and abroad, these properties include the ability to inhibit expression, activation, and extracellular activity of matrix metalloproteinases (MMPs), which represent a family of enzymes that help mediate connective tissue breakdown in various diseases, including periodontitis, osteoarthritis and rheumatoid arthritis, osteoporosis, cancer invasion and metastasis, abdominal aortic aneurysms, and atherosclerotic plaques. Tetracyclines also can suppress the production of inflammatory mediators involved in many of these disorders, such as prostaglandin E_2, nitric oxide, interleukin 11β, tumor necrosis factor α, and interleukin 6, and they can scavenge reactive oxygen metabolites such as hypochlous acid, superoxide anion, and hydroxyl anion. By synthesizing a series of nonantimicrobial analogs of tetracycline (chemically modified tetracyclines), we and others have shown that the tetracyclines can inhibit connective tissue breakdown by a mechanism(s) independent of their antibiotic activity.[2,3] We recently reported that both doxycycline and several nonantimicrobial chemically modified tetracyclines inhibit the development of aortic aneurysms in rats, an effect associated with suppressed MMP activity in the arterial wall.[4]

Disruption of atheromatous coronary artery plaques is considered one of the principal pathologic mechanisms underlying AMI, and substantial evidence exists to suggest that plaque rupture is mediated in part by local inflammation and MMP activity.[5] Because tetracyclines inhibit MMPs and suppress other inflammatory activities associated with plaque rupture, and because even intermittent treatment with tetracyclines can result in long-term preservation of connective tissue in vivo,[6] we propose that the observations reported by Meier et al may have been related to a salutary nonantimicrobial effect on plaque stability. Further studies examining any potential benefits of tetracyclines in cardiovascular disease will therefore need to distinguish the antibiotic effects of these compounds from their capacity to reduce MMP-mediated connective tissue degradation.

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1. Meier CR, Derby LE, Jick SS, Vasilakis C, Jick H. Antibiotics and risk of subsequent first-time acute myocardial infarction. JAMA. 1999;281:427-431.
2. Ryan ME, Greenwald RA, Golub LM. Potential of tetracyclines to modify cartilage breakdown in osteoarthritis. Curr Opin Rheumatol. 1996;8:238-247.
3. Golub LM, Lee HM, Ryan ME, Giannobile WV, Payne J, Sorsa T. Tetracyclines inhibit connective tissue breakdown by multiple non-antimicrobial mechanisms. Adv Dent Res. 1998;12:12-26.
4. Curci JA, Petrinec D, Liao S, Golub LM, Thompson RW. Pharmacologic suppression of experimental abdominal aortic aneurysms. J Vasc Surg. 1998;28:1082-1093.
5. Shah PK. Role of inflammation and metalloproteinases in plaque disruption and thrombosis. Vasc Med. 1998;3:199-206.
6. Crout RJ, Lee HM, Schroeder K, et al. The "cyclic" regimen of low-dose doxycycline for adult periodontitis: a preliminary study. J Periodontol. 1996;67:506-514.

To the Editor: Dr Meier and colleagues[1] interpreted their findings as consistent with an antibiotic effect against vascular infections that may have a causal role in myocardial infarction, but they were careful to emphasize that their data do not support the current use of antibiotics to prevent AMI.

In contrast, some evidence suggests that antibiotics might, under some circumstances, be associated with triggering AMI. A case-control study (980 cases, 3136 controls) of antibiotic use in the 6-month period prior to hospitalization for acute vascular events (mainly myocardial infarction and stroke) using an administrative database including 160 194 enrollees of a Wisconsin health maintenance organization found an overall "protective" effect of antibiotic use (18.7% of cases, 22.1% of controls; $P = .02$).[2] However, antibiotic use in the month prior to hospitalization was "protective" only for adults aged 70 years or older (odds ratio [OR], 0.6; 95% confidence interval [CI], 0.5-0.8), "neutral" for adults aged 60-69 years (OR, 1.1; 95% CI, 0.8-1.5), and a "risk factor" for adults younger than 60 years (OR, 1.6; 95% CI, 1.2-2.0). The authors hypothesized that 1 possible explanation for this age-related risk profile was that antibiotics produced unstable plaque leading to acute vascular events in younger patients with "soft" plaque containing C pneumoniae, as is the case for the Jarisch-Herxheimer reaction following penicillin treatment for syphilis, which can be disastrous if the lesions are located in coronary arteries.[3]

These data support the cautionary advice of Meier et al.[1] Recommendations regarding antibiotic use in atherosclerotic disease can be made only after results of carefully conducted randomized trials that report age-stratified adverse events are available.[2]

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1. Meier CR, Derby LE, Jick SS, Vasilakis C, Jick H. Antibiotics and risk of subsequent first-time acute myocardial infarction. JAMA. 1999;281:427-431.
2. Hahn DL, Werner NL. Age-dependent associations of acute vascular events with prior antibiotic prescriptions. In: Stephens RS, Byrne GI, Christiansen G, et al, eds. Proceedings of the Ninth International Symposium on Human Chlamydial Infection. Napa, Calif: 1998:183-186.
3. Wintrobe MM, Thorne GW, Adams RD, et al, eds. Harrison's Principles of Internal Medicine. New York, NY: McGraw-Hill Book Co; 1970:895.

To the Editor: The possible association of infection and atherosclerosis remains controversial. It is extremely difficult to retrospectively assume that an effect seen with an antibiotic is secondary to "treating" a specific organism as implied in the article by Meier and colleagues.[1] This is especially true for C pneumoniae, for which the data on treatment are extremely limited and are further complicated by the lack of standardized diagnostic methods.

