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Perspective

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Cardiovascular Risks with Azithromycin and Other Antibacterial Drugs

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Related article, p. 1704

In 2011, approximately 40.3 million people in the United States (roughly one eighth of the population) received an outpatient prescription for the macrolide azithromycin, according to IMS Health.

During that year, we at the Food and Drug Administration (FDA) reviewed the labels of azithromycin and other approved macrolide antibacterials in view of cardiovascular risks that had become evident from published studies and reports emerging through postmarketing surveillance. On the basis of its review, the FDA approved revisions to azithromycin product labels regarding risks of QT-interval prolongation and the associated ventricular arrhythmia torsades de pointes. The revised labels advise against using azithromycin in patients with known risk factors such as QT-interval prolongation, hypokalemia, hypomagnesemia, bradycardia, or use of certain antiarrhythmic agents, including class IA (e.g., quinidine and procainamide) and class III (e.g., dofetilide, amiodarone, and sotalol) — drugs that can prolong the QT interval. In March 2013, the FDA announced that azithromycin labels had been further revised to reflect the results of a clinical study showing that azithromycin can prolong the corrected QT interval.

In a 2012 observational study involving Tennessee Medicaid patients, Ray et al.[1] quantified the risk of death from cardiovascular causes associated with azithromycin as compared with other antibacterial drugs or nonuse. The study showed that the risks of death, both from any cause and from cardiovascular causes, associated with azithromycin were greater than those associated with amoxicillin. For every 21,000 outpatient prescriptions written for azithromycin, one cardiovascular death occurred in excess of those observed with the same number of amoxicillin prescriptions. The excess risk over amoxicillin varied considerably according to cardiovascular risk factors; the researchers estimated that there was one excess cardiovascular death per 4100 prescriptions among patients at high cardiovascular risk but less than one per 100,000 among patients with lower cardiovascular risk.

Agents Associated with Drug-Use Mentions for Chronic Sinusitis and Bronchitis, According to U.S. Office-Based Physician Practices (January 2002–December 2011).*

Medical Condition and Drug	No. of Drug-Use Mentions	Percent of Total Drug-Use Mentions
Chronic sinusitis		
Any drug	206,369,000	100.0
Amoxicillin	50,350,000	24.4
Azithromycin	34,077,000	16.5
Amoxicillin–clavulanate	33,233,000	16.1
Cefdinir	13,124,000	6.4
Clarithromycin	13,027,000	6.3
Moxifloxacin	10,691,000	5.2
Levofloxacin	9,821,000	4.8
Cefuroxime	5,650,000	2.7
Cephalexin	5,454,000	2.6
Trimethoprim–sulfamethoxazole	5,390,000	2.6
All others	25,552,000	12.4
Bronchitis		
Any drug	171,791,000	100.0
Azithromycin	69,790,000	40.6
Amoxicillin	17,934,000	10.4
Clarithromycin	17,413,000	10.1
Levofloxacin	12,167,000	7.1
Moxifloxacin	8,598,000	5.0
Doxycycline	7,693,000	4.5
Amoxicillin–clavulanate	7,361,000	4.3
Cephalexin	5,357,000	3.1
Cefdinir	3,784,000	2.2
Erythromycin	2,965,000	1.7
All others	18,729,000	10.9

* The term "drug-use mentions" refers to the mentioning of a drug by a clinician in association with a diagnosis during an office-based patient visit, as recorded by Encuity Research. It is important to note that a drug-use mention does not necessarily result in the generation of a prescription. Rather, the term indicates that a listed drug was mentioned during an office visit.

The study by Ray et al. has limitations that are intrinsic to observational, nonrandomized clinical studies. In particular, nonrandomized studies cannot exclude the possibility that patients receiving a drug under evaluation differ from control patients in some important but undetected way, causing bias in the results. Such confounding may bias comparisons not only between patients receiving antibacterial drugs and those receiving no antibacterials but also between patients receiving different antibacterials. Although Ray et al. used appropriate analytic methods to address potential confounding, we cannot know for certain whether these methods were fully successful. Replication of the authors' results, through analysis of a distinct data set, would provide more confidence in the finding of increased cardiovascular mortality among patients receiving azithromycin.

Despite such caveats, the results presented by Ray et al. warrant serious attention. A chief strength of the results is the time-limited pattern of the risk: the azithromycin-associated increase in the rates of death from any cause and from cardiovascular causes spanned days 1 through 5, reflecting the typical 5-day duration of azithromycin administration (e.g., Zithromax Z-Pak). On days 6 through 10, an elevated risk of death from cardiovascular causes was no longer detected. This pattern is consistent with the timing of peak plasma azithromycin concentrations and the concomitant risk of QT-interval prolongation. The elevated risk was statistically significant, regardless of whether azithromycin treatment was compared with amoxicillin or with nonuse of an antibacterial drug. Furthermore, the observed excess mortality was attributable solely to cardiovascular deaths and, in particular, to sudden cardiac death; although sudden cardiac death can result from causes other than arrhythmias, an increase in deaths in this category would be the pattern expected from an arrhythmogenic, QT-interval–prolonging drug. Also, the azithromycin-associated risk was higher among patients with cardiovascular disorders, which is consistent with a drug-related arrhythmia.

