

ORIGINAL ARTICLE

Oral Erythromycin and the Risk of Sudden Death from Cardiac Causes

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ABSTRACT

BACKGROUND

Oral erythromycin prolongs cardiac repolarization and is associated with case reports of torsades de pointes. Because erythromycin is extensively metabolized by cytochrome P-450 3A (CYP3A) isozymes, commonly used medications that inhibit the effects of CYP3A may increase plasma erythromycin concentrations, thereby increasing the risk of ventricular arrhythmias and sudden death. We studied the association between the use of erythromycin and the risk of sudden death from cardiac causes and whether this risk was increased with the concurrent use of strong inhibitors of CYP3A.

METHODS

We studied a previously identified Tennessee Medicaid cohort that included 1,249,943 person-years of follow-up and 1476 cases of confirmed sudden death from cardiac causes. The CYP3A inhibitors used in the study were nitroimidazole antifungal agents, diltiazem, verapamil, and troleandomycin; each doubles, at least, the area under the time-concentration curve for a CYP3A substrate. Amoxicillin, an antimicrobial agent with similar indications but which does not prolong cardiac repolarization, and former use of erythromycin also were studied, to assess possible confounding by indication.

RESULTS

The multivariate adjusted rate of sudden death from cardiac causes among patients currently using erythromycin was twice as high (incidence-rate ratio, 2.01; 95 percent confidence interval, 1.08 to 3.75; $P=0.03$) as that among those who had not used any of the study antibiotic medications. There was no significant increase in the risk of sudden death among former users of erythromycin (incidence-rate ratio, 0.89; 95 percent confidence interval, 0.72 to 1.09; $P=0.26$) or among those who were currently using amoxicillin (incidence-rate ratio, 1.18; 95 percent confidence interval, 0.59 to 2.36; $P=0.65$). The adjusted rate of sudden death from cardiac causes was five times as high (incidence-rate ratio, 5.35; 95 percent confidence interval, 1.72 to 16.64; $P=0.004$) among those who concurrently used CYP3A inhibitors and erythromycin as that among those who had used neither CYP3A inhibitors nor any of the study antibiotic medications. In contrast, there was no increase in the risk of sudden death among those who concurrently used amoxicillin and CYP3A inhibitors or those currently using any of the study antibiotic medications who had formerly used CYP3A inhibitors.

CONCLUSIONS

The concurrent use of erythromycin and strong inhibitors of CYP3A should be avoided.

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ERYTHROMYCIN IS A COMMONLY USED macrolide antimicrobial agent with a long history of use, and it is considered largely free of serious toxicity. However, there have been case reports of torsades de pointes in patients receiving both oral and intravenous erythromycin.¹⁻⁴ An increase in the risk of torsades de pointes is consistent with the effects of erythromycin on cardiac electrophysiology; studies have shown prolongation of the QT interval^{5,6} and blockade of the potassium channel encoded by the human ether-a-go-go-related gene (*HERG*).⁷

There are important clinical questions that these case reports have not addressed. Although there is an association between erythromycin and serious ventricular tachyarrhythmias, the magnitude of the risk of ventricular tachyarrhythmia has not been quantified in population-based studies. Studies of the association of erythromycin and arrhythmia have focused on the intravenous use of the drug,^{1,6} perhaps because this use is involved in the majority of the reported cases^{1,3} and because the rapid rise to peak concentrations may increase the risk of arrhythmia. However, in clinical practice, this drug is usually administered orally, and the perception that oral use is not associated with arrhythmias is unsupported by data. Pharmacokinetic drug-drug interactions also may increase the risk of sudden death from cardiac causes among patients using erythromycin. Erythromycin is extensively metabolized by cytochrome P-450 3A (CYP3A) isozymes.⁸ Many other commonly used medications inhibit the metabolism of drugs that is mediated by CYP3A, including nitroimidazole antifungal agents, certain calcium-channel blockers, and some antidepressant drugs. Although there have been reports of prolonged QT intervals⁹ and torsades de pointes⁴ among patients who were concurrently receiving oral erythromycin and CYP3A inhibitors, the clinical importance of this possible drug-drug interaction remains unclear.

In our population-based study, we sought to quantify the association between oral erythromycin and the risk of sudden death from cardiac causes, usually as the result of ventricular tachyarrhythmia. The primary questions posed in the study were whether the risk of sudden death was increased among those using oral erythromycin and whether this risk was altered by the concurrent use of erythromycin and potent inhibitors of CYP3A. To assess possible confounding by the indications for antimicrobial use, we also studied patients who were

currently using amoxicillin, an antibiotic drug that is used in clinical circumstances similar to those in which erythromycin is used.

