

Antibiotics and Risk of Subsequent First-time Acute Myocardial Infarction

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THERE IS INCREASING EVIDENCE from observational studies¹⁻⁶ and randomized clinical trials^{7,8} that certain bacterial infections may play a role in the etiology of coronary heart disease and subsequent acute myocardial infarction (AMI). In particular, *Chlamydia pneumoniae*, but also *Helicobacter pylori* and bacterial infections associated with periodontal diseases,⁹ have been related to an increased risk of developing AMI as well as thrombotic stroke.¹⁰

Such infections, particularly with *C pneumoniae*, have a high prevalence, and because they often have a mild or even asymptomatic clinical course,¹¹⁻¹³ they may often be undiagnosed and untreated. If the causal relationship between bacterial infections and AMI indeed exists, the attributable risk of such untreated chronic infections in the etiology of ischemic heart disease might be substantial. Under the assumption that certain bacteria play a causal role in the etiology of AMI, it might be expected that subjects who have been treated—for whatever indication—with certain antibiotics that have antibacterial activity against such organisms are at lower risk of developing AMI than subjects who have not received such antibiotic treatment.

We conducted a case-control analysis to explore the effect of previous use of tetracycline, macrolide, sulfonamide, quinolone, penicillin, and cep-

Context Increasing evidence supports the hypothesis of a causal association between certain bacterial infections and increased risk of developing acute myocardial infarction. If such a causal association exists, subjects who used antibiotics active against the bacteria, regardless of indication, might be at lower risk of developing acute myocardial infarction than nonusers.

Objective To determine whether previous use of antibiotics decreases the risk of developing a first-time acute myocardial infarction.

Design Population-based case-control analysis.

Setting The United Kingdom–based General Practice Research Database comprising 350 general practices.

Patients A total of 3315 case patients aged 75 years or younger with a diagnosis of first-time acute myocardial infarction between 1992 and 1997 and 13 139 controls without myocardial infarction matched to cases for age, sex, general practice attended, and calendar time.

Main Outcome Measures Use of antibiotics among those who did or did not have a first-time acute myocardial infarction.

Results Cases were significantly less likely to have used tetracycline antibiotics (adjusted odds ratio [OR], 0.70; 95% confidence interval [CI], 0.55-0.90) or quinolones (adjusted OR, 0.45; 95% CI, 0.21-0.95). No effect was found for previous use of macrolides (primarily erythromycin), sulfonamides, penicillins, or cephalosporins.

Conclusions The findings from this large case-control analysis provide further, albeit indirect, evidence for an association between bacterial infections with organisms susceptible to tetracycline or quinolone antibiotics and the risk of acute myocardial infarction. These results of preliminary nature should stimulate more research to further explore the role of infections in the etiology of acute myocardial infarction.

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alosporin antibiotics on the risk of developing subsequent first-time AMI.

METHODS

We conducted the study using data from more than 350 general practices in the United Kingdom. Computerized patient records from the United Kingdom include patient demographics, symptoms, diagnoses, referrals, hospitalizations, drug prescriptions (including route of administration, number of tablets, and dosage), and additional information (eg, height, weight, and smoking status). All information is recorded by general practitioners on an ongoing daily basis (replacing the former paper-based patient charts), regardless of

any future research hypotheses. Anonymous copies of hospital discharge and referral letters are available for review and validation purposes on request. This large database, known as the General Practice Research Database (GPRD), encompasses approximately 3 million actively enrolled persons in the United Kingdom. This system, which has been extensively validated^{14,15} and described in detail else-

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where,^{16,17} has been the source for numerous publications in peer-reviewed journals.