A new study by Svanström and colleagues (pages 1704–1712), using Danish national health care data, found no difference between

azithromycin and penicillin V in the 5-day risk of cardiovascular death (relative risk, 0.93; 95% confidence interval [CI], 0.56 to 1.55). However, the upper bound of the 95% confidence interval does not exclude an increased risk of as much as 55%. As Svanström et al. point out, the population they studied differed from that studied by Ray et al. with respect to the baseline risk of death and cardiovascular risk factors. Overall, the Danish patients had better cardiovascular health than the Tennessee Medicaid patients. In a subgroup analysis of patients with a history of cardiovascular disease, the risk ratio for azithromycin versus penicillin V was greater than 1, though the difference was not statistically significant (relative risk, 1.35; 95% CI, 0.69 to 2.64). Svanström et al. conclude that their results do not conflict with those of Ray et al. Rather, the effect on cardiovascular mortality may be limited to patients with cardiovascular disease.

One must, of course, weigh any observed drug-associated risk against clinical benefits, so it's appropriate to consider the possibility that certain offsetting benefits of azithromycin may not have been reflected in the risk data analyzed by Ray et al. For example, other studies have suggested that macrolides have an advantage over other antibacterial agents in terms of overall survival from community-acquired pneumonia. In a recent Canadian observational study, researchers followed 2973 outpatients with community-acquired pneumonia and found significantly lower 30-day mortality among patients receiving macrolides than among those receiving fluoroquinolones (adjusted odds ratio, 0.28; 95% CI, 0.09 to 0.86).[2] A recent meta-analysis of observational studies showed a statistically significant 25% difference in mortality among hospitalized patients with community-acquired pneumonia favoring macrolides over non-macrolide antibacterials.[3] Such findings, which must be considered with due regard for the limits of observational studies, do not necessarily contradict the results of Ray et al. Past the 5-day period of risk of azithromycin-associated cardiovascular death, the drug might reduce the longer-term (e.g., more-than-30-day) rate of death due to pneumonia. Pneumonia was an uncommon indication among the Tennessee Medicaid patients treated with azithromycin.

Clinicians must consider the arrhythmogenic potential not only of azithromycin but also of potential alternative antibacterial drugs. An earlier study showed an association between the use of erythromycin and sudden cardiac death, augmented by concomitant use of inhibitors of the cytochrome P-450 3A isozymes that metabolize erythromycin.[4] Labels for erythromycin and clarithromycin include warnings regarding QT-interval prolongation and arrhythmias. All labels for fluoroquinolone products similarly have warnings regarding QT-interval prolongation, and grepafloxacin was withdrawn from the market because of that risk. A recent observational study of elderly residents of Quebec, Canada, showed an association between outpatient fluoroquinolone use and serious arrhythmias (as defined by hospital discharge diagnoses of ventricular arrhythmia or sudden or unattended death).[5] And although Ray et al. found the risk of cardiovascular death to be greater with azithromycin than with ciprofloxacin, they found the risk with levofloxacin similar to that with azithromycin. The authors interpreted this similarity as evidence that levofloxacin may be proarrhythmic; however, levofloxacin was not implicated as proarrhythmic in the Canadian study.

We investigated the most common ambulatory indications for azithromycin by analyzing data from a survey conducted by Encuity Research of approximately 3200 office-based physicians for the decade from 2002 through 2011. Across all age groups of patients, the two most common indications for azithromycin were chronic sinusitis and bronchitis. The table shows the antibacterial drugs that were used most commonly in the United States for these indications. Azithromycin was the leading antibacterial drug for outpatient treatment of bronchitis during this period (even if amoxicillin is combined with amoxicillin–clavulanate). For chronic sinusitis, azithromycin ranked second after amoxicillin. Because the indications are reported by the prescribing physicians, these data don't allow us to assess the diagnostic certainty regarding the infections being treated.

The risks and benefits of antibacterial therapy should be considered in prescribing decisions. Pharmacologic and epidemiologic data point to lethal arrhythmias as a potential consequence of QT-interval prolongation with use of azithromycin, other macrolides, and fluoroquinolones. This possibility should give clinicians pause when they're considering prescribing antibacterial drugs, especially for patients with preexisting cardiovascular risk factors or

clinical conditions in which antibacterial drug therapy has limited benefits.

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

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Discrimination at the Doctor's Office

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Doctors dedicate themselves to helping others. But how selective can they be in deciding whom to help? Recent years have seen some highly publicized examples of doctors who reject patients not because of time constraints or limited expertise but on far more questionable grounds, including the patient's sexual orientation, parents' unwillingness to vaccinate (in surveys, as many as 30% of pediatricians say they have asked families to leave their practice for this reason), and most recently, the patient's weight.