METHODS

STUDY COHORT

We studied a cohort of Tennessee Medicaid enrollees¹⁰ who had been identified for previous investigations of sudden death from cardiac causes^{11,12} that included a review of the medical records for deaths occurring in the period from January 1, 1988, to December 31, 1993. Data on periods of enrollment in Medicaid and the demographic characteristics of each subject were included in an enrollment file that was linked with data from death certificates issued in Tennessee,¹³ including the date and cause of death. Data in medical-encounter files on filled prescriptions, outpatient visits, hospital admissions, and nursing home stays provided information that was used to identify the study cohort, to determine exposure to the study drugs, to identify potential cases of sudden death from cardiac causes, and to classify the members of the cohort according to preexisting cardiovascular conditions and other disease.

To be eligible for the study, subjects had to have had at least 365 days of continuous enrollment in Medicaid before entering the cohort, had to be between 15 and 84 years of age, could not be residing in a long-term care facility (except for subjects with mental disorders), and had to have no evidence of a life-threatening noncardiac illness.^{11,12} Persons who were receiving both erythromycin and amoxicillin were excluded. The follow-up began on January 1, 1988, or later, at the point when the criteria for enrollment in the cohort were met, and ended on December 31, 1993, the date of death, or the date on which the criteria for membership were no longer met, whichever occurred first.

USE OF MEDICATION

Prescriptions for erythromycin, amoxicillin, and other medications were identified from computerized Medicaid pharmacy files that included the drug, the dose, and the total medication dispensed (number of days of supply). Such records are an excellent source of data on prescription medications, because they are not subject to information bias^{14,15} and have a concordance of better than 90 percent with patients' self-reports on the use of medication.¹⁵⁻¹⁸

Before conducting the analysis, we reviewed the

literature to identify medications that are strong inhibitors of CYP3A *in vivo* and therefore could produce clinically important interactions with erythromycin. The *a priori* requirement was published prospective data (thus, case reports were excluded) that showed a doubling or more of the area under the time–plasma concentration curve (AUC) for a recognized CYP3A substrate. Thus, the drugs included azole antifungal drugs (ketoconazole,¹⁹ itraconazole,²⁰ and fluconazole,²¹ all administered systemically), diltiazem,²² verapamil,²² and troleandomycin.²³ Mibefradil²⁴ and nefazodone²⁵ met our criteria but were not marketed during the period of the study. Clarithromycin, a strong CYP3A inhibitor, was considered separately as a potential confounder, because it is linked with torsades de pointes and is metabolized by CYP3A. The protease inhibitors are potent CYP3A inhibitors, but the use of these drugs was considered an indicator of infection with the human immunodeficiency virus, and patients receiving them were excluded from the study. Other drugs that are commonly included on lists of CYP3A inhibitors^{26–29} (e.g., cimetidine) were not included, because *in vivo* data showed that their effect on CYP3A substrates did not meet our criteria for a doubling or more of the AUC.

Every person-day of follow-up was classified according to the study medication used and the type of use. Current use was defined according to days of supply from the day the prescription was filled. Nonuse of a medication was defined as no use within the previous 365 days. Former use was defined as some use of a study medication that was not current but had occurred within the previous 365 days. The characteristics of former users of the study medication should be similar to those of current users with regard to potential risk factors for sudden death that are difficult to measure and that are associated with receiving the study medication.

SUDDEN DEATH FROM CARDIAC CAUSES

The study outcome was sudden death from cardiac causes occurring in a community setting.^{30–33} Previous studies have suggested that 85 percent of such deaths are provoked by a ventricular tachyarrhythmia.^{30,31} In the present study, sudden death from cardiac causes was defined as a sudden pulseless condition that was fatal (within 48 hours) and that was consistent with a ventricular tachyarrhythmia occurring in the absence of a known noncardiac condition as the proximate cause of the death.³² Study cases^{11,12} were those that involved a wit-

nessed collapse or evidence that the person was alive within 24 hours before the death was reported. We excluded deaths from cardiac arrests that occurred in a hospital or another institutional setting, that were not sudden, or for which documentation suggested the presence of an underlying noncardiac cause (e.g., substance overdose or pneumonia) or a different cardiac cause (e.g., heart failure or bradyarrhythmia).