Case Selection and Validation

We identified all subjects who had a first-time diagnosis of AMI between January 1, 1992, and October 31, 1997 (by computer-recorded *International Classification of Diseases, Eighth Revision [ICD-8]* codes mapped onto Oxford Medical Information System [OXMIS] codes). We restricted the study to case patients who were 75 years or younger on the date of the diagnosis (index date) and free of clinical conditions potentially related to an increased risk of developing AMI; thus, all subjects with a history of ischemic heart disease, unexplained chest pain, cardiac arrhythmias, congestive heart failure, stroke, intermittent claudication, venous thromboembolism, chronic renal disease, hypertension, dyslipidemia, diabetes mellitus, connective tissue disorders, or cystic fibrosis were excluded. All cases had to be registered in the database for at least 3 years prior to the index date. Any information regarding antibiotic exposure was concealed when we reviewed computer records to identify potential

cases. The computer-recorded diagnosis of AMI was verified for a random sample of 40 cases as well as for more than 400 cases in 3 previous studies¹⁸⁻²⁰ by the presence of 2 or more of the following diagnostic criteria in the hospital discharge letter: characteristic cardiac pain, characteristic electrocardiogram results, characteristic serial cardiac enzyme levels, an arteriogram documenting a recent coronary occlusion, or fibrinolytic therapy. The computer-recorded AMI diagnosis was confirmed for a high percentage (>90%) of potential cases through these validation steps, and we therefore decided to include all potential cases who were initially identified by review of the computerized patient records.

Controls

For each case, we randomly selected 4 control subjects, matched to cases for age (same year of birth), sex, general practice attended, and calendar time (same index date). The same exclusion criteria as for cases (ie, circulatory or metabolic diseases predisposing for myocardial infarction as described herein) were applied to controls.

Exposure to Antibiotics

For each case and control, we assessed the exposure history for antibiotics in an arbitrarily chosen and predefined window of exactly 3 years preceding the index date. Based on this 3-year exposure history, all subjects were categorized into the following mutually exclusive categories: (1) no antibiotic use, (2) use of tetracyclines only, (3) use of macrolides only, (4) use of sulfonamides only, (5) use of quinolones only, (6) use of penicillins only, (7) use of cephalosporins only, or (8) use of any combination of antibiotics across these groups ("switchers").

Subjects who used antibiotics were further characterized according to the number of prescriptions for antibiotics in the 3 years prior to the index date (1 vs ≥ 2 prescriptions). For subjects who used tetracyclines, macrolides, quinolones, or sulfonamides, we also assessed the dose per tablet. Subjects who took no more than 250 mg of tetracycline/oxytetracycline, 100 mg of doxycycline, 100 mg of minocycline, 250 mg of erythromycin, 250 mg of clarithromycin, 250 mg of azithromycin, 250 mg of ciprofloxacin, 200 mg of ofloxacin, 400 mg of norfloxacin, 480 mg of sulfamethoxazole-trimethoprim, or 200 mg of trimethoprim per tablet were classified as users of a regular dosage, and those who received higher doses were classified as users of a high dosage.

We further assessed the indication for the use of antibiotics (where recorded) from the computerized patient histories. If subjects received more than 1 prescription for an antibiotic, the indication for the last prescription prior to the index date was recorded.

Analysis

We conducted a matched analysis (conditional logistic regression) using the software program SAS, Version 6.12 (SAS Institute Inc, Cary, NC). Odds ratios (ORs) are presented with 95% confidence intervals (CIs), and *P* values are 2-tailed.

RESULTS

We identified 3315 cases (74% male) and 13 139 matched controls (TABLE 1). The

Table 1. Characteristics of Cases and Controls in Relation to Risk of Developing AMI*

| Characteristics | Cases, No. (%) (n = 3315) | Controls, No. (%) (n = 13 139) | Odds Ratio (95% Confidence Interval) |
|------------------------------------|------------------------------|-----------------------------------|---|
| Age, y | | | |
| <40 | 91 (2.8) | 367 (2.8) | |
| 40-49 | 417 (12.6) | 1656 (12.6) | |
| 50-59 | 830 (25.0) | 3314 (25.2) | ... |
| 60-69 | 1227 (37.0) | 4832 (36.8) | |
| 70-75 | 750 (22.6) | 2970 (22.6) | |
| Sex | | | |
| Male | 2452 (74) | 9715 (74) | ... |
| Female | 863 (26) | 3424 (26) | |
| Died due to AMI† | 467 (14.1) | ... | ... |
| Smoking status | | | |
| Nonsmoker | 1079 (32.6) | 6204 (47.2) | 1.0 (Referent) |
| Current smoker | 1100 (33.2) | 2574 (19.6) | 2.6 (2.3-2.8)‡ |
| Ex-smoker | 376 (11.3) | 1353 (10.3) | 1.6 (1.4-1.9)‡ |
| Unknown | 760 (22.9) | 3008 (22.9) | 1.5 (1.3-1.6)‡ |
| Body mass index, kg/m ² | | | |
| <25 | 885 (26.7) | 4240 (32.3) | 1.0 (Referent) |
| 25-29.9 | 1100 (33.2) | 4004 (30.5) | 1.3 (1.2-1.5)‡ |
| ≥ 30 | 387 (11.7) | 1208 (9.2) | 1.5 (1.4-1.8)‡ |
| Unknown | 943 (28.4) | 3687 (28.0) | 1.2 (1.1-1.4)‡ |

