardiovascular deaths, which was most pronounced among patients with a high baseline risk of cardiovascular disease. (Funded by the National Heart, Lung, and Blood Institute and the Agency for Healthcare Quality and Research Centers for Education and Research on Therapeutics.)

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N Engl J Med 2012;366:1881-90.

Azithromycin, a broad-spectrum macrolide antibiotic, has been reported to be relatively free of cardiotoxic effects.[1] However, the closely related drugs erythromycin and clarithromycin can increase the risk of serious ventricular arrhythmias[2-7] and are associated with an increased risk of sudden cardiac death.[8-10] Furthermore, accumulating evidence suggests that azithromycin also may have proarrhythmic effects. There are at least seven published reports of patients with normal baseline QT intervals in whom azithromycin had arrhythmia-related adverse cardiac effects, including pronounced QT-interval prolongation,[11-13] torsades de pointes,[14-16] and polymorphic ventricular tachycardia in the absence of QT-interval prolongation.[17] The Food and Drug Administration's Adverse Event Reporting System includes at least 20 reports of torsades de pointes associated with azithromycin.[18]

Because the ventricular arrhythmias reported in conjunction with azithromycin use are often rapidly fatal, we conducted a retrospective cohort study of mortality among patients who used this antibiotic. We hypothesized that patients who took azithromycin, as compared with persons who did not take antibiotics and with patients who took other selected antibiotics, would have an increased risk of cardiovascular death, particularly sudden cardiac death.

METHODS

STUDY OVERSIGHT

The study was designed by the authors and approved by the local institutional review board and the Tennessee Bureau of TennCare and Department of Health, all of which waived the requirement for individual informed consent. The sponsors had no role in the study conduct or reporting.

STUDY COHORT

The study cohort consisted of persons enrolled in the Tennessee Medicaid program[19,20]; all data on patients in the study were appropriately deidentified. Computerized Medicaid data, which were linked to death certificates and to a statewide hospital-discharge database, provided information on Medicaid enrollment, medical care encounters, and dates and causes of death. Antibiotics and other medications that patients had taken were identified from Medicaid pharmacy files.[19,21-23]

The cohort included patients who had been prescribed azithromycin between 1992 (when azithromycin was introduced in the United States) and 2006 and met the eligibility criteria on the date on which the prescription was filled. These criteria were formulated to exclude persons at high risk for death from causes unrelated to a short-term effect of proarrhythmic medication (Tables 1 and 2 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Eligible cohort members were 30 to 74 years of age, had no life-threatening noncardiovascular illness, had not received a diagnosis of drug abuse or resided in a nursing home in the previous year, and had not been hospitalized in the prior 30 days. To ensure adequate data for study variables, cohort membership also required at least 365 days of Medicaid enrollment and regular use of medical care.

The study also included matched control periods (of similar length to the courses of antibiotic therapy) during which there was no use of study antibiotics. For each qualifying azithromycin prescription, we identified four such control periods, which were frequency-matched[24] according to a propensity score that was calculated from 153 covariates (Table 3 in the Supplementary Appendix). The persons in the control group had to satisfy the eligibility criteria on the day that the control period began and could not have used any study antibiotics during the prior 30 days.

To attempt to control for confounding by indication, we also included as additional control groups patients who took three other antibiotics: amoxicillin (including amoxicillin with clavulanate potassium), ciprofloxacin, and levofloxacin. Amoxicillin, the primary control antibiotic, has indications that are similar to those of azithromycin and has not been shown to have adverse cardiac effects.[8] The indications for ciprofloxacin and levofloxacin overlap those of azithromycin. Ciprofloxacin is thought to have minimal adverse electrophysiological effects, although there are case reports of torsades de pointes.[1,25] Levofloxacin, which is considered to have greater proarrhythmic potential than ciprofloxacin,[1,25] has been implicated in numerous case reports of torsades de pointes.[18]

A single person could have multiple prescriptions of the study antibiotics and also could have a control period with no use of study antibiotics.

However, for each person, these periods did not overlap, and the end point (death) occurred only once. Thus, assumptions of statistical independence were not violated (see the Supplementary Appendix).

STUDY END POINTS

The primary study end points were cardiovascular death (see the Supplementary Appendix) and death from any cause. We hypothesized that the incidence of cardiovascular death should be increased if azithromycin is proarrhythmic, particularly in a cohort chosen to reduce the likelihood of out-of-hospital deaths from serious illnesses. We included an analysis of death from any cause to guard against differential misclassification of deaths related to use of a study antibiotic. Given the study hypothesis, we also analyzed sudden cardiac deaths, identified with an independently validated computerized definition that is based on multiple sources of data (see the Supplementary Appendix) and that has a positive predictive value of 88%.[26]

STATISTICAL ANALYSIS

The study unit of analysis was the course of antibiotic therapy, which was defined as a fixed period, beginning with the date on which the prescription was filled, during which patients would have been advised to take the antibiotic. This should correspond to the period of greatest risk of adverse cardiac effects, given that the case reports for azithromycin suggest an acute mechanism.[11-17] Because the usual duration of treatment varies according to the specific study antibiotic, we analyzed two periods: the 5-day period that is generally recommended for azithromycin and the 10-day period most commonly suggested for the other study antibiotics. The 10-day analyses for azithromycin included an interval during which patients were unlikely to be taking the drug (days 6 through 10); these days were considered separately in several analyses. Although these periods usually had a fixed duration (5 or 10 days), the data were censored if the patient filled a subsequent prescription for a study antibiotic or ceased to meet the eligibility criteria.

The analysis estimated the cumulative incidence, or risk, of death during a course of antibiotic therapy. The unadjusted cumulative incidence was calculated by means of the product-limit method. The relative risk of death between the groups, defined by use of the study antibiotics, with adjustments for characteristics of the subjects, was calculated with the hazard ratio from Cox regression models (see the Supplementary Appendix).

