Carotid Atherosclerosis and Rheumatoid Arthritis

TO THE EDITOR: Roman and colleagues (1) concluded that compared with matched control participants, patients with rheumatoid arthritis have a much higher prevalence of ultrasonographically determined carotid atherosclerotic plaque independent of a broad spectrum of potential confounders. Unexpectedly, they did not find a significant association between the levels of plasma inflammatory markers (that is, C-reactive protein and some endothelial adhesion molecules) and carotid artery intima–media thickness and plaque among patients with rheumatoid arthritis. Nevertheless, the authors postulated that the biological mechanisms by which premature atherosclerosis develops in rheumatoid arthritis could be largely mediated by underlying chronic inflammation.

Given the cross-sectional design and the relatively small sample size of this study, it is clear that chronic inflammation (a typical feature in patients with rheumatoid arthritis regardless of their atherosclerotic status) could probably be a key mechanism in the development of atherosclerosis. It would be interesting to know whether significant associations were observed between the prevalence of carotid atherosclerotic plaque and the circulating levels of autoantibodies, such as rheumatoid factor titers, anticyclic citrullinated peptide (anti-CCP) antibodies, and antinuclear antibodies. This additional information could be potentially useful because it might further confirm the evidence of a possible biological link between autoimmune mechanisms and accelerated atherosclerosis in rheumatoid arthritis, as well as in other autoimmune diseases. Future interventional studies with disease-modifying agents that effectively suppress the production of autoantibodies are obviously necessary to determine whether these autoimmune mechanisms can really play a pathogenic role in rheumatoid arthritis atherogenesis, and whether these pharmacologic interventions may be effective in reducing increased cardiovascular risk in patients with rheumatoid arthritis.

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Potential Financial Conflicts of Interest: None disclosed.

Reference
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IN RESPONSE: We, too, expected to find a relationship between markers of systemic inflammation and evidence of carotid atherosclerosis in patients with rheumatoid arthritis. Although our study did not define the mediators of accelerated atherosclerosis or the markers that predict it, we believe our findings support an important role for chronic inflammation. The analyses suggested by Dr. Targher showed no association between autoantibodies (rheumatoid factor or anti-CCP antibodies) and the presence of carotid atherosclerosis in our patients. Carotid plaque was detected in 49% of patients with positive results for rheumatoid factor and in 46% of patients with negative results for rheumatoid factor (P = 0.78), as well as in 42% of patients with anti-CCP antibodies and 44% of those without anti-CCP antibodies (P = 0.84). Furthermore, although titers of anti-CCP antibodies may predict radiographic outcome and disease severity in rheumatoid arthritis (1), they did not predict carotid atherosclerosis. Mean levels (SD) for patients with and without plaque were 388 U/mL (SD, 783) and 480 U/mL (SD, 842), respectively (P = 0.85). However, the cross-sectional design of our study and our single measurements of autoantibodies and inflammatory mediators do not allow us to determine cumulative exposure; therefore, interpretation of our results is limited. These findings contrast with those of our study in patients with lupus (2), in whom the prevalence of atherosclerosis was similar to that in patients with rheumatoid arthritis; however, the presence of certain autoantibodies was inversely associated with carotid plaque. We agree that more focused and effective immunomodulatory therapy may prevent or attenuate morbidity and mortality due to atherosclerosis in rheumatoid arthritis. However, the specific targets for intervention are not yet clear. Indeed, it will be important to determine whether disease-modifying therapies that ameliorate symptoms and prevent joint damage in rheumatoid arthritis will also decrease the prevalence and severity of atherosclerosis in patients with rheumatoid arthritis.