For all deaths occurring among the study cohort during the follow-up period, we screened data from computerized death certificates and other records of medical encounters to identify potential cases that met the criteria for the study.^{11,12} Nurses employed by the study reviewed the records of terminal medical encounters. One of the authors, a physician, classified each death, and another author, a cardiac electrophysiologist, reviewed questionable cases; both were unaware of the patients' medication use.

Among members of the cohort there were 4404 potentially qualifying deaths. Of these, 614 (14 percent) occurred at home, with no record of a terminal medical encounter, and we were unable to obtain records for 822 deaths (19 percent). Of the 2968 deaths for which records were obtained, we excluded 174 that were the result of sudden death from cardiac causes occurring in a hospital or other institution, 505 that resulted from other causes, and 802 for which information on the circumstances of the death or the time when the subject was last known to be alive was missing from the records. The study also excluded 11 deaths among persons who had received both erythromycin and amoxicillin within the past year (although none of the subjects were currently using these medications), leaving 1476 cases of sudden death from cardiac causes.

STATISTICAL ANALYSIS

Multivariate incidence-rate ratios and 95 percent confidence intervals were estimated with the use of Poisson regression models. Potential confounders were evaluated for each person-day of the follow-up period, including calendar year and demographic characteristics as well as measures of the use of medical care and of the presence of coexisting conditions that had been identified at medical encounters within the 365 days preceding the death. The measures of medical encounters included a low frequency of outpatient encounters (i.e., no visits to physicians or the filling of no more than one prescription), the use of antipsychotic¹¹ and cyclic antidepressant¹² drugs, serious noncardiovascular so-

matic disease (requiring hospital admission), and a summary score for the risk of cardiovascular disease. As described previously,^{11,12} this score was calculated on the basis of medical care received for cardiovascular disease, including the specific medications the patient was given, hospital admissions, visits to emergency departments, and visits to physicians. The score was then classified into 10 values, with the lowest representing the absence of the diagnosis or treatment of cardiovascular disease and with the remaining 9 values approximate quantiles for the cohort.

Previous studies have reported a high degree of validity for the two main components of this score, the computerized records of medical encounters at which medications were provided¹⁴⁻¹⁸ and the diagnosis of cardiovascular disease that was made at the hospital.^{34,35} Furthermore, after adjustment for age and sex, there was a difference of a factor of eight in the risk of sudden death from cardiac causes between patients with the highest scores and those with the lowest. All statistical analyses were performed with the use of SAS software, version 8.0 (SAS Institute). All P values are two-sided. The study was approved by the Vanderbilt University Medical

Center committee for the protection of human subjects, and informed consent was waived.

RESULTS

The study cohort included 1,249,943 person-years of follow-up. The mean age among members of the cohort was 45 years; 25 percent of the subjects were 65 years of age or older. Female subjects accounted for 70 percent of the cohort (reflecting the demographics of the population covered by Medicaid¹⁰), and 58 percent of the subjects were white. There were 22 percent who had not had a visit with a physician in the year preceding the study, and 29 percent of the subjects had filled no more than one prescription in the past year. Of the cohort, 34 percent had medical encounters in the past year related to cardiovascular disease. Of the deaths among members of the cohort, a total of 1476 met the study definition of sudden death from cardiac causes, for a rate of 1.2 deaths per 1000 person-years.

The study included 5305 person-years of current use of erythromycin and 111,779 person-years of former use, as well as 6846 person-years of current use of amoxicillin. Current and former users

Table 1. Characteristics of the Cohort According to Antibiotic Use.*

Characteristic	Antibiotic Use			
	None	Former Use of Erythromycin	Current Use of Erythromycin	Current Use of Amoxicillin
Person-years (no.)	1,126,013	111,779	5305	6846
Age				
Mean (yr)	45.0	42.2	41.4	41.7
≥65 yr (%)	26.0	18.6	16.5	17.9
Female sex (%)	68.7	78.6	77.6	76.2
White race (%)	57.5	66.0	69.3	70.7
No outpatient visit in past year (%)	23.6	2.7	2.5	2.1
≤1 prescription in past year (%)	32.0	3.3	1.8	2.0
Encounters involving cardiovascular disease (%)				
Any	33.2	46.1	47.0	46.4
Medication prescribed†	31.8	45.2	46.1	45.5
Visit to emergency department or hospital admission	2.9	4.7	4.3	4.2
Visit to emergency department or admission for noncardiovascular condition (%)	11.6	19.2	17.8	16.4

* All characteristics were standardized with the use of the direct method according to the age and sex distribution of the full cohort (except for age, sex, and race).