Each study comparison was adjusted for an extensive set of covariates (reflecting status on the date on which the prescription was filled) that were possibly associated with both the use of the study antibiotic and the risk of death (Table 3 in the Supplementary Appendix). This adjustment used the propensity score[27] (the conditional probability of having a prescription for a study antibiotic, given the covariates). Specific propensity scores were estimated for each pairwise comparison (Tables 4 and 5 in the Supplementary Appendix). The propensity scores for comparisons between study antibiotics included the recorded antibiotic indication (see the Supplementary Appendix).

To check for misspecification of the propensity-score regression models, we evaluated whether the covariate distributions were balanced across the study groups. For the azithromycin group and the control group of persons not taking antibiotics, this distribution was unadjusted, because the propensity-score matching should ensure balance. For amoxicillin, the distribution was adjusted for the propensity score, with the use of a modified method for weighting by inverse probability of treatment[28] that standardized the distribution to that for azithromycin (Table 6 in the Supplementary Appendix).[29] We also checked for overlap of the distribution of propensity scores (Tables 4 and 5 in the Supplementary Appendix).

To provide a summary measure of the risk of cardiovascular death, we calculated a risk score for cardiovascular disease.[30] This score estimated the probability of cardiovascular death (in the absence of use of a study antibiotic) as a function of the indicators of coexisting conditions (see the Supplementary Appendix).

We estimated the difference between the cumulative incidence of cardiovascular death during a 5-day course of azithromycin and the incidence during a similar period of amoxicillin use. We defined the additional risk per course of azithromycin therapy as $(HR_a - 1) \times I_0$, where HR_a was the hazard ratio for azithromycin versus

Table 1. Demographic and Clinical Characteristics of Patients at the Time That the Prescriptions for the Study Antibiotics Were Filled and at the Beginning of the Control Period for Persons Who Received No Antibiotic Treatment.*

Characteristic	No Antibiotic	Amoxicillin†	Ciprofloxacin	Levofloxacin	Azithromycin
Prescriptions (no.)	1,391,180	1,348,672	264,626	193,906	347,795
Mean age (yr)	48.6	47.7	50.5	51.5	48.6
Female sex (%)	77.5	73.3	75.5	73.5	77.5
Current or past use of medications (%)					
Angiotensin-converting–enzyme inhibitor	28.1	24.0	28.4	32.8	28.1
Beta-blocker	21.6	17.3	20.9	24.8	21.5
Calcium-channel blocker	20.2	19.9	22.8	24.3	20.2
Digoxin	2.5	3.5	3.8	3.6	2.5
Loop diuretic	17.3	15.1	20.1	23.8	17.2
Other diuretic	25.9	22.4	26.3	28.9	25.9
Statin	28.1	17.9	25.2	34.5	28.0
Insulin	6.5	6.9	10.2	10.2	6.5
Oral hypoglycemic agent	16.5	13.1	18.9	21.9	16.5
Beta-agonist	40.5	28.1	28.6	43.5	40.3
Glucocorticoid	3.3	2.8	3.8	4.8	3.3
Coexisting conditions (%)					
Heart failure	4.3	3.9	5.3	6.8	4.3
Chronic obstructive pulmonary disease	5.5	4.6	5.1	6.8	5.4
Complications of diabetes‡	7.4	6.5	11.3	11.7	7.5
Incontinence of urine or feces	2.9	2.1	4.6	4.3	2.9
Use of wheelchair or walker	2.3	1.6	3.2	3.8	2.3
Hospitalization for cardiovascular condition (%)	7.2	6.0	8.5	9.5	7.2
Hospitalization for other condition (%)	15.7	14.8	19.1	20.4	15.8
Visit to emergency department in the past 30 days (%)	13.9	11.3	15.6	18.0	13.9
Use of any antibiotic in the past 30 days (%)	27.9	28.4	38.6	40.3	27.0§
Mean summary score for risk of cardiovascular disease¶	9.2	9.5	10.3	10.6	9.3

* Medications, diagnoses, and medical care encounters were for the 365 days before the time the prescription was filled, unless otherwise specified. Control periods with no antibiotic treatment were propensity-score–matched with the azithromycin prescriptions. P<0.01 for comparison of baseline characteristics between the amoxicillin, ciprofloxacin, and levofloxacin groups and the group of persons who did not use antibiotics. See Table 7 in the Supplementary Appendix for additional cohort characteristics.

† Data for amoxicillin included data for amoxicillin with clavulanate potassium.

‡ Complications of diabetes included dermatologic, neurologic, ocular, and renal complications, as well as hypoglycemia, hyperglycemia, diabetic coma, diabetic ketoacidosis, and others.

§ P<0.001 for comparison with the group of persons who received no antibiotic treatment.

¶ To provide a summary measure of the risk of cardiovascular death, we calculated a risk score for cardiovascular disease that estimated the probability of cardiovascular death (in the absence of use of a study antibiotic) as a function of the indicators of coexisting conditions (see the Supplementary Appendix).[30] Scores range from 0, indicating the lowest risk (5% of the cohort), to 19, indicating the highest risk (5%).

amoxicillin and I_0 was the unadjusted cumulative incidence of cardiovascular death for patients taking amoxicillin. The risk difference was also calculated according to the deciles of cardiovascular risk as defined by the risk score for cardiovascular disease.

We performed alternative analyses that tested the validity of several study assumptions. These included a repeated-measures analysis testing the validity of treating the prescription periods as independent observations and an analysis stratified by propensity-score deciles. All analyses were per-

Table 2. Cumulative Incidence of Death among Patients during a 5-Day Course of Azithromycin, as Compared with Persons Who Received No Antibiotic Treatment and Patients Who Took Amoxicillin, According to Cause of Death.