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Treatment of Community-Acquired Methicillin-Resistant Staphylococcus aureus Infection

TO THE EDITOR: We were delighted to read the article by King and associates (1) on the emergence of community-acquired methicillin-resistant Staphylococcus aureus (MRSA) USA 300 clone as the predominant cause of community-onset S. aureus skin and soft-tissue infections in the Atlanta, Georgia, area. However, we disagree with the authors’ statement that “the efficacy of nonglycopeptide antimicrobial agents in treating MRSA skin and soft-tissue infections remains incompletely defined, and clinical trials are needed to better define their role.” Despite wide clinical experience with and acceptance of glycopeptides (for example, vancomycin) as the treatment of choice, limited controlled data exist to support this notion. Previously, the lack of antimicrobial agents with reliable activity against MRSA precluded comparative trials, but several alternatives to gly-
copeptide agents have recently become available. Linezolid, for example, has been extensively studied for the treatment of complicated skin and soft-tissue infections (2). This trial (2) found linezolid to be at least as efficacious as, if not superior to, vancomycin for treatment of skin and soft-tissue infections in which most identified causative bacterial isolates were MRSA. Linezolid also inhibits toxin production, which may prove to be of significant benefit since the gene encoding for the production of Panton-Valentine leukocidin toxin (which promotes inflammation and tissue necrosis) is almost always found in community-acquired MRSA strains (3). Coincidentally, this trial also provides some of the best available data on the efficacy of vancomycin for these types of infections. Although the empirical use of trimethoprim–sulfamethoxazole, minocycline, doxycycline, and clindamycin is often recommended, few published clinical data are available to substantiate their use, and most data precede the recent emergence of MRSA as a common pathogen in community-acquired skin and soft-tissue infections (4, 5). Daptomycin and tigecycline are additional treatment options, although they are hampered by their parenteral-only route of administration; in addition, few patients with MRSA infection were enrolled in trials that studied these drugs. Perhaps linezolid should be considered as one of the antimicrobial agents of choice for empirical treatment of skin and soft-tissue infections in areas with a high prevalence of community-acquired MRSA, especially with its 100% oral bioavailability, which potentially eliminates the need for hospital admission in many cases.

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Potential Financial Conflicts of Interest: Dr. de Almeida is a member of the Pfizer Speakers’ Bureau.

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TO THE EDITOR: King and colleagues (1) cite clindamycin, trimethoprim–sulfamethoxazole, and linezolid as alternatives to vancomycin for outpatient treatment of localized skin and soft-tissue infections due to MRSA. However, they point out the uncertain efficacy of these agents in MRSA infections and the problem of inducible clindamycin resistance. Mising from this list of alternatives, and from the susceptibility data included in the paper and in the Editors’ Notes, are the tetracyclines, of which minocycline is the most potent against staphylococci and with which there is the most clinical experience in treating MRSA infections (2).

Tetracyclines are highly orally bioavailable, inexpensive, and well tolerated, and remain active against nearly 100% of S. aureus isolates (whether methicillin-resistant or methicillin-susceptible) in many U.S. locales. These agents represent an economical option that avoids certain problems associated with clindamycin and trimethoprim–sulfamethoxazole. They deserve more attention in commentaries and should be studied in clinical trials to establish their comparative efficacy for treatment of MRSA infections.

