Use of Antibiotics Is Not Associated With Decreased Risk of Myocardial Infarction Among Patients With Diabetes

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OBJECTIVE — To study the relationship between exposure to antibiotic treatment and risk of subsequent myocardial infarction (MI) in patients with diabetes.

RESEARCH DESIGN AND METHODS — A case-control design was used to assess the effect of previous antibiotic exposure in diabetes patients with acute, nonfatal or fatal MI (case subjects) and individually matched control subjects (four control subjects to one case subject, matched on sex, age, and index date). Subjects were sampled from the Northern California Kaiser Permanente Diabetes Registry, a well-characterized, ethnically diverse diabetic population from Kaiser Permanente Medical Care Program, Northern California Region. MI events were ascertained during a 2-year observation period (1998–1999). Separate conditional logistic regression models were specified to assess antibiotic exposure history (cephalosporins only, penicillins only, macrolides only, quinolones only, sulfonamides only, tetracyclines only, as well as more than one, any, or no antibiotic) for three nested windows before the index date (0–6 months, 0–12 months, 0–24 months), facilitating assessment of whether the potential effect was dependent on the timing of the exposure.

RESULTS — A total of 1,401 MI case subjects were observed. Odds ratios were calculated in models adjusted for age, sex, race, education attainment, time since diabetes diagnosis, diabetes type and treatment, use of diet and exercise, total cholesterol, HDL cholesterol, triglyceride levels, hypertension, elevated urinary albumin excretion, serum creatinine, BMI, and smoking. We found no evidence of a protective effect of any of these therapeutic classes of antibiotics during any of the three time frames.

CONCLUSIONS — Our study does not support the hypothesis that use of antibiotics has a protective effect for prevention of coronary heart disease in diabetic patients.

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In the past decade, there has been a rekindled interest in the potential etiologic role of infection in the development of coronary heart disease (CHD). Bacteria (specifically *Chlamydia pneumoniae* and *Helicobacter pylori),* viruses (including herpes simplex and cytomegalovirus), and infections associated with severe periodontal disease have been associated with an increased risk of myocardial infarction (MI) (1–8). Several potential mechanisms have been proposed whereby infection could contribute to the development of CHD, including direct endothelial injury from the infectious agent, indirect endothelial injury (from serum lipids or circulating immune complexes), an increased propensity for thrombus formation (e.g., via changes in fibrinogen levels), and promotion of smooth muscle cell proliferation (1,9,10).

Infection with *C. pneumoniae,* a common respiratory pathogen, has acquired the most convincing evidence for a causal link to CHD events (1,9,11). Antibodies to *C. pneumoniae* have been associated with an increased risk of CHD in cross-sectional, retrospective, and prospective studies. *C. pneumoniae* has been found in atherosclerotic plaques in human coronary and carotid arteries (12,13). In animal models, infection with *C. pneumoniae* leads to atherosclerosis, and treatment with macrolide antibiotics such as azithromycin blocks this effect (14–16). Two small studies have suggested that treating patients with antichlamydial antibiotics may reduce the risk of coronary events (17,18). Three large randomized, controlled trials are in progress to assess the effect of antibiotics on secondary prevention of CHD (19–21). Additional findings supporting this hypothesis were reported in a recent case-control study in nondiabetic subjects, where patients with MI were significantly less likely than control subjects to have been exposed during the previous 3 years to the antichlamydial antibiotic groups of quinolones (odds ratio [OR] 0.45) or tetracyclines (OR 0.70) (22). Given the prevalence of *C. pneumoniae* infection, if *C. pneumoniae* does increase risk of CHD, the proportion of CHD attributable to this agent would be substantial.

Studying the association between infection and CHD in diabetic patients is of interest because patients with diabetes have a substantially increased risk of MI relative to normoglycemic patients (23), and diabetes affects immune response to infections (24). The one study that has examined the association between *C. pneumoniae* antibodies and CHD in patients with type 1 diabetes found no association (25). However, the prevalence of elevated *C. pneumoniae* antibody titers in this study was much higher than is gen-

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Abbreviations: CHD, coronary heart disease; KP, Kaiser Permanente Medical Care Program; MI, myocardial infarction.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

erally found in the U.S. There are no reported studies of the association between antibiotic exposure and MI in diabetic subjects. The current study was undertaken to investigate the potential association between infection and MI by assessing the protective effect of antibiotic exposure on MI events in a large, well-characterized group of adults with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Study population