Deaths	No Antibiotic	Amoxicillin	Azithromycin
Total cardiovascular			
No.	41	42	29
Cumulative incidence (no./1 million courses)	29.8	31.5	85.2
Hazard ratio (95% CI)	1	0.95 (0.55–1.63)	2.88 (1.79–4.63)
P value		0.85	<0.001
Sudden cardiac			
No.	33	29	22
Cumulative incidence (no./1 million courses)	24.0	21.8	64.6
Hazard ratio (95% CI)	1	0.85 (0.45–1.60)	2.71 (1.58–4.64)
P value		0.62	<0.001
Other cardiovascular			
No.	8	13	7
Cumulative incidence (no./1 million courses)	5.8	9.7	20.6
Hazard ratio (95% CI)	1	1.30 (0.44–3.84)	3.54 (1.28–9.76)
P value		0.64	0.01
Other cause			
No.	38	28	7
Cumulative incidence (no./1 million courses)	27.6	21.0	20.7
Hazard ratio (95% CI)	1	0.76 (0.42–1.37)	0.74 (0.33–1.67)
P value		0.35	0.47
Total			
No.	79	70	36
Cumulative incidence (no./1 million courses)	57.4	52.6	105.9
Hazard ratio (95% CI)	1	0.86 (0.58–1.28)	1.85 (1.25–2.75)
P value		0.45	0.002

formed with SAS software, version 9.3 (SAS Institute). All reported P values are two-sided.

RESULTS

CHARACTERISTICS OF THE STUDY COHORT

The study cohort included persons with 347,795 prescriptions for azithromycin, 1,391,180 matched control periods with no study antibiotic treatment, 1,348,672 prescriptions for amoxicillin, 264,626 prescriptions for ciprofloxacin, and 193,906 prescriptions for levofloxacin. Azithromycin users were primarily women (77.5%), had a mean age of 49 years, and had frequent use of cardiovascular or respiratory medications, visits to the emergency department, and prior use of antibiotics (Table 1, and Table 7 in the Supplementary Appendix). The characteristics of patients receiving azithromycin prescriptions and the propensity-score matched controls were very similar. In contrast, patients who were prescribed ciprofloxacin or levofloxacin were generally more likely to have complications of diabetes, incontinence, and wheelchair or walker use. The mean summary cardiovascular risk scores for patients taking amoxicillin (9.5), ciprofloxacin (10.3), and levofloxacin (10.6) were higher than the scores for those taking azithromycin (9.3) (Table 1).

For both azithromycin and amoxicillin, the most common indications were infections of the ear, nose, or throat and bronchitis, respectively accounting for 62% and 63% of the prescriptions

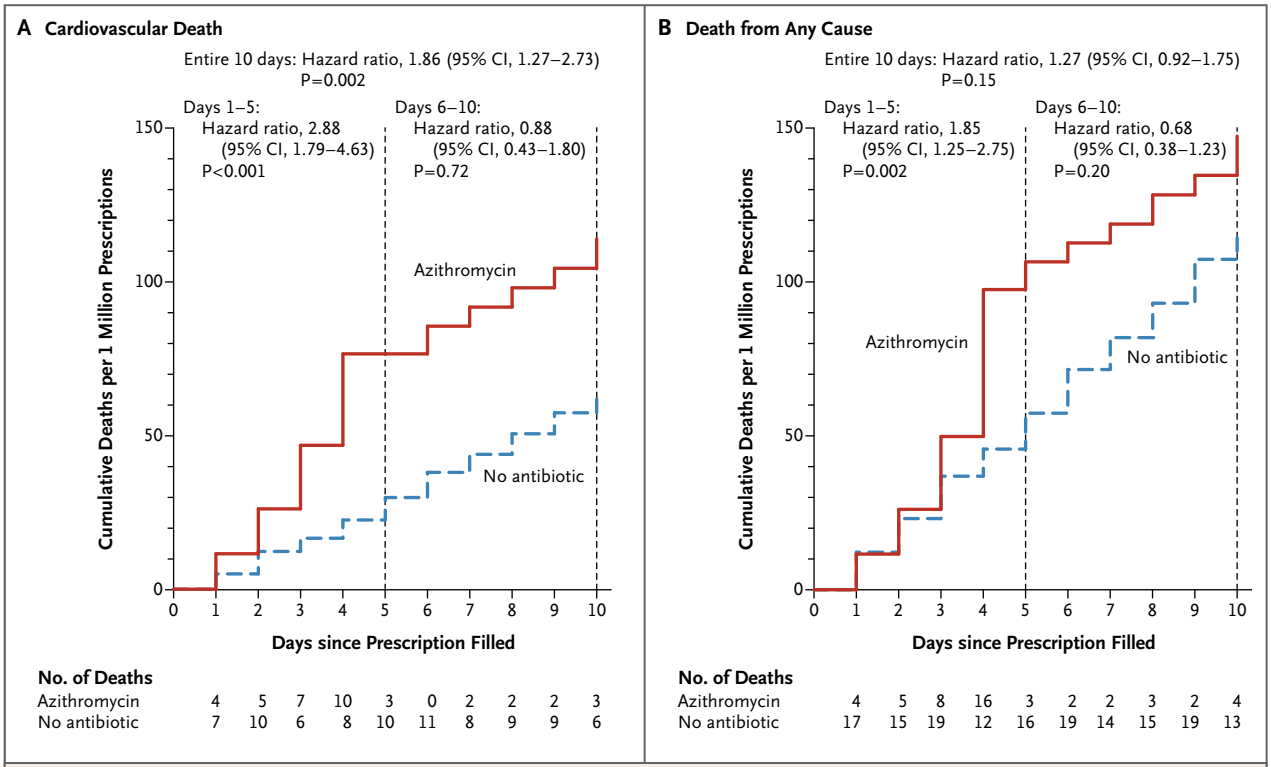

Figure 1. Cumulative Incidence of Cardiovascular Death and Death from Any Cause among Patients Who Took Azithromycin and Persons Who Did Not Take Study Antibiotics during a 10-Day Period.