Sometimes these refusals are couched in terms of a physician's conscientious beliefs or appear to be attempts to encourage behavior the physician deems desirable. In other cases, the physician seeks to justify such actions using outwardly neutral terms. For example, the Massachusetts doctor who recently decided to reject all new patients weighing more than 200 lb claimed that she needed to protect her staff from injuries.[1] Similarly, 14% of obstetrics–gynecology practices polled by the *South Florida Sun-Sentinel* in 2011 said they have set weight limits for new patients, citing reasons ranging from lack of specialized equipment to fear of malpractice suits over complications caused by obesity.

Despite the varied rationales, patients who are rejected are likely to feel discriminated against. Unlike physicians who refuse to provide a particular service across the board, so that no patient can argue that he or she has been treated differently from others, the physicians in these instances do treat certain patients differently because of their personal characteristics. Of course, physicians ought to tailor their behavior to patients' characteristics when doing so is medically relevant, but differential treatment based on negative moral judgments about patients should not be tolerated. Indeed, the American Medical Association's Ethical Rule 10.05 permits refusal of services that are beyond the physician's competence, not medically indicated, or "incompatible with the physician's personal, religious, or moral beliefs" but emphasizes that physicians "cannot refuse to care for patients based on race, gender, sexual orientation, gender identity, or any other criteria that would constitute invidious discrimination."

Legal standards largely accord with this formulation, with some additional nuance. Although physicians owe substantial duties to their existing patients, including an obligation to avoid abandonment, initiation of a doctor–patient relationship is voluntary for both parties. There is, however, an important exception: physicians may refuse a prospective patient only for a reason that is not prohibited by contract or law. Local, state, and federal laws prohibit certain types of discrimination against patients. For example, many states prohibit places of "public accommodation," including doctors' offices and hospitals, from discriminating on the basis of characteristics such as race, color, national origin, nationality, ancestry, religion, creed, age, marital status, familial status, sex, sexual orientation, gender identity, medical condition, disability, or other personal features — although, beyond the baseline federal protections, the grounds that are included vary by jurisdiction. Title VI of the federal Civil Rights Act of

ORIGINAL ARTICLE

Use of Azithromycin and Death from Cardiovascular Causes

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ABSTRACT

BACKGROUND

Azithromycin use is associated with an increased risk of death from cardiovascular causes among patients at high baseline risk. Whether azithromycin confers a similar risk in the unselected general population is unknown.

METHODS

We conducted a nationwide historical cohort study involving Danish adults (18 to 64 years of age), linking registry data on filled prescriptions, causes of death, and patient characteristics for the period from 1997 through 2010. We estimated rate ratios for death from cardiovascular causes, comparing 1,102,050 episodes of azithromycin use with no use of antibiotic agents (matched in a 1:1 ratio according to propensity score, for a total of 2,204,100 episodes) and comparing 1,102,419 episodes of azithromycin use with 7,364,292 episodes of penicillin V use (an antibiotic with similar indications; analysis was conducted with adjustment for propensity score).

RESULTS

The risk of death from cardiovascular causes was significantly increased with current use of azithromycin (defined as a 5-day treatment episode), as compared with no use of antibiotics (rate ratio, 2.85; 95% confidence interval [CI], 1.13 to 7.24). The analysis relative to an antibiotic comparator included 17 deaths from cardiovascular causes during current azithromycin use (crude rate, 1.1 per 1000 person-years) and 146 during current penicillin V use (crude rate, 1.5 per 1000 person-years). With adjustment for propensity scores, current azithromycin use was not associated with an increased risk of cardiovascular death, as compared with penicillin V (rate ratio, 0.93; 95% CI, 0.56 to 1.55). The adjusted absolute risk difference for current use of azithromycin, as compared with penicillin V, was –1 cardiovascular death (95% CI, –9 to 11) per 1 million treatment episodes.

CONCLUSIONS

Azithromycin use was not associated with an increased risk of death from cardiovascular causes in a general population of young and middle-aged adults. (Funded by the Danish Medical Research Council.)

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Azithromycin is a macrolide antibiotic agent primarily used for the treatment of lower and upper respiratory infections and some sexually transmitted infections. This commonly used agent is considered to be generally free of serious adverse effects, including cardiac toxicity.[1-5]

A recent observational study, however, showed that use of azithromycin was associated with a risk of death from cardiovascular causes that was 2 to 3 times as high as the risk associated with no use of antibiotics and the risk associated with amoxicillin treatment.[6] Given that certain other macrolides are known to prolong the QT interval and therefore are thought to increase the risk of potentially lethal arrhythmias,[4,7,8] it has been suggested that the increased risk of death from cardiovascular causes may be attributable to a proarrhythmic effect of azithromycin.[6]

The reported association was found in a study involving Medicaid beneficiaries in the United States, a population characterized by a high prevalence of coexisting conditions and high mortality rates.[6,9] Consequently, it is uncertain whether an association between azithromycin use and cardiovascular death can be generalized to populations encountered in routine clinical practice, which have a relatively lower baseline risk of cardiovascular disease than the population of Medicaid beneficiaries in which the reported association was found. We investigated whether azithromycin was associated with an increased risk of death from cardiovascular causes, as compared with no use of antibiotics and with use of penicillin V, in a cohort of young to middle-aged adults in Denmark.