The setting for this study was the Kaiser Permanente Medical Care Program (KP), Northern California Region, which is a prepaid, group model health plan with 37 hospitals and clinics offering comprehensive medical and mental health services. This health maintenance organization (HMO) has high market penetration: the average census was 2.7 million members in 1999, or 25% of the region's population. The KP membership closely approximates the sociodemographics of the general population in the region, except for the extreme tails of the socioeconomic distribution (26–28), and thus, this study should be generalizable to insured populations with diabetes. The Northern California Kaiser Permanente Diabetes Registry identifies health plan members with diabetes from automated databases for pharmacy, laboratory, and hospitalization records as well as outpatient diagnoses. Mortality, clinical outcomes, laboratory results, prescriptions, inpatient and outpatient diagnoses, utilization, costs of care, and monthly membership data are downloaded annually. As of January 1, 1998, there were 101,698 active members with diabetes in this registry, which has been estimated to include ~98% of KP members with diabetes. Similar to the whole KP membership, this cohort with diabetes is racially diverse (59% non-Hispanic white, 12% African-American, 12% Hispanic, 12% Asian/Pacific Islander, 3% Native American). During 1994–1997, each member included in the diabetes registry was sent a survey. A total of 83% of these members responded, providing detailed information about race, type of diabetes, medical history, health behaviors, and family history of diabetes. More complete descriptions of the registry, the survey, and its development have been published previously (29–34).

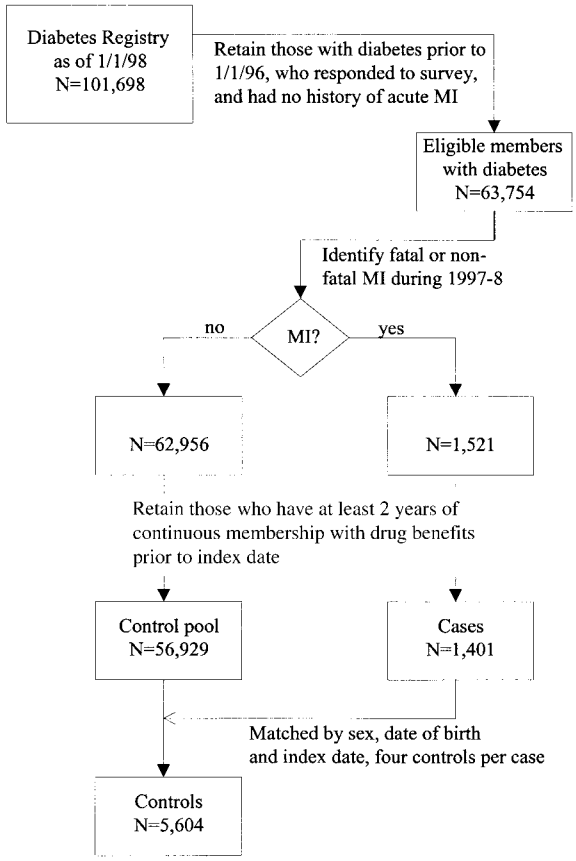

Figure 1—*Case and control subject selection for 1997–1998.*

The source population (63,754) from which case and control subjects were selected included the subset of registry members who *1*) were identified as having diabetes on or before January 1, 1996; *2*) responded to a diabetes survey (83% response rate); and *3*) had no record of a hospitalization for acute MI before December 31, 1996 (see Fig. 1). Restriction to survey responders was necessary, because most of the covariate information, including type of diabetes, duration of disease, and demographics, was available only for those who responded to the diabetes survey. We excluded 9% of the members because they lacked a window of at least 24 continuous months of follow-up or lacked a benefit plan that included drug coverage. Those lacking a drug benefit were excluded from the study, because they were more likely to purchase their medications in non-KP pharmacies; therefore, exposure may be misclassified when relying solely on our KP pharmacy database. We identified 1,401 fatal or nonfatal MIs during 1997–1998. From the remaining pool of 56,929 members, we selected 5,604 control subjects: four for each case, matched by sex, date of birth, and index date.