The 10-day period began with the date on which the prescription was filled for patients who took azithromycin, with a matched period for persons who did not take study antibiotics (the reference group). The cumulative incidence in the reference group was not adjusted; the cumulative incidence in the group of patients who took azithromycin was adjusted for demographic factors and propensity score by multiplying the unadjusted incidence by the ratio of the adjusted to the unadjusted hazard ratio for the 10-day period.

for which an indication was known (43% and 40% of total prescriptions) (Tables 8 and 9 in the Supplementary Appendix). The most frequent indication for ciprofloxacin was infection of the genitourinary tract. Levofloxacin was commonly prescribed for infections of the ear, nose, or throat and for other respiratory and for genitourinary indications.

CARDIOVASCULAR DEATH AND TOTAL DEATHS

Among patients who took azithromycin, there were 29 cardiovascular deaths during the 5-day course of treatment (85.2 per 1 million courses) (Table 2). Of these, 22 (64.6 per 1 million courses) were sudden cardiac deaths. During matched 5-day intervals among persons who did not take antibiotics, there were 41 cardiovascular deaths (29.8 per 1 million periods) and 33 sudden cardiac deaths (24.0 per 1 million periods). During the first 5 days of a course of amoxicillin therapy, there were 42 cardiovascular deaths (31.5 per 1 million courses) and 29 sudden cardiac deaths (21.8 per 1 million courses).

When a 5-day course of azithromycin therapy was compared with a matched period of no antibiotic treatment, azithromycin was associated with an increased risk of both cardiovascular death and death from any cause during that 5-day interval (Fig. 1 and Table 2). For cardiovascular death, the hazard ratio was 2.88 (95% confidence interval [CI], 1.79 to 4.63; P<0.001); the risk was increased for both sudden cardiac death and other cardiovascular deaths. Although there was no increased risk of death from noncardiovascular causes, the risk of death from any cause was increased (hazard ratio, 1.85; 95% CI, 1.25 to 2.75; P=0.002). For the 10-day period after the prescription was filled, azithromycin use was associated with an increased risk of cardiovascular death (hazard ratio, 1.86; 95% CI, 1.27 to 2.73; P=0.002), but the risk of death from any cause was not significantly increased

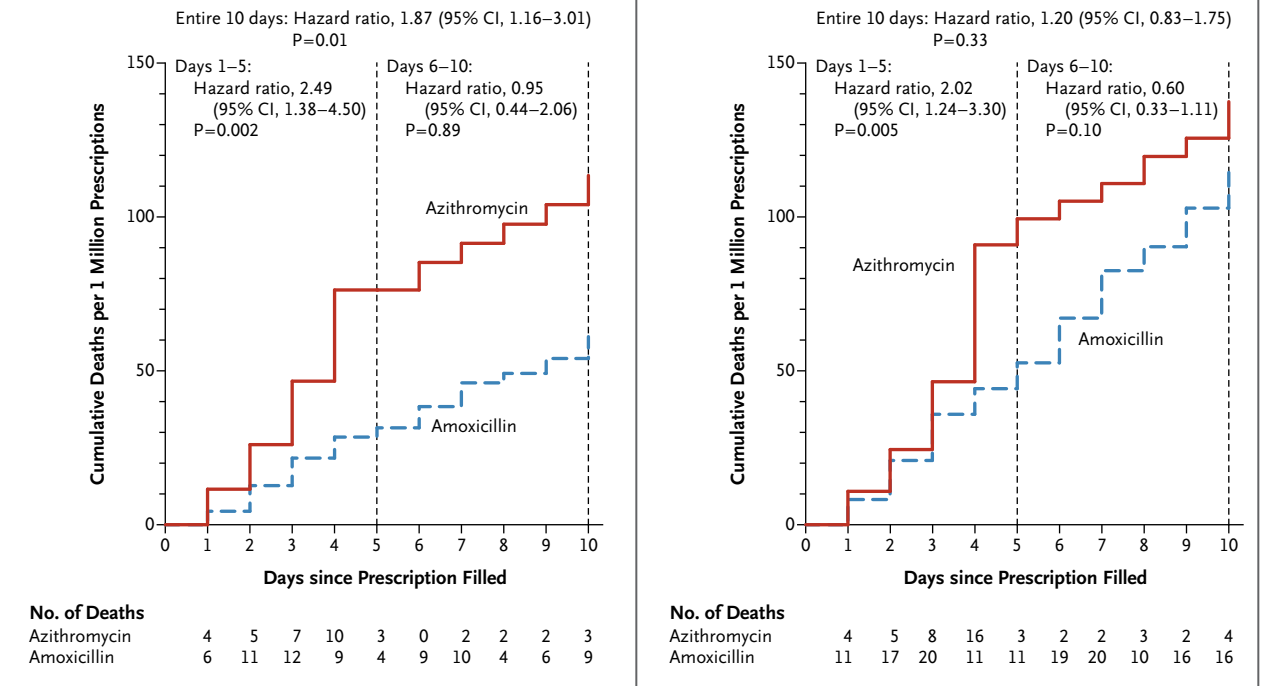

Figure 2. Cumulative Incidence of Cardiovascular Death and Death from Any Cause for Patients Who Took Azithromycin or Amoxicillin during a 10-Day Period.

The 10-day period began with the date on which the prescription was filled. The cumulative incidence for patients who took amoxicillin (the reference group) was not adjusted; the cumulative incidence for patients who took azithromycin was adjusted for demographic factors and propensity score by multiplying the unadjusted incidence by the ratio of adjusted to unadjusted hazard ratios for the 10-day period.