*AMI indicates acute myocardial infarction; ellipses, odds ratio not calculated.

†Autopsy finding (patient did not reach the hospital alive).

‡*P*<.001.

relative risk estimates of developing a first-time AMI in relation to previous use of various antibiotics are shown in **TABLE 2**.

Subjects who took tetracyclines on 1 or more occasions in the 3 years preceding the index date were at a significantly reduced risk of developing a first-time AMI compared with nonusers, which resulted in an OR of 0.70 (95% CI, 0.55-0.90) after adjustment for smoking and body mass index (calculated as weight in kilograms divided by the square of height in meters). Previous use of quinolones was also associated with a reduced risk of developing AMI (adjusted OR, 0.45; 95% CI, 0.21-0.95). On the other hand, previous use of macrolides (adjusted OR, 0.93), sulfonamides (OR, 1.01), penicillins (OR, 0.94), or cephalosporins (OR, 0.90) did not differ significantly between cases and controls.

The results were consistent across age strata. Previous tetracycline use resulted in an OR of 0.66 (95% CI, 0.50-0.87) in men and 0.89 (95% CI, 0.52-1.50) in women compared with nonuse of any antibiotics. Current and past smoking (vs nonsmoking), and a body mass index of at least 30 kg/m² (vs <25 kg/m²) were independent risk factors for AMI, but they did not confound the association between antibiotic use and AMI. Current use of aspirin at the index date (OR, 0.54; 95% CI, 0.32-0.89), longer-term estrogen replacement therapy of 10 or more prescriptions prior to the index date among women (OR, 0.64; 95% CI, 0.44-0.94), and the presence of an acute respiratory tract infection²⁰ within 10 days prior to the index date (OR, 3.8; 95% CI, 2.8-5.3) were all independently associated with either a decreased or an increased risk of AMI, but adjusting the analysis for these parameters in the multivariate regression model did not change the results. Further adjustment for the presence of an asthma diagnosis prior to the index date (yes or no) or the number of practice visits in the 3 years preceding the index date (1-4, 5-19, or ≥20) also did not confound the association between antibiotic exposure and risk of AMI.

Use of a regular dosage or a high dosage of a tetracycline antibiotic resulted in adjusted relative risk estimates of 0.71 (95% CI, 0.55-0.91) and 0.67 (95% CI, 0.30-1.53), respectively, compared with no antibiotic use. We could not stratify those taking quinolone because all case patients used regular dosages. There also was no suggestion of a substantial difference between those taking regular and high dosages of macrolides (OR, 0.97 and 0.85, respectively) or sulfonamides (OR, 1.01 and 0.94, respectively).

Further stratification of subjects taking antibiotics into those who received either 1 or 2 or more prescriptions prior to the index date resulted in similar relative risk estimates for all antibiotics but macrolides: the OR for 1 prescription was 1.03 (95% CI, 0.79-1.36) and for 2 or more prescriptions was 0.61 (95% CI, 0.34-1.11), compared with no antibiotic use.

We also stratified the switcher group (ie, those who used >1 type of antibiotic in the 3 years preceding the index date) into those who took tetracyclines plus quinolones and those who took all other combinations of antibiotics, which supposedly have no effect on the risk of AMI. This additional stratification did not yield different results between these 2 groups.

The distribution of the various indications (ie, types of infections that led to antibiotic treatment) did not differ substantially between the antibiotic treatment groups. For all antibiotics but sulfonamides, respiratory tract

infections accounted for approximately 40% to 50% of all prescriptions issued. For sulfonamides, this proportion was lower (approximately 20%); most prescriptions for sulfonamides were issued for urinary tract infections (approximately 50%). Within the various groups of antibiotics, the indications did not differ materially between cases and controls.