Sources of data

To ascertain exposure to antibiotics, we used a computerized pharmacy database (Pharmacy Information Management System), which is used for all KP pharmacy operations. Pharmacy personnel enter data in real time on each outpatient and inpatient prescription filled before the prescription can be issued. Because the data are used to prepare the prescription label, they are considered complete and accurate. Similarly, all laboratory tests are performed at KP regional and facility laboratories and entered into a regional database that is used by clinicians to order tests, obtain results, and share them with patients; therefore, the data are of higher quality than a chart review study could achieve. A database with all KP hospitalizations since 1971 is maintained with one principal and up to 12 secondary discharge diagnoses and codes for up to 7 procedures (comparable to the UB-92

forms required of hospitals in California). Diagnoses and procedures were coded according to the ICD-9-CM. This study's case definition for MI was based on an ICD-9-CM code 410 specified as either a primary hospitalization discharge diagnosis or the underlying cause of death on a death certificate. We excluded secondary diagnoses coded as 410 because these are sometimes misused as an indicator of an old MI, which should have been coded as 412, when the medical coder considers the old MI as potentially contributing to the current condition. A second database contains referral and claims data for all hospitalizations in non-KP hospitals for which KP incurs a charge. Previous studies have validated KP hospital discharge diagnoses of MI by medical chart review. In a recent (year 2000) random sample of 602 hospital discharge diagnoses of MI based on computerized data, 98.7% were confirmed by medical chart review based on standard criteria including consistent symptoms, elevated cardiac enzymes, and/or diagnostic electrocardiographic changes (unpublished data). CAMLIS, a validated software program (35), was used to identify deaths due to MI through linkage with the computerized State of California Death Certificate files. All health plan members with diabetes who were older than 19 years were surveyed during 1994–1996. The primary goal of the survey was to capture individual-level information on, among other items, ethnicity, education, behavioral risk factors, type of diabetes, and duration of disease. For patients taking insulin, type of diabetes was determined by a decision algorithm based on age at diagnosis, length of time between initial diagnosis and start of insulin treatment, history of insulin "holidays" (intervals of 3 months or longer off insulin after initiation), and presence of obesity based on BMI at diagnosis (>27.8 in men and >27.3 kg/m^2 in women) (30). The survey accommodated non–English-speaking members as well as those with vision impairment. There were 77,726 responders (~83% response rate).

Analytic methods

A case-control design was used to assess the effect of previous antibiotic exposure in diabetes patients with nonfatal or fatal MI (case subjects) and control subjects. We identified all cases of MI occurring within our source population (active members of the Northern California Kaiser Permanente Diabetes Registry) during the observation period. We used individual matching and risk-set sampling of control subjects (36), which entailed randomly selecting four control subjects from the same source population that were individually matched on 5-year age categories, sex, and the index date of each case. The index date is relevant for the control subjects, because it functioned as the end date for the defined window of antibiotic exposure. This study design was chosen for comparability with previous studies that were almost exclusively case-control designs and because risk-set sampling is an efficient way to study defined time windows of exposure to therapy.

For each case and control subject, antibiotic exposure history was defined as having occurred in three predefined windows before the index date (≤6, ≤12, and ≤24 months), facilitating assessment of whether the potential effect was dependent on the timing of the exposure. Antibiotic exposure was based on all recorded outpatient or inpatient prescriptions filled within the window of observation and was categorized as cephalosporins only, penicillins only, macrolides only, quinolones only, sulfonamides only, or tetracyclines only, as well as more than one, any, or no antibiotic. Aminoglycosides were excluded as an individual exposure because their use is too rare (one exposure per 8,390 diabetes person-years).

Conditional logistic regression modeling was used to estimate the effect (protective or otherwise) of antibiotic therapy relative to no history of antibiotic therapy. All models were rerun for the three time windows before the index date (6, 12, and 24 months prior) to assess whether potential antibiotic effects were dependent on the timing of the exposure. Standard approaches were used to assess and minimize confounding (36); models were adjusted for age, sex, race, education attainment, time since diabetes diagnosis, type of diabetes, and treatment regimen (e.g., use of oral hypoglycemic agents versus insulin, as markers for diabetes severity), use of diet and exercise in treatment regimen, dyslipidemia (total cholesterol, HDL cholesterol, triglyceride levels), hypertension, elevated urinary albumin excretion, serum creatinine level, BMI, and smoking. Laboratory tests (e.g., lipids, creatinine, and urine albumin) were assessed separately for the windows of time before the index date. If more than one measure was available within a given window, the average was taken. Additionally, a summary comorbidity score was added to models to adjust for other comorbidities (37). We used missing variable indicators ("indicator method") (38,39) for subjects for whom covariate information was missing. Because the analysis for the same individuals was repeated for three different time windows, we used a Bonferroni correction to adjust our level of significance ($\alpha/3 = 0.0167$) and the level of confidence for confidence intervals (98.33%).