(hazard ratio, 1.27; 95% CI, 0.92 to 1.75; P=0.20). In contrast, amoxicillin use was not associated with a significantly increased risk of death from cardiovascular or noncardiovascular causes or of death from any cause during either the first 5 or all 10 days of therapy (Table 2, and Fig. 1 in the Supplementary Appendix).

A 5-day course of azithromycin therapy, as compared with the first 5 days of a course of amoxicillin therapy, was associated with significant increases in the risk of both cardiovascular death (hazard ratio, 2.49; 95% CI, 1.38 to 4.50; P=0.002) and death from any cause (hazard ratio, 2.02; 95% CI, 1.24 to 3.30; P=0.005) (Fig. 2, and Table 10 in the Supplementary Appendix). Thus, patients who took azithromycin had an estimated 47 additional cardiovascular deaths per 1 million 5-day courses of therapy. Alternative analyses, including a repeated-measures analysis, an analysis stratified by propensity score, and an analysis with a model that included terms for other proarrhythmic drugs, had similar results (Table 11 in the Supplementary Appendix). The risk of cardiovascular death was significantly higher for a 10-day period (hazard ratio, 1.87; 95% CI, 1.16 to 3.01; P=0.01) (Fig. 2), although the risk was not increased for days 6 through 10. The risk of death from any cause was not significantly increased during the 10-day period.

As compared with patients who took amoxicillin, those who took ciprofloxacin did not have an increased risk of either cardiovascular death or death from any cause during a 10-day course of therapy, whereas there was a nonsignificant trend toward an increased risk of cardiovascular death with the use of levofloxacin (hazard ratio, 1.50; 95% CI, 0.82 to 2.72; P=0.18) (Fig. 2 in the Supplementary Appendix). A 5-day course of azithromycin therapy, as compared with the first 5 days of a course of ciprofloxacin therapy, was associated with an increased risk of cardiovascular death (hazard ratio, 3.49; 95% CI, 1.32 to 9.26; P=0.01) and a nonsignificant trend toward an increase in death from any cause (hazard ratio, 1.75; 95% CI, 0.91 to 3.37; P=0.09). However, mortality with azithromycin did not differ signifi-

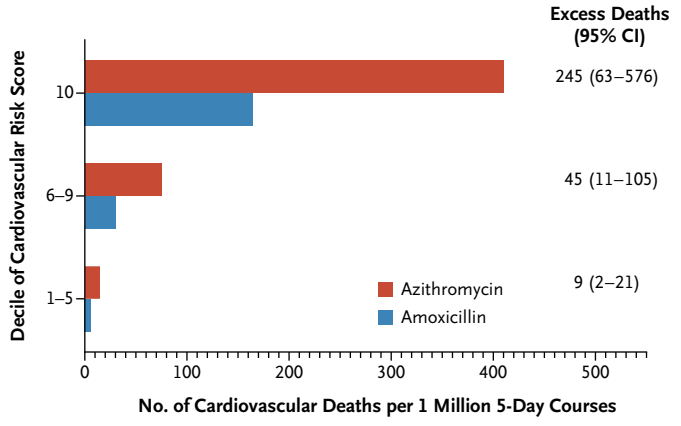

Figure 3. Excess Risk of Cardiovascular Death with Azithromycin as Compared with Amoxicillin, According to Decile of Cardiovascular Risk Score.

The analysis of excess risk was adjusted for demographic factors and propensity score, which included the recorded antibiotic indication. The excess risk of cardiovascular death with azithromycin (i.e., the difference in the cumulative incidence of cardiovascular death with azithromycin and with amoxicillin) is shown, with the 95% confidence interval (CI), according to the risk-score decile. The characteristics of the patients who took azithromycin, according to decile of risk score for cardiovascular disease, are shown in Table 12 in the Supplementary Appendix.

cantly from that with levofloxacin (hazard ratio for cardiovascular death, 1.27; 95% CI, 0.66 to 2.47; P=0.48; hazard ratio for death from any cause, 1.07; 95% CI, 0.61 to 1.85; P=0.82).

The absolute excess risk of cardiovascular death for patients who took azithromycin, as compared with those who took amoxicillin, varied according to the baseline risk score for cardiovascular disease (Fig. 3, and Table 12 in the Supplementary Appendix). For patients in the highest decile of risk scores, who accounted for 59% of the cardiovascular deaths during azithromycin therapy, there were an estimated 245 additional cardiovascular deaths per 1 million 5-day courses of azithromycin therapy.

DISCUSSION

We found that a 5-day course of azithromycin was associated with a small absolute increase in the risk of cardiovascular death, which was most pronounced for patients in the highest decile of the baseline risk of cardiovascular disease. There was no increased risk of death from noncardiovascular causes among patients who took azithromycin, but there was an increase in the risk of death from any cause. The risk of cardiovascular death was significantly greater with azithromycin than with either amoxicillin or ciprofloxacin but did not differ significantly from the risk with levofloxacin.

An important concern in this observational study was confounding by factors associated with both azithromycin use and an increased risk of cardiovascular death. These factors include cardiovascular disease and other coexisting conditions, behavioral risk factors associated with cardiovascular disease (e.g., smoking, high body-mass index, poor diet, and low physical activity), and indication for antibiotic therapy.

We included two distinct control groups in an effort to minimize confounding. One group comprised control periods that were propensity-score–matched with courses of azithromycin therapy. This balanced the prevalence of recorded cardiovascular disease and other coexisting conditions and probably provided some control for behavioral risk factors, given that their effects may be partially mediated through variables more readily identified in the database, such as diagnosed hyperlipidemia, hypertension, diabetes, heart failure, angina, or myocardial infarction. To minimize confounding by the short-term effects of infections, we included a second control group that comprised courses of amoxicillin therapy, which has indications similar to those for azithromycin. Patients who took amoxicillin had no increase in the risk of either cardiovascular death or death from any cause during the study period, which is consistent with our previous findings.[8] When azithromycin was directly compared with amoxicillin, in an analysis that also controlled for recorded antibiotic indication, the increased risk persisted for azithromycin.