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IN RESPONSE: We thank Drs. de Almeida and Bush and Dr. Johnson for their interest in our study, which demonstrated that the MRSA USA 300 clone has emerged as the predominant cause of community-onset skin and soft-tissue infections (accounting for nearly two thirds of all such infections) in urban Atlanta, Georgia. Our findings have important consequences for empirical antibiotic selection in these cases. Vancomycin is now the preferred choice for empirical therapy for patients with severe skin and soft-tissue infections who require admission to Grady Memorial Hospital in Atlanta, pending results of culture and susceptibility tests. Newer agents for the treatment of complicated gram-positive skin and soft-tissue infections, including linezolid, daptomycin, and tigecycline, have become available in recent years, as de Almeida and Bush noted. However, data from controlled trials comparing linezolid and vancomycin (1) and more limited data comparing the other newer agents with vancomycin suggest that these newer agents may be equivalent but not superior to vancomycin for the treatment of complicated skin and soft-tissue infections, including those due to MRSA. These newer agents are significantly more expensive than vancomycin (the daily cost at our institution for vancomycin is $10 compared with $134 for linezolid, $159 for daptomycin, and $133 for tigecycline). As Moellerling noted in an editorial about our study (2) and as a recent publication by an expert panel convened by the Centers for Disease Control and Prevention (CDC) stated, “data from controlled clinical trials are needed to establish optimal therapy for MRSA SSTIs [skin and soft-tissue infections]” (3). This is particularly the case for patients with mild to moderate infection who can be treated as outpatients and may require oral therapy. Incision and drainage are recommended primary therapies for furuncles and abscesses; in some cases, additional oral therapy may be of benefit. To
treat the large numbers of patients who have community-acquired MRSA skin and soft-tissue infections with oral linezolid, as de Almeida and Bush suggest, would be extremely expensive. In addition, there are major concerns about the potential for emergence of linezolid-resistant MRSA, such that the CDC expert panel recommended that “clinicians should consider reserving linezolid for use in more severe infections in consultation with an infectious disease specialist” (3). We agree with Dr. Johnson that tetracyclines (for example, minocycline or doxycycline) should be studied in controlled trials, as should the efficacy of other older agents (for example, trimethoprim–sulfamethoxazole and clindamycin), which generally have excellent activity in vitro against community-acquired MRSA (in particular USA 300) and for which data from controlled trials are currently lacking (4, 5). Fortunately, it now appears that this is likely to happen, given the National Institutes of Health’s recent request for proposals for a clinical trial for treatment of community-acquired MRSA infections.

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Potential Financial Conflicts of Interest: None disclosed.

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Cost-Effectiveness of Statins Added to Aspirin Therapy

TO THE EDITOR: Pignone and colleagues (1) concluded that adding a statin to aspirin therapy is cost-effective when the risk for coronary heart disease (CHD) is greater than 10%. In their model, the authors used a yearly statin cost of $730, which was the average of the Red Book costs for 10 mg of lovastatin and 10 mg of simvastatin.

I ﬁnd in my clinical practice that patients need higher doses of these drugs, more potent statins, or even a second lipid-lowering drug to reach the guidelines set by the National Cholesterol Educa-

tion Program Expert Panel (2). These approaches are more expensive than the model indicates. Does the authors’ model tell us what 10-year CHD risk would make it cost-effective to use 80 mg of atorvastatin, for instance?

Previous authors have questioned the cost-effectiveness of statins as primary prevention for younger, lower-risk patients (3). I hope that Pignone and colleagues’ conclusions are heeded by the organizations that are trying to measure quality. Patients’ baseline CHD risk should be considered when report cards are issued. However, in this era of looming “pay-for-performance” incentives, physicians may feel compelled to use statin therapy in more patients and to try to get all patients to certain low-density lipoprotein cholesterol goals, regardless of their estimated 10-year risk.

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Potential Financial Conflicts of Interest: None disclosed.

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IN RESPONSE: The effectiveness of high-dose statins or combination lipid-lowering therapy for primary prevention of CHD events has not been studied to date and was not included as part of our model. The trials that formed the basis of our estimates of costs and effectiveness in CHD risk reduction used low to medium doses of a single agent and minimal or no adjustment based on lipid levels (1). If more aggressive lipid-lowering treatment were to be found more effective in CHD event prevention, then further analyses would need to consider whether the additional costs and potential increase in adverse effects were sufﬁciently offset by the additional degree of effectiveness.

Our analysis identiﬁed a lower cost per quality-adjusted life-year gained than the previous analysis by Prosser and colleagues (2). Its results are similar to those of other models that have examined the cost-effectiveness of statins for primary prevention (3). Further studies are required to better identify reasons for the observed differences in results (4).