RESULTS — A total of 1,401 cases of fatal or nonfatal MI occurred during the observation period of January 1, 1998, through December 31, 1999. A total of 5,604 control subjects were matched as described previously. The characteristics of the case and control subjects are shown in Table 1. As expected, when comparing subjects experiencing MI events with control subjects, there were significant differences between the two groups; in particular, known cardiovascular risk factors were more apparent in the case group. Conditional logistic regression models were used to estimate the effects of antecedent antibiotic use on MI during each of the three time windows. ORs were calculated for six classes of antibiotics (cephalosporins, macrolides, penicillins, sulfonamides, tetracyclines, and quinolones). Models were adjusted first for age and sex only (model 1) and then additionally for race, education attainment, time since diabetes diagnosis, diabetes type and treatment, use of diet and exercise, total cholesterol, HDL cholesterol, triglyceride levels, hypertension, elevated urinary albumin excretion, serum creatinine level, BMI, and smoking (model 2). Adjusted OR estimates failed to provide evidence of a protective effect of any of the therapeutic classes of antibiotics during any of the three time frames (Table 2). In fact, adjusted models suggested increased odds of MI associated with use of "cephalosporin only" during the previous 6 months or 12 months, "penicillin only" during the previous 6 months, and multiple antibiotic use (two or more) during each time period. Furthermore, the evidence (not shown) suggests increased odds of MI associated with any use of cephalosporin (including with use of

Table 1—*Characteristics of case and control subjects*

	Case subjects (n = 1,401)	Control subjects (n = 5,604)	P (χ^2 test)
Demographic			
Age (years)	68.2 ± 10.8	65.6 ± 11.0	0.0001
Sex, female	588 (42.0)	2,352 (41.8)	
Race			
White	936 (66.8)	3,200 (57.10	0.001
Black	128 (9.1)	695 (12.4)	
Hispanic	91 (6.5)	476 (8.5)	
Asian	103 (7.4)	629 (11.2)	
Pacific Island	19 (1.4)	37 (0.7)	
Native American	6 (0.4)	23 (0.4)	
Other	5 (0.4)	20 (0.4)	
Multi-ethnic	69 (4.9)	372 (6.6)	
Unknown	44 (3.1)	152 (2.7)	
Socioeconomic status			
Education			
High school or less	680 (48.5)	2,293 (40.9)	0.001
Some college	317 (22.6)	1,444 (25.8)	
College graduate or higher	258 (18.4)	1,252 (22.3)	
Unknown	146 (10.4)	615 (11.0)	
Behavior			
Smoking status			
Never	547 (39.0)	2,388 (42.6)	0.001
Former	528 (37.7)	2,106 (37.6)	
Current	182 (13.0)	464 (8.8)	
Unknown	144 (10.3)	616 (11.0)	
Diabetes treatment - exercise	560 (40.0)	2,815 (50.2)	0.001
Diabetes treatment - diet	765 (54.6)	3,377 (60.3)	0.001
Clinical			
Type of diabetes			
Type 1	42 (3.00)	122 (2.18)	0.038
Type 2	1,323 (94.4)	5,379 (96.0)	
Unknown	36 (2.6)	103 (1.8)	
Age of onset (years)	53.12 ± 14.1	53.26 ± 13.4	0.74
Duration of diabetes (years)	14.82 ± 11.3	11.94 ± 10.5	0.0001
Family history of diabetes	669 (47.8)	2,424 (43.2)	0.005
BMI (kg/m^2)	29.29 ± 5.7	29.47 ± 6.1	0.35
Peripheral neuropathy	418 (29.8)	1,273 (22.7)	0.001
Hypertension	1,310 (93.5)	4,315 (77.0)	0.001
Diabetes prescription within 2 years			
Insulin only	414 (29.6)	1,179 (21.0)	0.001
Oral hyperglycemic agent	651 (46.5)	3,047 (54.4)	
Combination	205 (14.6)	580 (10.4)	
No treatment	131 (9.4)	798 (14.2)	
Antilipemics	441 (31.5)	1,074 (19.2)	0.001
Clinical (laboratory)			
Albumin (micro/macro)	537 (38.3)	1,342 (24.0)	0.001
Serum creatinine level (mg/dl)	1.48 ± 1.4	1.10 ± 0.8	0.0001
HDL cholesterol (mg/dl)	38.81 ± 11.3	41.45 ± 12.6	0.0001
LDL cholesterol (mg/dl)	143.65 ± 39.3	135.26 ± 34.8	0.0001
Total cholesterol (mg/dl)	227.04 ± 51.8	215.78 ± 42.4	0.0001
Total cholesterol/HDL ratio	6.26 ± 2.2	5.59 ± 1.8	0.0001
Triglycerides (mg/dl)	235.58 ± 198.5	219.70 ± 182.6	0.066
HbA_{1c} (%)	8.33 ± 1.8	8.29 ± 1.8	0.56