METHODS

STUDY DESIGN

In a prospective study involving a historical cohort of persons using azithromycin during the period from 1997 through 2010, we compared use with no use of antibiotics and with use of penicillin V (by far the most commonly used antibiotic in Scandinavia). The primary outcome was cardiovascular death, and the secondary outcome was death from other causes. Although the hypothesized proarrhythmic effect[6] would primarily suggest a risk of cardiac death, we used the outcome of cardiovascular death to facilitate the comparison of our results with those of the study that showed an increased cardiovascular risk with azithromycin; cardiac death was analyzed in a sensitivity analysis.

We used multiple strategies to minimize confounding and thereby increase the probability of isolating an effect attributable to azithromycin. First, we chose to study a population of young and middle-aged adults because both the baseline risk of death from cardiovascular causes and the indications for azithromycin are heterogeneous across age groups; whereas the risk of death from cardiovascular causes increases with age, the use of azithromycin is relatively uncommon among older persons in Denmark. Second, because a comparison of antibiotic use with nonuse may be susceptible to confounding by indication, azithromycin was also compared with penicillin V, each of which is indicated for upper and lower respiratory tract infections as well as for skin and soft-tissue infections. Azithromycin is also used for chlamydia, mycoplasma, and legionella infections. Third, to account for pretreatment risk factors for death from cardiovascular causes, propensity-score methods were used to incorporate a wide range of potential confounders in all analyses.

The study was approved by the Danish Data Protection Agency. Approval by an ethics committee is not required for registry-based research in Denmark.

DATA SOURCES

The study population was defined with the use of the Danish Civil Registration System[10] and included all persons living in Denmark who were 18 to 64 years of age between 1997 and 2010. Unique personal identifiers were used to link information on prescription-drug use, cause of death, and potential confounders. Data on use of azithromycin and use of penicillin V were obtained from the Danish National Prescription Registry,[11] and data on causes of death were obtained from the Danish Register of Causes of Death.[12] Information on potential baseline confounders and demographic characteristics, history of prescription-drug use, and medical history were obtained from the Civil Registration System,[10] the National Prescription Registry,[11] and the Danish National Patient Register,[13] respectively. Registers, outcome definitions, and

potential confounding variables are described in the Supplementary Appendix, available with the full text of this article at NEJM.org.

STUDY COHORT

The cohort included all persons with episodes of use of oral azithromycin or penicillin V during the study period, and each participant could have multiple prescriptions during the study period. Also included were control episodes of no use of antibiotics (see the Supplementary Appendix). For inclusion, participants were required not to have been hospitalized or to have used any antibiotics within 30 days before the index date. If a person filled prescriptions for more than one antibiotic on the index date, all prescriptions on that date were excluded. To ensure adequate covariate assessment, participants were required to have lived in Denmark for at least 2 years and to have filled at least one prescription within 1 year before the index date.

PROPENSITY-SCORE MODELS

We estimated two separate propensity-score models, one including episodes of use of azithromycin and no use of antibiotics and the other including episodes of use of azithromycin and penicillin V. The individual propensities for starting azithromycin treatment were estimated with the use of logistic regression. As predictors, both propensity-score models included the same set of variables; a list of 61 potential confounders is provided in Table S1 in the Supplementary Appendix.

After propensity-score estimation, episodes of azithromycin use and no antibiotic use were matched according to propensity score in a 1:1 ratio for the analysis of azithromycin versus no use of antibiotics.[14,15] The cohort used in the analysis of azithromycin versus penicillin V included all episodes with the respective drugs, grouped according to propensity-score distribution categorized in quintiles. To assess the robustness of the results, azithromycin was also compared with penicillin V and with amoxicillin in sensitivity analyses that used propensity-score–matched information in a 1:1 ratio.

FOLLOW-UP AND TREATMENT CLASSIFICATION

Follow-up started on the index date and ended on the date of the first instance of one of the following: loss to follow-up (owing to emigration or disappearance), crossover to another antibiotic, hospitalization, end of study (January 1, 2011), day 35 after the start of treatment, or death due to noncardiovascular or cardiovascular causes.

The timing of treatment was classified as follows: current use (1 to 5 days, starting from the index date), recent use (6 to 10 days), and past use (11 to 35 days). This classification allowed us to assess the risk associated with use of azithromycin in time periods incorporating the standard treatment duration of 5 days and up to 30 days after the treatment had ended. An increase in risk that was restricted to periods of current use and that disappeared in periods of past use would reflect an acute toxic mechanism. Conversely, an increase in risk that was also present in periods of past use would reflect another mechanism or suggest unmeasured confounding.

STATISTICAL ANALYSIS

The statistical analyses were performed by means of Poisson regression. Poisson regression is appropriate in studies of rare discrete outcomes in which the risk is assumed to vary over time. P values were based on Wald tests. All statistical tests were two-sided, with P values of less than 0.05 considered to indicate statistical significance. We estimated the adjusted absolute difference in risk per 1 million treatment episodes with azithromycin as the sum of the adjusted rate ratio minus 1, times the crude rate among persons using penicillin V (see the Supplementary Appendix). Analyses were performed with the use of SAS software, version 9.3 (SAS Institute).