I agree with Dr. Chelmowski’s recommendation that baseline risk for CHD events be considered when measuring quality and developing pay-for-performance programs for CHD prevention. Recent efforts to develop methods to perform more informative evaluations are promising but will require improved informatics systems to be feasible for broad application (5).

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Objective: To investigate the possible association between erythropoietin and nephrogenic fibrosing dermopathy.

Methods and Findings: Data on clinical, laboratory, and erythropoietin variables were collected for 22 consecutive biopsy-proven cases of nephrogenic fibrosing dermopathy. Data on 50 consecutive patients from our center who were receiving long-term hemodialysis were collected for comparison. Univariate analysis was performed by using the Pearson chi-square test and analysis of variance. Multivariable analysis was performed by using a logistic regression model in which nephrogenic fibrosing dermopathy was the dependent variable and laboratory variables that differed between patients with nephrogenic fibrosing dermopathy and control patients at a P value of 0.10 or less were independent variables. Variables that did not follow a normal distribution (age, body weight, hemoglobin level, serum ferritin level, transferrin saturation, parathyroid hormone level, and erythropoietin dose) were log-transformed.

Pertinent demographic and laboratory data are summarized in the Table. Twenty-one of 22 patients with nephrogenic fibrosing dermopathy were receiving hemodialysis (5 short-term and 16 long-term) at diagnosis. All control patients and all patients with nephrogenic fibrosing dermopathy received recombinant human erythropoietin or darbepoetin-α. Patients with nephrogenic fibrosing dermopathy received a significantly higher dose of erythropoietin than control patients (427 U/kg of body weight per week [range, 66 to 1195 U/kg per week] vs. 198 U/kg per week [range, 14 to 720 U/kg per week]; P < 0.001) (Table). Patients with nephrogenic fibrosing dermopathy also had lower serum albumin concentrations and higher serum ferritin levels but similar hemoglobin concentrations compared with controls. In multivariable analysis, serum ferritin level (P < 0.001), parathyroid hormone level (P = 0.018), and erythropoietin dose (P = 0.016) were independently associated with nephrogenic fibrosing dermopathy.

In every case, nephrogenic fibrosing dermopathy developed after

### Table. Comparison of Clinical and Laboratory Data for Patients with Nephrogenic Fibrosing Dermopathy and for Control Patients*

| Variable                                      | Patients with Nephrogenic Fibrosing Dermopathy (n = 22) | Control Patients (n = 50) | P Value |
|-----------------------------------------------|--------------------------------------------------------|---------------------------|---------|
| Age, y                                        | 57.0 (32–84)                                           | 68.5 (24–86)              | 0.42    |
| Sex (women/men), n/n                         | 13/9                                                   | 22/28                     | 0.18    |
| Body weight, kg                              | 67.8 (42.6–168.0)                                     | 75.3 (48.0–135.8)         | 0.14    |
| Hemoglobin level, g/dL                       | 102 (82–163)                                          | 116 (88–144)              | 0.25    |
| Serum albumin level, g/L                     | 30.0 (18–40)                                          | 37.5 (23.0–49.0)          | <0.001  |
| Serum ferritin level, μg/L                   | 801 (134–3798)                                        | 162 (4–848)               | <0.001  |
| Transferrin saturation, %                    | 26 (14–88)                                            | 24 (1–80)                 | 0.12    |
| Serum calcium level mmol/L                   | 2.3 (1.6–2.7)                                         | 2.2 (1.8–2.7)             | 0.85    |
| mg/dL                                        | 9.2 (6.4–10.8)                                        | 8.8 (7.2–10.8)            |         |
| Serum phosphorous level mmol/L               | 1.6 (0.7–2.7)                                         | 1.6 (0.5–4.0)             | 0.66    |
| mg/dL                                        | 5.0 (2.2–8.4)                                         | 5.0 (1.5–12.4)            |         |
| Serum parathyroid hormone level, pmol/L      | 20.5 (4.1–85.5)                                       | 15.5 (4.4–75.7)           | 0.100   |
| Erythropoietin dosage, U/kg of body weight per wk | 427 (66–1195)                                        | 198 (14–740)              | <0.001  |