Our study was prompted by evidence that azithromycin is proarrhythmic,[11-17] which led us to hypothesize that it would increase the risk of sudden cardiac death. Patients who took azithromycin did have an increased risk of sudden cardiac death, as identified from a previously developed computer definition.[26] However, they also had a similarly increased risk of other, out-of-hospital cardiovascular deaths, although the numbers of these deaths were small. This finding could be due to misclassification, given that our definition of sudden cardiac death was designed to be specific; our prior study suggested that as many as 25% of patients would be misclassified as having died from other cardiovascular causes.[26] Alterna-

tively, a proarrhythmic effect of azithromycin might increase the risk of other types of cardiovascular death. Thus, although our data are consistent with an adverse cardiac effect of azithromycin, they cannot establish a specific causal mechanism.

The increased risk of cardiovascular death during the usual 5-day course of azithromycin therapy did not persist after the course of therapy ended. Although concentrations of azithromycin remain elevated in tissue for several days after cessation of oral therapy, serum concentrations decline more rapidly, falling to trough levels within 24 hours.[31] For many other drugs with proarrhythmic effects, an elevated serum concentration is a key determinant of increased risk,[32] which is an important reason why rapid infusion of erythromycin is not recommended.[25]

The cohort also included patients who had taken ciprofloxacin and levofloxacin, which provided information on the relative safety of these broad-spectrum fluoroquinolones. For ciprofloxacin, the risks of both cardiovascular death and death from any cause during the study period were similar to those for amoxicillin, a finding that is consistent with the current opinion that ciprofloxacin has limited proarrhythmic liability.[1,25] In contrast, levofloxacin, which has recognized proarrhythmic potential,[1,25] was associated with a trend toward an increased risk of cardiovascular death, although the point estimates were not significant. When azithromycin was compared directly with levofloxacin, there was no significant difference in the risk of either cardiovascular death or death from any cause.

In conclusion, during 5 days of azithromycin therapy, there was a small absolute increase in cardiovascular deaths. As compared with amoxicillin, there were 47 additional cardiovascular deaths per 1 million courses of azithromycin therapy; for patients in the highest decile of baseline risk of cardiovascular disease, there were 245 additional cardiovascular deaths per 1 million courses.

Supported by a grant from the National Heart, Lung, and Blood Institute (HL081707) and a cooperative agreement from the Agency for Healthcare Quality and Research Centers for Education and Research on Therapeutics (HS1-0384).

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the Tennessee Bureau of TennCare and Department of Health for providing the study data.

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failure who do not have an indication for aspirin (e.g., secondary prevention of atherosclerotic disease).[1,2] In the WARCEF trial, only 42% of patients had ischemic cardiomyopathy, and 48% of patients had a history of myocardial infarction. Thus, the majority of patients did not have an indication for aspirin therapy. Further clarity is needed as to whether patients with heart failure without another indication for antiplatelet therapy would benefit from aspirin.

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DOI: 10.1056/NEJMc1207385

THE AUTHORS REPLY: We agree with Shah and colleagues that it is important to identify subgroups that may benefit from one of the treatments being studied, particularly if such groups can be easily identified in clinical practice and constitute a substantial portion of the patients with heart failure. We are in the process of conducting analyses toward this end with respect to the primary outcome and its components, and hope that the results may help to individualize treatment, subject to the recognized limitations of subgroup analyses.[1] The dose of aspirin is also an important issue. We used the dose selected in atrial fibrillation trials and the Warfarin–Aspirin Recurrent Stroke Study.[2,3] However, we agree that a lower aspirin dose or the systematic use of gastroprotective agents may reduce gastrointestinal hemorrhage.

Regarding the comments from Chua and colleagues: the guidelines in place before the WARCEF trial began the recruitment process in 2002 did not provide specific recommendations on the use of aspirin to reduce thromboembolic events or the risk of death in patients with nonischemic heart failure in sinus rhythm. Guidelines discouraging aspirin use were mainly driven by a concern that aspirin might attenuate the effect of angiotensin-converting–enzyme inhibitors without proven beneficial effect, leading to worsening heart failure. Of note is the finding in WARCEF that the overall rate of hospitalization for heart failure was similar for the warfarin and aspirin groups. We are in the process of exploring whether there is a difference in the safety and effectiveness of aspirin and warfarin in patients with and without ischemic cardiomyopathy.

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Since publication of their article, the authors report no further potential conflict of interest.

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DOI: 10.1056/NEJMc1207385

Azithromycin and the Risk of Cardiovascular Death

TO THE EDITOR: Ray et al. (May 17 issue)[1] report findings from an observational retrospective study that must be placed into context with other available data. Two large, randomized, placebo-controlled trials involving 11,759 patients with stable coronary artery disease showed no increase in mortality with 600 mg of weekly azithromycin therapy for 3 or 12 months.[2,3] Azithromycin is a weak hERG (human ether-a-go-go–related gene) inhibitor, and, in several studies in animals, it lacked proarrhythmic activity above therapeutic concentrations.[4,5] No significant QT-interval pro-

longation was observed in clinical studies of various doses of intravenous azithromycin leading to drug plasma levels that were 10 times as high as those of approved oral-dosage forms.[6]

Aside from these reliable data from randomized, controlled trials, and although analyses of retrospective database studies provide insights, the interpretation of these results requires caution because of the potential for residual confounding, particularly according to indication. Ultimately, benefit–risk assessments of a medicine must consider the hierarchy of evidence from diverse sources of information. Standards for interpreting results of observational studies should require integration of the totality of data from predictive in vitro assays, animal models, and randomized, controlled trials.

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Drs. Knirsch and Chandra report being employees of Pfizer and having equity interest in the company. No other potential conflict of interest relevant to this letter was reported.