RESULTS

COHORT SELECTION

From a source population of 4,732,867 persons, we identified 1,697,710 episodes of azithromycin use and 10,473,102 episodes of penicillin V use during the study period. The study inclusion criteria were met for 1,102,419 episodes of azithromycin use, 7,364,292 episodes of penicillin V use, and 7,084,184 control episodes of no antibiotic use. After propensity-score estimation and matching in a 1:1 ratio, the cohort used in the analysis of azithromycin versus no use of antibiotics included a total of 2,204,100 episodes. The cohort selection is shown in Figure 1.

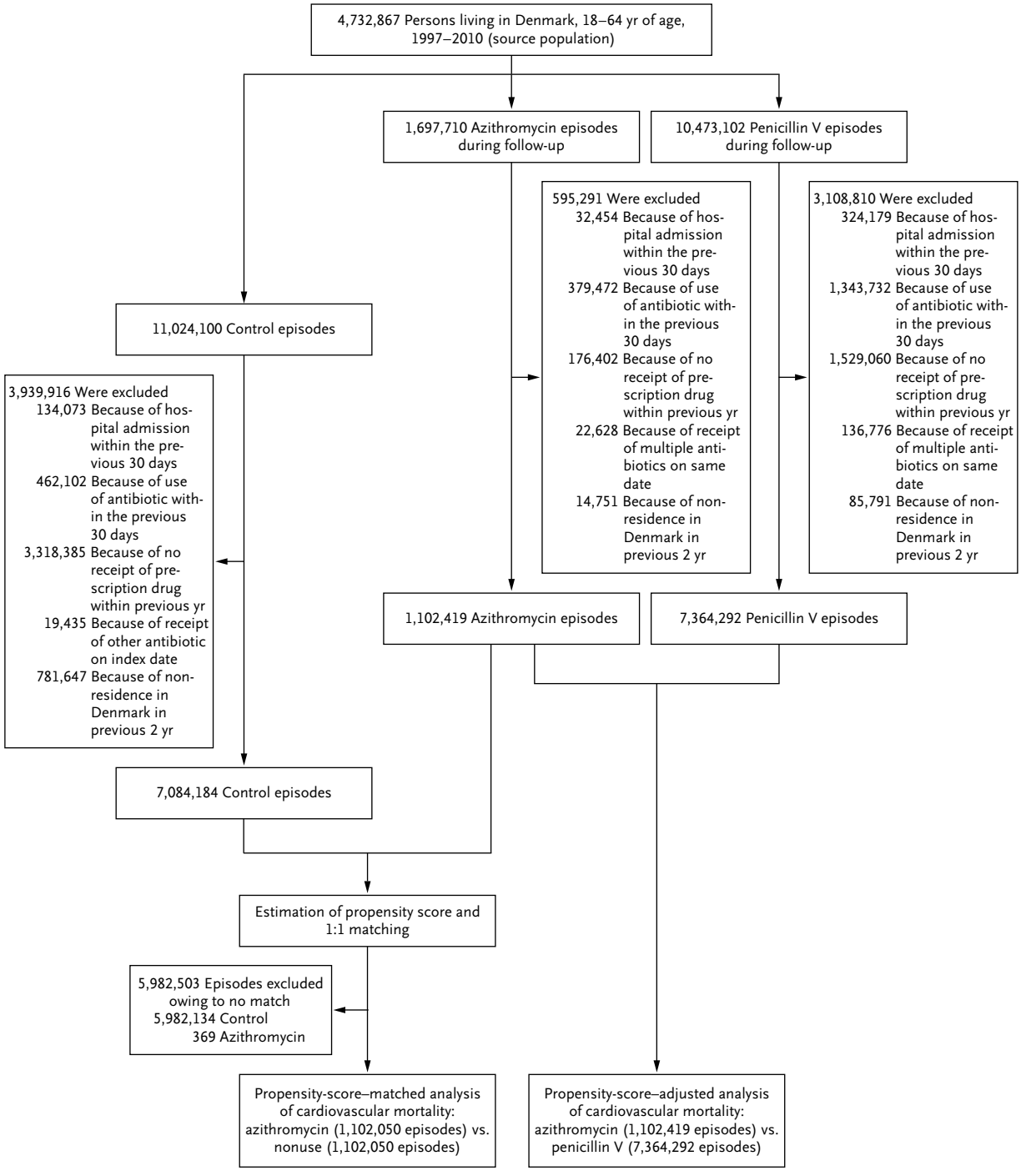

Figure 1. Cohort of Persons with Azithromycin Use, Matched Nonuse, and Penicillin V Use.

For each episode of azithromycin use, up to 10 control episodes among persons who had the same sex and date of birth but who were not using azithromycin were randomly assigned as potential matches. Values for the exclusion criteria do not sum to the totals shown because some records were excluded for more than one reason.

Table 1. Baseline Characteristics of Persons with Azithromycin Use Included in Analyses, as Compared with Persons with No Antibiotic Use and Persons with Penicillin V Use.