COMMENT

The findings of this large observational study indirectly support the hypothesis that certain chronic bacterial infections may play a role in the etiology of ischemic heart disease and that use of tetracyclines or quinolones for any indication might alter the course of such chronic infections and thereby reduce the risk of subsequent first-time AMI.

We explored the association between previous use of antibiotics and the risk of subsequent AMI because several observational studies previously reported a possible link between bacterial infections and subsequent coronary heart disease or AMI; however, these studies did not assess the exposure history of study subjects to antibiotics. Furthermore, 2 recent randomized clinical trials that were relatively small and must be considered preliminary reported that patients with AMI and elevated anti-*C pneumoniae* antibody titers had significantly lower recurrence and cardiac complication rates if they received post-AMI treatment with either azithromycin or roxithromycin

Table 2. Odds Ratios of Developing First-Time AMI in Relation to Use of Antibiotics in the 3 Years Preceding the Date of AMI*

| Antibiotic Group | No. of Cases (n = 3315) | No. of Controls (n = 13 139) | Odds Ratio (95% Confidence Interval)† | P Value |
|---------------------|----------------------------|---------------------------------|--|------------|
| No antibiotics | 1403 | 5318 | 1.0 (Referent) | . . . |
| Tetracyclines only | 82 | 452 | 0.70 (0.55-0.90) | <.01 |
| Macrolides only | 83 | 345 | 0.93 (0.73-1.20) | .59 |
| Sulfonamides only | 90 | 343 | 1.01 (0.79-1.29) | .96 |
| Quinolones only | 8 | 62 | 0.45 (0.21-0.95) | .04 |
| Penicillins only | 773 | 3094 | 0.94 (0.85-1.04) | .20 |
| Cephalosporins only | 62 | 253 | 0.90 (0.67-1.22) | .50 |
| "Switchers"‡ | 814 | 3272 | 0.91 (0.82-1.01) | .06 |

*AMI indicates acute myocardial infarction; ellipses, data not applicable.

†Data are adjusted for body mass index (weight in kilograms divided by the square of height in meters) and smoking.

‡"Switchers" are those who used a combination of antibiotic groups.

compared with placebo-treated patients.^{7,8} Whereas these 2 randomized trials explored the effect of antibiotics on the follow-up of subjects after AMI, our analysis was designed to explore the effect of antibiotics on the risk of developing a first-time AMI in previously healthy subjects in the absence of apparent clinical risk factors for AMI. To our knowledge, this is the first study of its kind. The well-documented risk factors for AMI (eg, hyperlipidemia, hypertension, and smoking) do not account for all incident AMI cases; it has therefore been postulated that additional risk factors for AMI must exist. To test whether bacterial infections may be such an independent additional risk factor, we a priori restricted the study to subjects without cardiovascular or metabolic diseases predisposing for AMI because any effect of a newly hypothesized risk factor for AMI would most likely become apparent in this relatively healthy study population.

The findings for tetracyclines were more distinct in men than in women. However, most of the study population (74%) was men, and stratification into small subgroups can easily result in chance findings. The same holds true for quinolone use, for which the finding was based on only 8 cases and 62 controls.

The optimal antibiotic treatment for *C pneumoniae* infections has not been established yet in well-designed clinical trials; most treatment recommendations stem from anecdotal reports and in vitro studies.^{21,22} However, based on current treatment strategies,²¹ our findings of a reduced risk of developing AMI in subjects who had taken tetracyclines or quinolones, but not macrolides, sulfonamides, penicillins, or cephalosporins, would fit well with the hypothesis that respiratory tract infections with *C pneumoniae* may play a role in the etiology of ischemic heart disease.