† Medications included digitalis glycosides, loop diuretics, thiazide diuretics, antiarrhythmic drugs, angiotensin-converting-enzyme inhibitors, beta-blockers, calcium-channel blockers, hypoglycemic agents, lipid-lowering drugs, nitrates, anticoagulant agents, antiplatelet and blood-viscosity agents, and other antihypertensive medications.

of the study antibiotic drugs were slightly younger than nonusers (Table 1) and more likely to be female and white. After adjustment for age and sex, nonusers had fewer previous medical encounters of any kind and fewer medical encounters with reference to cardiovascular disease than did users of erythromycin or amoxicillin. However, current and former users of erythromycin and current users of amoxicillin were very similar with regard to their demographic characteristics and medical encounters in the year preceding the study related to both cardiovascular disease and other diseases.

The rate of sudden death from cardiac causes was twice as high among current users of erythromycin (incidence-rate ratio, 2.01; 95 percent confidence interval, 1.08 to 3.75; $P=0.03$) (Table 2) as among those who did not use any of the study antibiotic medications. In contrast, there was no significant increase in the risk of sudden death among former users of erythromycin (incidence rate ratio, 0.89; 95 percent confidence interval, 0.72 to 1.09; $P=0.26$) or current users of amoxicillin (incidence rate ratio, 1.18; 95 percent confidence interval, 0.59 to 2.36; $P=0.65$).

There was a marked increase in the risk of sudden death from cardiac causes among concurrent users of the study CYP3A inhibitors and erythromycin (Table 3 and Fig. 1). Among these patients, there were 3 such deaths during 194 person-years of follow-up, or 15.5 deaths per 1000 person-years. In the multivariate analysis, the incidence-rate ratio was 5.35 (95 percent confidence interval, 1.72 to 16.64; $P=0.004$), indicating a risk of sudden death more than five times as high as that among those who used neither CYP3A inhibitors nor study antibiotics. Among other patients currently using CYP3A inhibitors, there was no evidence of an increase in the risk of sudden death from cardiac causes among those who were concurrently using amoxicillin or those who were not currently using any of the study antibiotic medications (Table 3). There was also no evidence of an increase in the risk of sudden death from cardiac causes among those who had formerly used CYP3A inhibitors, regardless of their use or nonuse of any of the study antibiotic medications.

When we estimated the effect of specific CYP3A inhibitors that were used concurrently with erythromycin, calcium-channel blockers accounted for nearly all the person-years of follow-up and all cases of sudden death from cardiac causes. There was one death in 106 person-years among current users of diltiazem and two deaths in 78 person-years among

Table 2. Incidence-Rate Ratio for Sudden Death from Cardiac Causes, According to Antibiotic Use.*

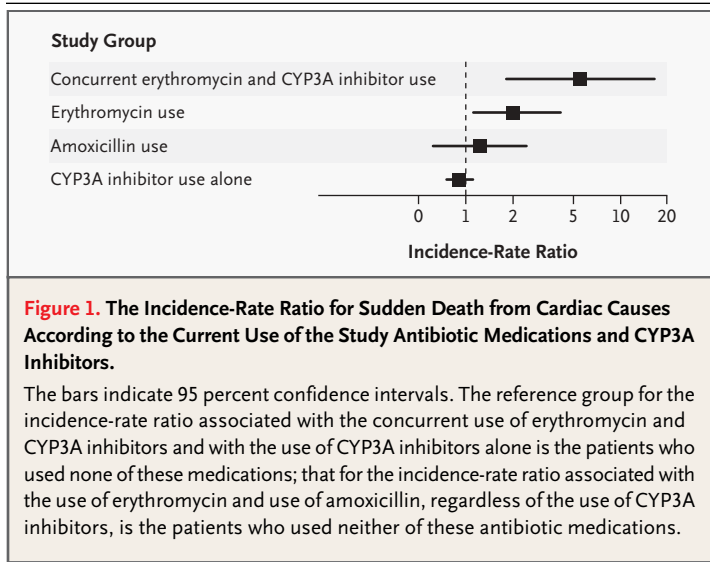
Antibiotic Use	Person-Years	Deaths	Incidence-Rate Ratio (95% CI)
	number		
Current use of erythromycin	5,305	10	2.01 (1.08–3.75)
Current use of amoxicillin	6,846	8	1.18 (0.59–2.36)
Former use of erythromycin	111,779	100	0.89 (0.72–1.09)
None	1,126,013	1358	1.00

* Incidence-rate ratios were adjusted by Poisson regression for the following variables: calendar year; age, sex, and race; type of Medicaid enrollment; low frequency of outpatient medical encounters; score for the risk of cardiovascular disease; dose of antipsychotic and tricyclic antidepressant medications; and hospital admission or visit to the emergency department for noncardiovascular disease. Incidence-rate ratios and 95 percent confidence intervals (CIs) were calculated directly from the regression model. The group with no use of study antibiotics was the reference group.