Characteristic	Propensity-Score–Matched Cohort			Unmatched Cohort		
	Azithromycin (N=1,102,050)	No Antibiotic (N=1,102,050)	P Value	Azithromycin (N=1,102,419)	Penicillin V (N=7,364,292)	P Value
Age — yr	39.7±13.9	39.5±13.8	<0.001	39.7±13.9	42.0±12.8	<0.001
Male sex — no. (%)	383,973 (35)	390,485 (35)	<0.001	384,279 (35)	2,822,420 (38)	<0.001
Acute coronary syndrome — no. (%)	13,850 (1)	13,686 (1)	0.32	13,860 (1)	114,441 (2)	<0.001
Other ischemic heart disease — no. (%)	29,316 (3)	29,052 (3)	0.27	29,358 (3)	226,568 (3)	<0.001
Heart failure or cardiomyopathy — no. (%)	7,384 (1)	7,301 (1)	0.49	7,388 (1)	56,850 (1)	<0.001
Cerebrovascular disease — no. (%)	14,098 (1)	13,837 (1)	0.12	14,098 (1)	116,359 (2)	<0.001
Renal disease — no. (%)	6,852 (1)	6,835 (1)	0.88	6,854 (1)	52,035 (1)	<0.001
Chronic lung disease — no. (%)	90,675 (8)	88,131 (8)	<0.001	90,980 (8)	464,349 (6)	<0.001
Cancer — no. (%)	31,836 (3)	31,566 (3)	0.28	31,859 (3)	224,943 (3)	<0.001
Prescription-drug use in previous yr — no. (%)						
ARB or ACE inhibitor	65,581 (6)	64,241 (6)	<0.001	65,598 (6)	497,673 (7)	<0.001
Loop diuretic	26,280 (2)	25,707 (2)	0.01	26,308 (2)	187,579 (3)	<0.001
Beta-blocker	51,250 (5)	50,468 (5)	0.01	51,255 (5)	403,018 (5)	<0.001
Platelet inhibitor	36,719 (3)	36,106 (3)	0.02	36,732 (3)	301,629 (4)	<0.001
Lipid-lowering drug	44,906 (4)	44,399 (4)	0.08	44,913 (4)	357,209 (5)	<0.001
Oral antidiabetic drug	15,956 (1)	15,993 (1)	0.83	15,959 (1)	149,626 (2)	<0.001
Insulin	12,015 (1)	12,009 (1)	0.97	12,018 (1)	107,568 (1)	<0.001
Antidepressant	110,479 (10)	109,915 (10)	0.21	110,539 (10)	758,977 (10)	<0.001
Glucocorticoid inhalant	109,120 (10)	105,068 (10)	<0.001	109,452 (10)	536,086 (7)	<0.001
No. of drugs used			<0.001			<0.001
1 or 2	386,451 (35)	384,078 (35)		386,451 (35)	2,927,365 (40)	
3–5	382,923 (35)	390,211 (35)		382,923 (35)	2,572,583 (35)	
6–9	211,575 (19)	212,851 (19)		211,576 (19)	1,257,287 (17)	
≥10	121,101 (11)	114,910 (10)		121,469 (11)	607,057 (8)	

* Plus–minus values are means ±SD. Table S3 in the Supplementary Appendix shows the distribution of all 61 baseline covariates that were included in the propensity-score models. ACE denotes angiotensin-converting enzyme, and ARB angiotensin-receptor blocker.

AZITHROMYCIN VS. NO USE OF ANTIBIOTICS

The baseline characteristics of participants with matched episodes of azithromycin use and no use of antibiotics are shown in Table 1, and in Table S3 in the Supplementary Appendix. The rate ratios for death from cardiovascular causes associated with use of azithromycin, as compared with no use of antibiotics, are shown in Table 2.

We found that the risk of death from cardiovascular causes was significantly increased with current use of azithromycin (rate ratio, 2.85; 95% confidence interval [CI], 1.13 to 7.24). No significantly increased risk was observed for recent or past use. With respect to the secondary outcome of noncardiovascular death, the rate ratio associated with current use of azithromycin was 1.60 (95% CI, 1.00 to 2.54). In a sensitivity analysis, the rate ratio for cardiac death associated with current use of azithromycin versus no antibiotic use was 3.27 (95% CI, 1.07 to 10.04).

AZITHROMYCIN VS. PENICILLIN V

Table 1 and Table S3 in the Supplementary Appendix also show baseline characteristics for persons using azithromycin or penicillin V. As compared with persons who used penicillin V, those who used azithromycin were less likely to be men, were on average somewhat younger, were

Table 2. Risk of Death from Cardiovascular Causes with Azithromycin Use as Compared with No Antibiotic Use or Use of Penicillin V.