Data are means ± SD or n (%).

Table 2—*Adjusted OR estimates of MI given antecedent antibiotic use*

	Case subjects (*n*)	Control subjects (*n*)	Model 1			Model 2		
			OR*	98.33% CI	*P*‡	OR†	98.33% CI	*P*‡
6 months prior to index date								
No antibiotic (reference)	781	3,772						
Cephalosporin only	126	341	1.72	(1.28–2.31)	0.0001	1.46	(1.05–2.02)	0.0059
Erythromycin only	33	136	1.22	(0.74–2.03)	0.35	1.31	(0.75–2.28)	0.24
Penicillin only	129	441	1.40	(1.05–1.84)	0.0044	1.31	(0.97–1.79)	0.0340
Sulfonamide only	69	237	1.36	(0.94–1.96)	0.0451	1.38	(0.92–2.05)	0.0554
Tetracycline only	18	74	1.17	(0.60–2.28)	0.56	1.14	(0.54–2.39)	0.67
Quinolones only	33	99	1.72	(1.00–2.95)	0.0162	1.21	(0.67–2.20)	0.44
Multiple (two or more)	212	504	1.93	(1.52–2.46)	0.0001	1.29	(0.98–1.69)	0.0254
12 months prior to index date								
No antibiotic (reference)	566	2,787						
Cephalosporin only	142	452	1.55	(1.17–2.05)	0.0002	1.30	(0.95–1.78)	0.0428
Erythromycin only	38	195	1.02	(0.64–1.63)	0.91	1.02	(0.62–1.69)	0.93
Penicillin only	151	600	1.22	(0.94–1.59)	0.07	1.17	(0.88–1.55)	0.20
Sulfonamide only	73	297	1.16	(0.81–1.65)	0.32	1.11	(0.76–1.63)	0.50
Tetracycline only	17	100	0.89	(0.46–1.73)	0.67	0.70	(0.34–1.45)	0.24
Quinolones only	26	96	1.40	(0.77–2.52)	0.18	1.14	(0.59–2.18)	0.64
Multiple (two or more)	388	1,077	1.67	(1.37–2.04)	0.0001	1.20	(0.96–1.50)	0.0560
24 months prior to index date								
No antibiotic (reference)	346	1,764						
Cephalosporin only	100	449	1.18	(0.86–1.63)	0.21	1.02	(0.72–1.45)	0.90
Erythromycin only	41	224	0.91	(0.57–1.45)	0.62	0.96	(0.58–1.58)	0.84
Penicillin only	151	679	1.16	(0.88–1.53)	0.19	1.16	(0.86–1.57)	0.22
Sulfonamide only	65	296	1.19	(0.81–1.73)	0.28	1.04	(0.69–1.55)	0.84
Tetracycline only	16	80	1.09	(0.53–2.24)	0.78	1.12	(0.51–2.44)	0.73
Quinolones only	25	90	1.60	(0.89–2.89)	0.057	1.28	(0.67–2.42)	0.36
Multiple (two or more)	657	2,022	1.67	(1.37–2.02)	0.0001	1.22	(0.98–1.52)	0.0280