Table 3. Incidence-Rate Ratio for Sudden Death from Cardiac Causes, According to Use of CYP3A Inhibitors and Antibiotic Drugs.*

Drug Use	Person-Years	Deaths	Incidence-Rate Ratio (95% CI)
	number		
Current use of CYP3A inhibitor			
Current use of erythromycin	194	3	5.35 (1.72–16.64)
Current use of amoxicillin	254	0	—
No current antibiotic use	36,518	116	0.93 (0.76–1.13)
Former use of CYP3A inhibitor			
Current use of erythromycin	236	0	—
Current use of amoxicillin	288	0	—
No current antibiotic use	38,187	107	0.97 (0.79–1.19)
No use of CYP3A inhibitor			
Current use of erythromycin	4,874	7	1.79 (0.85–3.76)
Current use of amoxicillin	6,304	8	1.48 (0.74–2.97)
No current antibiotic use	1,163,087	1235	1.00

* Incidence-rate ratios were adjusted by Poisson regression for the following variables: calendar year; age, sex, and race; type of Medicaid enrollment; low frequency of outpatient medical encounters; score for the risk of cardiovascular disease; dose of antipsychotic and tricyclic antidepressant medications; and hospital admission or visit to the emergency department for noncardiovascular disease. The total number of person-years with current use of erythromycin in this table (5304) differs from the total in the study (5305) because of rounding. Incidence-rate ratios and 95 percent confidence intervals were calculated directly from the regression model. Patients with no use of a CYP3A inhibitor and no antibiotic use were the reference group. CI denotes confidence interval.



current users of verapamil. There were no deaths in the 10 person-years of exposure to nitroimidazoles or to more than a single CYP3A inhibitor. We also identified 114 person-years of concurrent use of erythromycin and other calcium-channel blockers that did not inhibit CYP3A to a clinically important degree (nearly all for nifedipine); there were no sudden deaths from cardiac causes in this group.

We performed several supplementary analyses to determine whether the increase in the risk of sudden death from cardiac causes that was associated with the current use of erythromycin was confounded by other medications thought to predispose patients to arrhythmias. These analyses included other drugs that can cause torsades de pointes the metabolism of which is likely to be inhibited by erythromycin (including cisapride,³⁶ terfenadine,³⁷ astemizole,³⁸ clarithromycin,³⁹ and pimozide⁴⁰), antiarrhythmic medications considered to cause torsades de pointes with relatively high frequency (including disopyramide, procainamide, amiodarone, and sotalol⁴¹), as well as quinidine, an antiarrhythmic drug that can cause torsades de pointes and is a CYP3A substrate,⁴² and other medications thought to cause torsades de pointes¹ or to prolong the QT interval.^{43,44} The association between erythromycin and the risk of sudden death from cardiac causes was unchanged in all of these analyses.

DISCUSSION

Case reports have long suggested that erythromycin is associated with an increase in the risk of tor-

sades de pointes. Two reviews of data from the Adverse Drug Event reporting system of the Food and Drug Administration identified 346 reports of cardiac arrhythmias² and 82 reports consistent with torsades de pointes³ in which erythromycin was mentioned. The present controlled study provides confirmatory evidence: the rate of sudden death from cardiac causes was twice as high among patients who were current users of oral erythromycin as among those who had not used any of the study antibiotic drugs. In contrast, those who had formerly used erythromycin or were currently using amoxicillin had no significant increase in risk. A key finding was that the risk was greatest among those concomitantly using erythromycin and the study drugs that were likely to inhibit its metabolism. Among such patients, the risk of sudden death from cardiac causes was five times as high as that among those who were not using any of the study antibiotic drugs or CYP3A inhibitors. These findings were not affected by the concurrent use of other drugs known to increase the risk of ventricular arrhythmias the metabolism of which is inhibited by erythromycin or by use of other potentially arrhythmogenic drugs.