Antibiotic Use*	Propensity-Score–Matched Analysis			Propensity-Score–Adjusted Analysis		
	Azithromycin (N=1,102,050)	No Antibiotic (N=1,102,050)	Rate Ratio (95% CI)	Azithromycin (N=1,102,419)	Penicillin V (N=7,364,292)	Rate Ratio (95% CI)
Current use						
No. of events	17	6		17	146	
No./1000 patient-yr	1.1	0.4	2.85 (1.13–7.24)	1.1	1.5	0.93 (0.56–1.55)
Recent use						
No. of events	7	5		7	74	
No./1000 patient-yr	0.5	0.3	1.44 (0.46–4.54)	0.5	0.8	0.75 (0.34–1.62)
Past use						
No. of events	23	35		23	192	
No./1000 patient-yr	0.3	0.5	0.69 (0.41–1.17)	0.3	0.4	0.92 (0.60–1.42)

* Current use was defined as days 1 through 5 after the initiation of treatment, recent use as days 6 through 10, and past use as days 11 through 35.

more likely to live in the greater Copenhagen area, were more likely to be taking drugs for asthma and chronic obstructive pulmonary disease, had used a larger number of prescription drugs in the previous year, and were less likely to have had an emergency department visit in the previous month.

The rate ratios for the risk of death from cardiovascular causes associated with use of azithromycin, as compared with penicillin V, are shown in Table 2. In an unadjusted analysis, current use of azithromycin, as compared with penicillin V, was not significantly associated with an increased risk of death from cardiovascular causes (rate ratio, 0.78; 95% CI, 0.47 to 1.28). Similarly, there was no significantly increased risk associated with recent or past use.

After adjustment for propensity scores, the results were similar; current use of azithromycin was not associated with a significantly increased risk of death from cardiovascular causes (rate ratio, 0.93; 95% CI, 0.56 to 1.55), and neither was recent use (rate ratio, 0.75; 95% CI, 0.34 to 1.62) or past use (rate ratio, 0.92; 95% CI, 0.60 to 1.42). The adjusted absolute risk difference for current azithromycin use, as compared with penicillin V use, was –1 cardiovascular death (95% CI, –9 to 11) per 1 million treatment episodes. There were 46 deaths due to noncardiovascular causes during current use of azithromycin (incidence rate, 3.1 per 1000 person-years) and 410 during current use of penicillin V (incidence rate, 4.1 per 1000 person-years), for an unadjusted rate ratio of 0.75 (95% CI, 0.55 to 1.01) and an adjusted rate ratio of 0.82 (95% CI, 0.61 to 1.12).

SUBGROUP ANALYSES

Table 3 presents the risk of cardiovascular death in subgroups according to sex, age, and status with respect to a history of cardiovascular disease. Although the small number of events in these subgroups should be taken into account, the risk of death from cardiovascular causes during current use of azithromycin, as compared with penicillin V, did not differ significantly according to sex or according to age. The risk during current use of azithromycin appeared to be higher among persons with a history of cardiovascular disease than among those without such a history, although the difference was not significant.

SENSITIVITY ANALYSES

In a sensitivity analysis, the use of azithromycin, as compared with penicillin V, was not associated with an increased risk of cardiac death (adjusted rate ratio, 1.06; 95% CI, 0.60 to 1.90). The risk of death from cardiovascular causes was also analyzed after propensity-score matching (in a 1:1 ratio) of episodes of azithromycin use and penicillin V use (see Table S4 in the Supplementary Appendix); current use of azithromycin was not associated with an increased risk (rate ratio, 1.06; 95% CI, 0.54 to 2.10) (Table 4). In a post hoc analysis, azithromycin use was compared with amoxicillin

Table 3. Subgroup Analyses of the Risk of Death from Cardiovascular Causes with Current Use of Azithromycin as Compared with Penicillin V.

Analysis	Azithromycin (N=1,102,419)		Penicillin V (N=7,364,292)		Rate Ratio (95% CI)*	P Value†
	no. of events	*no./1000 patient-yr*	*no. of events*	*no./1000 patient-yr*		
Primary analysis	17	1.1	146	1.5	0.93 (0.56–1.55)	0.79
Subgroup analysis						
Sex						0.73
Male	9	1.7	87	2.3	0.86 (0.43–1.72)	
Female	8	0.8	59	1.0	1.03 (0.49–2.16)	
Age						0.50
18–44 yr	3	0.3	17	0.3	1.42 (0.41–4.90)	
45–64 yr	14	2.5	129	3.1	0.88 (0.51–1.53)	
History of cardiovascular disease‡						0.16
Yes	10	9.7	62	8.0	1.35 (0.69–2.64)	
No	7	0.5	84	0.9	0.65 (0.30–1.41)	

* The rate ratio was adjusted for the propensity score.
† The P value for the primary analysis refers to the risk estimate for current azithromycin use versus current penicillin V use, whereas the P values for the subgroup analyses refer to the homogeneity of the risk estimate between the respective subgroup levels.
‡ Included in this category were an acute coronary syndrome, other ischemic heart disease, heart failure or cardiomyopathy, valve disorder, congenital heart disease, cardiac surgery or other invasive cardiac procedure, cerebrovascular disease, arterial disease, and arrhythmia.

use in a propensity-score–matched analysis with a ratio of 1:1; azithromycin use was not associated with a significantly increased risk of death from cardiovascular causes (rate ratio, 0.60; 95% CI, 0.29 to 1.23) (Tables S5 and S6 in the Supplementary Appendix).

Table 4. Sensitivity Analysis of Risk of Death from Cardiovascular Causes with Azithromycin Use as Compared with Penicillin V Use, with Propensity-Score Matching in a 1:1 Ratio.