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DOI: 10.1056/NEJMc1207269

TO THE EDITOR: In a large, observational study, Ray and colleagues report that azithromycin increased the risk of cardiovascular death. In a recent randomized, placebo-controlled trial involving 1142 patients with chronic obstructive pulmonary disease (COPD), we found that daily azithromycin for 1 year reduced the risk of acute exacerbations of COPD.[1] We did not observe prolonged corrected QT (QTc), increases in death, or adverse cardiac events (Table 1). We excluded 6% of candidates at screening for having a QTc interval of more than 450 msec, taking medications that prolong the QTc interval, or having a resting heart rate of more than 100 beats per minute, a history of congestive heart failure, hypokalemia, or a family history of a prolonged QTc interval. Ten patients were withdrawn (6 receiving azithromycin and 4 receiving placebo) because their QTc interval exceeded 450 msec 1 month after randomization.

Table 1. Rates of Serious Adverse Events, According to Study Group.*

Event	Azithromycin (N=558)	Placebo (N=559)
	no. (%)	
Nonfatal		
QTc prolongation	1 (0.2)	2 (0.4)
Other cardiovascular event	29 (5.2)	33 (5.9)
Fatal		
Cardiovascular	1 (0.2)	1 (0.2)
Other	18 (3.2)	20 (3.6)

* QTc denotes corrected QT interval.

Given the inherent weaknesses of observational studies,[2-4] the excess deaths reported by Ray and colleagues may or may not have been due to azithromycin. Our randomized trial, however, indicated that long-term use of azithromycin had benefits that outweighed potential cardiovascular risks when patients at greatest risk were excluded and the QTc interval was monitored.

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DOI: 10.1056/NEJMc1207269

TO THE EDITOR: As a pediatric specialist who prescribes the antibiotics described in the article by Ray et al., I was interested in the study methods and conclusions. The authors were careful in accounting for confounding variables and propensities in selecting and analyzing the control group (persons who took no antibiotics). However, they did not use the same approach for comparing azithromycin with the other antibiotics. For example, Table 1 of their article shows that the azithromycin group seemed at higher risk than the amoxicillin group in general, given that they were "worse" in 18 of 22 characteristics (excluding sex and the number of prescriptions). The different use of statins and beta-agonists seems remarkable in the azithromycin group as compared with the amoxicillin group. Despite the nearly equal mean summary score for the risk of cardiovascular disease, might the conclusions be explained on that basis?

The other astounding finding seems to be the cumulative incidence of death in the study population, even in the control group of persons who were not taking antibiotics. Was that finding as expected, or does it reflect demographic characteristics and issues related to access to care?

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No potential conflict of interest relevant to this letter was reported.

DOI: 10.1056/NEJMc1207269

TO THE EDITOR: The increased risk of cardiovascular death with the use of azithromycin reported by Ray et al. appears to arouse a considerable concern about the use of this commonly prescribed antibiotic. However, it is important to evaluate carefully the question of whether this association is causal.

Although the study weighed several confounding factors, it is still likely that the increase in cardiovascular death is related to patient characteristics that were not assessed in the analysis. The condition for which antibiotics are prescribed is a possible contributor to an increased risk of cardiac death. For instance, *Chlamydophila pneumoniae*, a common pathogen of the upper and lower respiratory tracts,[1] can be associated with an increased risk of sudden cardiac death.[2] Macrolides such as azithromycin may be preferentially prescribed for *C. pneumoniae* infections. Similarly, macrolides are likely to be prescribed for influenza,[3] which may increase the risk of sudden cardiac death.[3] More information about the patients would be needed to clarify the causal association between the drug and the increased risk of sudden cardiac death.

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DOI: 10.1056/NEJMc1207269

TO THE EDITOR: Ray et al. found a small absolute increase in cardiovascular deaths with azithromycin use. More than 1 million of the patients in the study received antimicrobial agents to treat ear, nose, or throat infections or bronchitis (see Table 8 in the Supplementary Appendix, available with the full text of the article by Ray et al. at NEJM.org). There are substantial data showing that the benefit of using antimicrobial agents for treating acute sinusitis,[1,2] otitis media,[3] and bronchitis[4] is small or questionable. A recent trial showed that amoxicillin was not superior to placebo for uncomplicated acute sinusitis in adults.[2]

Assuming that the 214,589 patients in the study by Ray et al. who took azithromycin for ear, nose, or throat infections or bronchitis may not have had an unquestionable indication for antibiotic use, one could estimate that it may have been possible to prevent nine cardiovascular deaths due to inappropriate azithromycin use

by administering no antibiotics at all. Clinicians need to weigh the aforementioned small benefits of the use of antimicrobial agents against the potential adverse effects in individual patients and in the general population.

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DOI: 10.1056/NEJMc1207269

THE AUTHORS REPLY: Knirsch and Chandra cite findings from two animal models as evidence that azithromycin is not proarrhythmic. The uncertain predictive validity of these models is apparent in the study of chronic atrioventricular block in dogs, which showed "no proarrhythmic properties" for moxifloxacin, which is recognized as a cause of torsades de pointes.[1] The current azithromycin label does not include the specific human QT data they reference. The label for azithromycin extended-release oral suspension was modified in March 2012 to reinforce warnings regarding QT-interval prolongation and torsades de pointes.[2] Data are lacking on the mechanisms underlying adverse cardiovascular effects associated with azithromycin.

Knirsch and Chandra and Albert and colleagues emphasize that trials of azithromycin in secondary prevention of cardiovascular disease and COPD showed no excess of cardiovascular deaths. However, in these trials, there was considerably less current azithromycin use (the most relevant exposure) than in our study. The trials involving patients with cardiovascular disease had an estimated 454 person-years of current use and the trial involving patients with COPD had 501 person-years, a total of one fifth of the 4764 person-years in our study. Furthermore, the trial involving patients with COPD carefully excluded patients who were potentially susceptible to a proarrhythmic effect of azithromycin.