There were several limitations to the study. Although the cohort included both a large number of subjects who had used the study antibiotic drugs and a large number of sudden deaths from cardiac causes, there were only 194 person-years of follow-up for the concurrent use of erythromycin and the study CYP3A inhibitors, with three sudden deaths from cardiac causes. Nevertheless, given the low incidence of sudden death from cardiac causes among members of the study cohort (1.2 per 1000 person-years of follow-up), this finding was significant ($P=0.004$) and, thus, unlikely to be due to chance. Indeed, in a similar group of patients (who were concurrently using amoxicillin and CYP3A inhibitors or were currently using amoxicillin or erythromycin and had formerly used CYP3A inhibitors), with a total of 778 person-years of follow-up, there were no sudden deaths from cardiac causes.

The study data did not include information on a variety of behavioral risk factors that are associated with cardiovascular disease, including smoking, higher body-mass index, high consumption of saturated fats, and lack of physical activity. We addressed this potential confounding in several ways. First, adverse effects of these risk factors are likely to be mediated to a large extent by other variables, such as the presence of hyperlipidemia, hypertension, diabetes mellitus, and preexisting cardiovascular dis-

ease, such as heart failure, angina, and myocardial infarction. If such conditions were diagnosed and treated, they were controlled for in the statistical analysis. Second, the study included several control groups that, with regard to unmeasured confounders, should be very similar to the group that used erythromycin and the group that used the study CYP3A inhibitors. These control groups included concurrent users of amoxicillin and the CYP3A inhibitors, current users of erythromycin and former, not current, users of CYP3A inhibitors, and current users of erythromycin and calcium-channel blockers that do not affect CYP3A metabolism. None of these groups had an increase in the risk of sudden death from cardiac causes.

Drugs that have the potential to interact with erythromycin were restricted to the inhibitors of CYP3A for which a prospective study showed a doubling or more of the AUC of a recognized CYP3A substrate. Thus, cimetidine²⁶ and several other less potent CYP3A inhibitors were not included in the study. We reasoned that the increase in the risk of sudden death from cardiac causes would be mediated by the increase in plasma erythromycin concentrations. Hence, drug interactions that result in small increases in erythromycin concentrations would be less likely to cause adverse clinical outcomes and thus more difficult to detect. Because erythromycin is an old drug, there are a limited number of studies on potential CYP-mediated drug-drug interactions. We thus inferred an effect of the study CYP3A inhibitors on erythromycin from their effects on other well-recognized CYP3A substrates. This inference is reasonable, since the mechanism of the interaction is understood and its effects are predictable.

The study provided no direct data with regard to the mechanisms by which the concomitant use of erythromycin and the study CYP3A inhibitors increased the risk of sudden death from cardiac causes. We believe that the most probable explanation is that the concurrent use resulted in an increase in the plasma erythromycin concentrations, thereby

increasing the risk of QT prolongation (a known, dose-associated effect of erythromycin⁶) and thus of serious ventricular arrhythmias. However, other factors may be involved. Two calcium-channel blockers, verapamil and diltiazem, accounted for nearly all the use of CYP3A inhibitors in the study. Both drugs are CYP3A substrates, and erythromycin, a CYP3A inhibitor, is likely to increase their plasma concentrations. Furthermore, erythromycin and verapamil are also substrates and inhibitors of P-glycoprotein, a drug-efflux pump, and each could therefore alter the other's concentration. Well-recognized consequences of an overdose of a calcium-channel blocker are bradycardia, hypotension, and heart block, which can provoke sudden death from cardiac causes.⁴⁵

The cohort had limited use of clarithromycin and several other drugs that prolong the QT interval and are metabolized by CYP3A.³⁶⁻⁴⁰ Although the absence of such drugs from the study did not confound the association between erythromycin and the risk of sudden death from cardiac causes, the sample size was insufficient to study the independent association of these drugs with an increase in risk. Further investigations are needed.

In conclusion, patients who used both erythromycin and the study CYP3A inhibitors had a risk of sudden death from cardiac causes that was five times as great as that among patients who had not used these drugs. Given that there are alternatives to erythromycin and to most CYP3A inhibitors, the use of this combination should be avoided in clinical practice.

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Dr. Ray reports having served as a consultant to Pfizer and Bristol-Myers Squibb, receiving research funding from Pfizer, and having provided expert testimony for litigation involving cerivastatin, fenfluramine derivatives, and rofecoxib. Dr. Murray reports having served as a consultant to Procter & Gamble. Dr. Stein reports having served as a consultant to Bristol-Myers Squibb.

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