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

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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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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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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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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.

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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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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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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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