* All data are presented as median (range), except sex.
treatment with erythropoietin. In 15 of the 22 cases, the disorder developed 1 month (range, 0.5 to 4 months) after erythropoietin initiation. In 6 cases in which erythropoietin therapy was started more than 12 months before onset of nephrogenic fibrosing dermopathy, the dose was increased by a median of 312 U/kg per week (range, 155 to 597 U/kg per week) 1 month (range, 1 to 9 months) before symptoms began. Information regarding erythropoietin escalation was unavailable for 1 patient.

Median follow-up of case-patients with nephrogenic fibrosing dermopathy was 7.5 months (range, 0 to 30 months). Erythropoietin therapy was discontinued in 5 cases, resulting in improvement in 2 and stabilization in 2; data were not available in the remaining case. In 4 other cases, erythropoietin dose was decreased with subsequent clinical improvement in 3 cases and no improvement in 1 case. Six of the 12 patients whose erythropoietin therapy was not changed have died. In the surviving 6 patients, symptoms remained stable in 4, improved in 1, and worsened in 1. Survivors were followed for a range of 3 to 26 months, and those who died were followed for 2 to 21 months.

Discussion: Drugs, including erythropoietin, have been suspected in the pathogenesis of nephrogenic fibrosing dermopathy (4). We observed that patients undergoing dialysis who develop this disorder typically receive high doses of erythropoietin before diagnosis, often in the context of acute illness. This association may indicate a common etiologic link between erythropoietin resistance and nephrogenic fibrosing dermopathy, such as prolonged inflammatory states or development of antienterohpoietin antibodies (5, 6). It is also possible that high-level exposure to erythropoietin is an independent contributor to the disease. The expression of CD34 on spindle-like cells in skin affected by nephrogenic fibrosing dermopathy suggests infiltration by bone marrow–derived progenitors. Erythropoietin is known to increase numbers of circulating hematopoietic stem cells and endothelial progenitors by as much 300%. Furthermore, erythropoietin has been shown in vivo to trigger an exaggerated fibrin-induced wound-healing response that is histologically similar to nephrogenic fibrosing dermopathy (7).

The association between nephrogenic fibrosing dermopathy and high-dose erythropoietin therapy in our small study must be interpreted with caution. Patients were selected without randomization and received complex and varied therapeutic and dialysis regimens. Furthermore, high erythropoietin dosage may be a surrogate marker for 1 or more unmeasured (or unknown) pathogenic factors associated with renal impairment and dialysis in patients developing nephrogenic fibrosing dermopathy. Nonetheless, further study of the interplay between systemic inflammation and erythropoietin resistance and the nonerythropoietic effects of erythropoietin in patients undergoing dialysis is merited.

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CORRECTIONS

Correction: Computerization Can Create Safety Hazards: A Bar-Coding Near Miss
In an article on computerization and safety hazards (1), the fifth sentence under the heading “System-Based Redundancy” contained an error. The square of 0.4% is 0.16%, not 0.016%.

Reference
1. McDonald CJ. Computerization can create safety hazards: a bar-coding near miss. Ann Intern Med. 2006;144:510-6. [PMID: 16585665]

Correction: Bisphosphonates and Osteonecrosis of the Jaws
In a recent issue, a narrative review by Woo and colleagues (1) was misclassified as a systematic review. The title should have read, “Narrative Review: Bisphosphonates and Osteonecrosis of the Jaws.”

Reference
1. Woo SB, Hellstein JW, Kalmar JR. Systematic review: bisphosphonates and osteonecrosis of the jaws. Ann Intern Med. 2006;144:753-61. [PMID: 16702591]