Louie notes that the amoxicillin group in our study, unlike the control group of persons who were not taking antibiotics, was not matched to the azithromycin group, and he wonders how this affected the study findings. Because matching would have substantially decreased the sample size and thus the statistical power, the study included all available amoxicillin prescriptions. Differences in baseline characteristics were controlled for in the statistical analysis by both inclusion of the propensity score in regression models and by stratification according to the propensity score.

Koga and Imaoka suggest that our findings might be explained by confounding by indication. They refer to a series of 16 sudden cardiac deaths in elite athletes undergoing strenuous training, some of which were possibly related to *C. pneumoniae* myocarditis, as well as to an ecologic study reporting a seasonal correlation between the prescription of macrolides and cases of influenza. These data have limited relevance to our study, which involved patients 30 to 74 years of age. Azithromycin use in this population primarily was for minor ear, nose, or throat infections and for respiratory infections. The recorded indications were similar to those for amoxicillin, and this variable was controlled for in the statistical analysis.

We strongly concur with Pires dos Santos and Kuchenbecker that our findings reinforce the need to prescribe antimicrobial agents only when there is good evidence that the benefits outweigh the risks. For azithromycin, our data indicate there should be more careful attention to the baseline cardiovascular risk.

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Since publication of their article, the authors report no further potential conflict of interest.

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DOI: 10.1056/NEJMc1207269

Lack of Association between Azithromycin and Death from Cardiovascular Causes

TO THE EDITOR: Azithromycin (at a single dose of 1 g) is one of two therapies recommended by the Centers for Disease Control and Prevention (CDC) for the treatment of chlamydia, and it is part of the regimen recommended by the CDC for the treatment of gonorrhea.[1] Recently, Ray and colleagues[2] reported an increased risk of death from cardiovascular causes associated with a 5-day course of azithromycin. This finding was not confirmed in a subsequent Danish study.[3] Data are lacking on the use of azithromycin and the risk of death from cardiovascular causes among patients with sexually transmitted diseases (STDs).

We studied data from the Oregon Public Health Division on cases of chlamydia and gonorrhea in patients who received treatment between 1996 and 2012 and data from Public Health–Seattle and King County on cases of these infections in patients who received treatment between 1993 and 2010. We matched case-report data to death-record data (using Registry Plus Link Plus software[4]) to determine how many of these patients died within 10 days after treatment.

Cases of gonorrhea, chlamydia, or both in 269,179 patients were reported during the study period; complete treatment information was available for 260,048 of these patients (97%). Among the patients for whom data were available, 162,385 (62%) received azithromycin; among the 97,663 who did not receive azithromycin, the majority (77%) received a tetracycline. The mean age of the patients was 24 years, 65% were female, and 84% had chlamydia. We identified no deaths from cardiovascular causes among patients treated with azithromycin or another drug (Table 1). Five deaths that were not from cardiovascular causes were classified as being due to suicide (2 patients), homicide (1 patient), drug overdose (1 patient), and rectal cancer (1 patient).

Our findings are consistent with those of the study by Svanström et al.[3] that examined the association between azithromycin and the risk of death from cardiovascular causes among Danish adults between 18 to 64 years of age who had a low baseline risk of cardiovascular disease, but they differ from the findings in the study by Ray and colleagues, which included a substantially older population (patients who were 30 to 74 years of age) than patients who are typically treated for an STD (patients between the ages of 15 and 25 years).[2] Of note, Ray observed only one death in 144,165 persons in the lowest four deciles of risk scores for cardiovascular disease (Ray W: personal communication). At that low level of risk (seven deaths per 1 million 5-day courses), we would expect only one death from cardiovascular causes associated with azithromycin use in our study population, and our study would have to involve more than 1 million persons to define the upper limit of the 95% confidence interval as being less than seven deaths per 1 million doses.

Our findings should be reassuring to health care providers who prescribe azithromycin to treat gonorrhea and chlamydia, and they support the conclusion of the CDC that research related

Table 1. Cumulative Incidence of Death among 260,048 Patients with Chlamydia, Gonorrhea, or Both, According to Prescribed Treatment (Oregon, 1996–2012, and King County, Washington, 1993–2010).*

Deaths	Azithromycin (N = 162,385)	Other Drug (N = 97,663)	Relative Risk (95% CI)†
Cardiovascular cause			
No. of deaths	0	0	Not determined
No. of deaths per 1 million doses (95% CI)	0 (0–18.5)	0 (0–30.7)	
Other cause			
No. of deaths	3	2	0.90 (0.15–5.40)
No. of deaths per 1 million doses (95% CI)	18.5 (3.8–54.0)	20.5 (2.5–74.0)	

* CI denotes confidence interval.
† The group of patients who received other treatment was the reference group.

to possible cardiac toxicity associated with azithromycin should not lead to a change in current treatment guidelines for STDs.[5]

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Supported by grants from Public Health–Seattle and King County, the Oregon Public Health Division, and the National Institutes of Health (K23MH090923, to Dr. Dombrowski; and T32 AI07140, to Dr. Khosropour).

Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

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DOI: 10.1056/NEJMc1401831

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CORRECTION

Case 8-2014: A 29-Year-Old Man with Headache, Vomiting, and Diplopia (March 13, 2014;370:1049-59). In the Pathological Discussion (page 1055), the second sentence should have begun, "The diagnostic procedure on the second admission was a left frontal craniotomy . . . ," rather than ". . . a right frontal craniotomy . . . ." The article is correct at NEJM.org.

NOTICES

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The workshops, available at introductory, intermediate, and advanced levels, will be offered in Minneapolis, Sept. 11–13. They are presented by the National Pediatric Hypnosis Training Institute and co-sponsored by the University of Minnesota Department of Pediatrics and the Minnesota Society of Clinical Hypnosis.

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