Antibiotic Use	Azithromycin (N=1,102,419)	Penicillin V (N=1,102,419)	Rate Ratio (95% CI)
Current use			
No. of events	17	16	
No./1000 patient-yr	1.1	1.1	1.06 (0.54–2.10)
Recent use			
No. of events	7	8	
No./1000 patient-yr	0.5	0.6	0.86 (0.31–2.37)
Past use			
No. of events	23	21	
No./1000 patient-yr	0.3	0.3	1.05 (0.58–1.89)

DISCUSSION

In this nationwide cohort study, we evaluated the association between use of azithromycin and death from cardiovascular causes, as compared with no use of antibiotics and with use of penicillin V, in young and middle-aged adults. As compared with no use of antibiotics, use of azithromycin was associated with a significantly increased risk of cardiovascular death. As compared with penicillin V, however, azithromycin was not associated with a significantly increased risk, indicating that the increased risk that was observed in the comparison with no antibiotic use was entirely attributable to the risk of death associated with acute infection (or some other adverse health characteristic in persons receiving antibiotic treatment, as compared with those not treated with antibiotics) rather than with its treatment.

The study included more than 1 million episodes of azithromycin use and, given the upper limit of the confidence interval, was powered to rule out a moderate-to-high increase (>55%) in the relative risk of death from cardiovascular causes.

In terms of absolute risk, any residual risk would account for a maximum of 11 additional deaths from cardiovascular causes per 1 million treatment episodes.

We did not find an increased risk of cardiovascular death associated with azithromycin, whereas Ray et al. reported a significantly increased risk that was 2 to 3 times as high as the risk associated with no antibiotic use and with amoxicillin treatment.[6] Given the profound differences in the characteristics of the study participants and the baseline risk of death between the two studies, our results provide a clinically relevant complement to, rather than a contrast with, the findings of Ray et al. Whereas their study, which examined the risk of death from cardiovascular causes associated with azithromycin in a population of U.S. Medicaid beneficiaries, provides evidence to support the hypothesis that azithromycin has an effect on cardiovascular mortality in a selected population,[6] our study shows that this effect is not present in the general population.

The mortality rates in that study were markedly higher, indicating that the study population had a higher baseline risk, as compared with the population in our study. For example, the cardiovascular mortality rate in the study by Ray et al.[6] was 85.2 deaths per 1 million courses of azithromycin, as compared with 15.4 deaths per 1 million courses in our study. The difference in the results of the two studies could thus probably be attributed to treatment-effect heterogeneity — that is, an increased risk that was largely restricted to high-risk patients. Our results also point toward an increased risk among patients with a history of cardiovascular disease, although no significant difference was observed in a comparison with patients who did not have such a history.

This study has a number of strengths. Given the large, nationally representative study population, the results are likely to be widely generalizable to young and middle-aged adult populations. We used multiple strategies to minimize confounding. The risk associated with azithromycin use was analyzed relative to two separate references: no use of antibiotics and use of penicillin V. By means of the application of propensity-score methods, we were able to take into account a wide range of pretreatment risk factors for cardiovascular death. Finally, the analysis in which penicillin V was used as the reference allowed us to compare azithromycin with a drug that has similar indications, reducing the potential for confounding by indication and unmeasured confounding.[16,17]

The study also has limitations. We did not have information on the indication for treatment for individual patients or information on several known risk factors for cardiovascular disease and death (e.g., smoking and body-mass index). Thus, residual confounding cannot be ruled out. On the assumption that propensity-score matching may provide more robust control regarding confounders than adjustment does, persons who used azithromycin were matched to those who used penicillin V in a sensitivity analysis; the results were similar to, albeit less precise than, those of the primary analysis. Furthermore, the fact that there was no significant difference between azithromycin and penicillin V among persons with past use indicates that a differential baseline risk of cardiovascular death between users of the study drugs is unlikely to have obscured a true risk associated with current use of azithromycin. The risk of cardiovascular death among persons with past use, as compared with current use, is less influenced by (or is not influenced by) the acute effects of the infection for which the treatment was previously used and is more likely to represent the baseline risk of this outcome.

In addition, the number of events in the subgroup analyses was low. The primary outcome definition, including all cardiovascular causes of death, was broad and may not have been sufficiently specific to detect an increased risk that was due to a previously hypothesized proarrhythmic effect.[6] A sensitivity analysis with the outcome restricted to cardiac deaths had similar results.

This study was prompted by a reported association between azithromycin use and cardiovascular death.[6] In a large, representative population of young and middle-aged adults, we found no significantly increased risk of death from cardiovascular causes associated with azithromycin. Viewed together with previous data,[6] our findings indicate that the risk of cardiac toxic effects associated with azithromycin may not be generalizable but may rather be limited to high-risk populations. The implications of these findings for clinical decision making are reassuring; they indicate that for the general population of

patients seen in office practice, azithromycin can be prescribed without concern about an increased risk of death from cardiovascular causes, whereas the benefits of therapy need to be weighed against the risk of death from cardiovascular causes among patients with a high baseline risk of cardiovascular disease.

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

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