*Model 1 adjusted for age and sex. †Model 2 adjusted for age, sex, race, education, type of diabetes, time since diabetes diagnosis, first-degree family history of diabetes, use of diet and exercise to treat diabetes, diabetes therapy, antilipemics, hypertension, peripheral neuropathy, smoking status, obesity (BMI), urinary albumin excretion, serum creatinine, HDL, HbA_{1c}, total cholesterol, and triglycerides. Missing variable indicators were included for variables that were incomplete. ‡$Pr > \chi^2$; use Bonferroni corrected level of significance: 0.05/3 = 0.0167.

other antibiotic classes during the same window) during the previous 6 months (OR 1.25, 95% CI 1.03–1.53) or 12 months (1.19, 1.00–1.41) or any use of tetracyline during the previous 6 months (1.71, 1.13–2.59). We have previously compared the demographic composition (age, sex, and socioeconomic status) in the source population (survey responders) from which case and control subjects were drawn with those excluded from this study because of survey nonresponse (31). Relative to responders, nonrespondents were slightly younger (56 vs. 61 years of age) and slightly less likely to be women (45 vs. 47%) but were of similar socioeconomic status (e.g., 25% of block group with at least a high school education for both responders and nonresponders). Additionally, the rates of MI were somewhat lower, albeit not significantly so, among nonresponders (age and sex-adjusted hazard ratio 0.85; $P = 0.06$). Although such differences between responders and nonresponders are not unexpected, they are unlikely to modify the relationship between antibiotic use and subsequent MI.

CONCLUSIONS — We found no evidence that usual antibiotic treatment among patients with diabetes was associated with reduced fatal or nonfatal MI events for periods of 6, 12, or 24 months after such treatment. Use of some antibiotics, particularly cephalosporins, was associated with slightly increased odds of subsequent MI events. No evidence of a protective effect was seen when antibiotic exposure was examined in three different time periods before the index MI event.

Other studies that have investigated the possible role of infection in CHD by examining the association between exposure to antibiotics and subsequent risk of CHD have found mixed results. One study reported a protective association between tetracyclines (adjusted OR 0.70, 95% CI 0.55–0.90) and quinolones (0.45, 0.21–0.95) and the risk of subsequent MI (22), whereas three studies found no evidence of a benefit (40–42).

Interpreting the results of such studies, including the current study, is difficult. Without randomization, results may be confounded by unmeasured factors associated with both the probability of a CHD event and antibiotic exposure, which could lead to over- or underestimations of the true association. Our findings of increased risk are likely due to residual confounding by comorbidities (2,43) rather than a causal association between antibiotic exposure and MI events. Sicker patients are more likely to experience MI events and are more likely to require an-

tibiotic treatments for reasons unrelated to the MI, thus leading to an artifactual relationship between antibiotics and MI. One of the strengths of the current study is the control for multiple CHD risk factors. However, it is still possible that the unexpected positive association between exposure to cephalosporins and CHD is due to confounding (by severity) (43) from one or more unmeasured comorbid conditions associated with both CHD and cephalosporin use (e.g., chronic lung diseases).

It is important to note that the lack of association between recent exposure to antichlamydial antibiotics and CHD seen in the current study does not preclude the possibility that *C. pneumoniae* plays an etiologic role in the initiation or progression of atherosclerosis or that treatment for *C. pneumoniae* will be effective in reducing CHD. Conventional treatment with antichlamydial antibiotics for typical infections may show little effect on CHD risk because they are given at the wrong time or in insufficient doses or duration to have an effect. Chlamydia is an intracellular bacteria that can be difficult to eradicate. The three ongoing clinical trials (19, 20,44) of antibiotic treatment for secondary prevention of coronary artery disease use azithromycin for 3 or 12 months, compared with the typical treatment course of 7–10 days used for most infections. It is also possible that *C. pneumoniae* plays its main role in the initiation of atherosclerosis, and thus is not amenable to treatment later in life, or that any treatment benefits would require a period longer than the 2-year period we investigated to become apparent.

The current study has several important strengths. This is the first large study of this hypothesized effect in a population with diabetes. Study subjects were drawn from a large, well-characterized population that is generally representative of the population in the area. The study had reasonable power to detect the associations of interest. Data on subjects allowed for multivariate analyses that adjusted for many potentially confounding variables. Because the ascertainment of exposure is based on highly accurate electronic medical records, this study was not subject to recall bias.

Our study found no evidence to support the hypothesis that use of antibiotics has a protective effect for prevention of CHD in diabetic patients.

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