The finding of a protective effect with prior treatment with quinolones and tetracyclines, but not macrolides, is inconsistent and not explained by the statement that erythromycin has "uncertain efficacy" or is less effective than the other antibiotics. Erythromycin is one of the most active antibiotics against C pneumoniae. Doxycycline and erythromycin have both been recommended for treatment of C pneumoniae infections in

adults.[2] Clinical and microbiological failures have occurred following 3-week courses of both drugs.[3] The results of 2 published treatment studies have found that erythromycin, clarithromycin, and azithromycin had approximately 80% efficacy in eradicating C pneumoniae from the respiratory tract of children with pneumonia.[4,5] Two of the quinolones used by patients in the study by Meier et al, ciprofloxacin and norfloxacin, are significantly less active than erythromycin against C pneumoniae in vitro.[2] Although ofloxacin has an indication for treatment of genital C trachomatis infection, data on its efficacy for C pneumoniae infection are not available.

Meier and colleagues also suggested that if serologic tests had been performed to identify those patients with C pneumoniae infection, then a stronger effect of tetracyclines or quinolones would have been seen. However, in a large multicenter study of treatment of community-acquired pneumonia in adults, File et al[5] reported a clinical cure rate of 98% among patients who were treated with levofloxacin compared with 93% of those treated with ceftriaxone and/or cefuroxime axetil; either erythromycin or doxycycline could be added at the discretion of the investigator. The response rate of those with serologic evidence of C pneumoniae infection did not differ between those patients who received a cephalosporin alone or who had erythromycin or doxycycline added to their treatment regimen. The authors had some difficulty explaining why patients with "definite" serologic evidence of C pneumoniae infection responded to treatment with cephalosporins alone, which are considered to be ineffective against C pneumoniae infections.

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1. Meier CR, Derby LE, Jick SS, Vasilakis C, Jick H. Antibiotics and risk of subsequent first-time acute myocardial infarction. JAMA. 1999;281:427-431.
2. Hammerschlag MR. Antimicrobial susceptibility and therapy of infections due to Chlamydia pneumoniae. Antimicrob Agents Chemother. 1994;38:1873-1878.
3. Hammerschlag MR, Chirgwin K, Roblin PM, et al. Persistent infection with Chlamydia pneumoniae following acute respiratory illness. Clin Infect Dis. 1992;14: 178-182.
4. Block S, Hedrick J, Hammerschlag MR, Cassell GH. Mycoplasma pneumoniae and Chlamydia pneumoniae in pediatric community-acquired pneumonia. Pediatr Infect Dis J. 1995;14:471-477.
5. File TM, Segreti J, Dunbar L, et al. A multicenter, randomized study comparing the efficacy and safety of intravenous and/or oral levofloxacin versus ceftriaxone and/or cefuroxime axetil in treatment of adults with community-acquired pneumonia. Antimicrob Agents Chemother. 1997;41:1965-1972.

In Reply: Dr Haider and colleagues state that residual confounding, chance, or bias may be alternative explanations for our findings. We agree, as discussed in detail in our article. However, 3 reasons speak against selection bias (ie, antibiotic users differ from nonusers with regard to cardiovascular risk factors and medical attention sought): (1) there were no subjects with diagnosed cardiovascular diseases in our study; (2) we adjusted the analysis for number of practice visits (and therefore for medical attention sought) with no effect on the results; and (3) we analyzed antibiotic use in groups and not just users vs nonusers, which would mean that any bias had to selectively affect users of certain antibiotics but not others.

Dr Glenn suggested further adjustment for number of comparisons. Such statistical adjustment may slightly affect results that already were based on small numbers and marginally significant. For this reason, we discussed the quinolone finding cautiously in our article, and we emphasize that neither the weak quinolone nor the stronger tetracycline finding should lead to premature conclusions about beneficial effects of antibiotics in the prevention or treatment of AMI.

Dr Golub and colleagues provide possible alternative mechanisms for how antibiotics may have an effect on plaque stability other than through antimicrobial activity. We agree and stated in our article the possibility that "the tetracycline and quinolone effects were not due to antibiotic activity but to some different pharmacological mechanism."

We agree with Dr Hahn's comments that both the timing of antibiotic exposure as well as the patient's age may have an important effect on the association between antibiotic exposure and AMI risk, if the association is indeed real.

Dr Hammerschlag provides additional insight into the limited data regarding the efficacy of antibiotics against C pneumoniae. The relative lack of data in humans and the fact that in vitro and in vivo data may differ substantially for certain antibiotics led us to cautious conclusions. We did not, however, claim in our article that "if serologic tests had been done to identify those with C pneumoniae infection, a stronger effect of tetracyclines would have been seen." We speculated that "a stronger effect . . . may have resulted if we were able to restrict the analysis to subjects who have been previously infected with C pneumoniae." This statement was based on the notion that eliminating nondifferential misclassification usually leads to a stronger association in an observational study, given that a real relationship of exposure to outcome exists. We hope that our study, which does not prove a causal relationship of C pneumoniae to AMI, stimulates further research on the etiologic role of infections in cardiovascular diseases and that more data on treatment strategies against C pneumoniae will become available.

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National Stroke Association Guidelines to Prevent Stroke

To the Editor: The National Stroke Association (NSA) guidelines on prevention of a first stroke address an important public health problem.[1] However, the statements in the article regarding the value of carotid endarterectomy (CE) for patients with asymptomatic stenosis are highly suspect.

The guidelines state that CE is useful in individuals with asymptomatic carotid narrowing of greater than 60% if the sur-