Tetracyclines are considered first-line treatment for *C pneumoniae* infections.²¹ The newer macrolides (eg, azithromycin, clarithromycin) have substantial antibacterial activity against *C pneumoniae*.²¹ However, most macrolide use in this study

(75%) was erythromycin, which has been reported to be of uncertain efficacy against *C pneumoniae*^{11,21}; this may explain the lack of an apparent macrolide effect in our study. Furthermore, 71% of cases who used macrolides used tablet doses of only 250 mg, which might be insufficient to eradicate *C pneumoniae* infections.²¹ There was a suggestion that the risk of AMI became lower with increasing exposure to macrolides (based on number of treatment courses), but this finding has to be interpreted cautiously because it could be a chance finding.

The effect of previous quinolone use on the risk of developing AMI also has to be interpreted with caution because it is based on a relatively small number of cases. However, quinolones do have antibacterial activity against *C pneumoniae*^{21,22} in vitro, but their efficacy in vivo has been rather poorly established as yet. The lack of an effect of sulfonamides and β -lactam antibiotics would also not be unexpected because they are considered ineffective against *C pneumoniae* infections.²¹

Despite the fact that our findings fit well into the hypothesis of a causal role of bacterial infections (ie, particularly *C pneumoniae*) in the etiology of AMI,¹⁻⁶ they need careful interpretation for the following reasons.

First, any observed effect of antibiotics on the risk of AMI is only an indirect marker for an etiologic role of bacterial infections. It is an association, but it does not prove the existence of a causal relationship. It is possible in theory that the tetracycline and quinolone effects were not due to antibiotic activity but to some different pharmacological mechanism.

Second, it is not possible to infer the involvement of particular bacteria in the etiology of AMI. Despite the fact that the findings differed across antibiotic groups and that the observed pattern would be consistent with the hypothesis of a causal role of *C pneumoniae* infections in the etiology of ischemic heart disease, we cannot rule out that bacteria other than *C pneumoniae* (or mixed infections) could be involved. We were not in a position to specifically identify subjects who had

a history of *C pneumoniae* infections because serologic tests to detect anti-*Chlamydia* antibodies are not routinely done in general practice. Therefore, considerable misclassification could not be avoided, but an even stronger effect of tetracycline or quinolone antibiotics may have resulted if we were able to restrict the analysis to subjects who have been previously infected with *C pneumoniae*.

Third, confounding by socioeconomic status (SES) has been proposed as a possible reason for an increased positive *C pneumoniae* seroprevalence among patients with AMI (ie, subjects with a low SES have an increased risk for AMI and they also have more infections than subjects with higher SES). Socioeconomic status is difficult to define and measure; in an attempt to reduce the risk of confounding by SES (and geography), we matched cases to controls on the same general practice attended. Furthermore, we did not study the effect of infections in general, but the effect of different groups of antibiotics on the risk of AMI. Socioeconomic status would therefore confound our findings if tetracyclines and quinolones, but not other antibiotics, were particularly given to subjects with high SES, which seems to be unlikely. In addition, we adjusted the analysis for number of practice visits; the average number of practice visits in the 3 years preceding the index date was closely similar for both cases and controls and was independent of use of particular antibiotics. This indicates that accessibility to medical care (as a marker for SES) did not confound our findings.

Finally, we cannot completely exclude chance or unknown confounders or biases as an explanation for the findings of this observational study. However, by a priori exclusion of all cases and controls with documented clinical risk factors for AMI, we minimized the risk of possible confounding by cardiovascular diseases (eg, hypertension, congestive heart failure) or metabolic disturbances (eg, diabetes mellitus).

It is a strength of the study that we were in a position to not only compare subjects who had taken antibiotics with those who had not, but also to distinguish

among different types of antibiotics with differing antibacterial activities. The fact that previous use of tetracyclines and quinolones (eg, not of β -lactam antibiotics) was associated with a lower risk for AMI in our study population provides indirect evidence that infections with organisms susceptible to tetracycline antibiotics might be involved in the etiology of ischemic heart disease.

It must be emphasized that these observational findings should not be interpreted as suggesting that antibiotics should be given to patients to prevent AMI. These potentially important findings on the role of chronic infections in the etiology of AMI need further confirmation, particularly from large-scale prospective randomized trials.

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Courage is the price that life exacts for granting peace.
The soul that knows it not, knows no release
From little things;
Knows not the livid loneliness of fear,
Nor mountain heights where bitter joy can hear
The sound of wings.
—Amelia Earhart Putnam (1898-1937)