sponsor. The GAIT ancillary trial was designed to be exploratory, and the hypothesis-generating procedure incorporated the most accurate assumptions about OA disease progression and outcome measures available at the time. Even today, the optimal radiographic measure of disease progression in OA remains a point of debate (2–5). The nonfluoroscopic MTP view utilized in the current study was optimized by the standard use of foot positioning templates at each visit to obtain consistent tibial plateau alignment.

After recruitment for the GAIT study began, several studies, including the GAIT ancillary trial, demonstrated that the progression of OA (as assessed by radiographic JSN) was substantially slower than had been assumed when GAIT protocols were developed (6–8). These reports, in part, led to our concerns about the limited power of the current study, as was clearly indicated in our report. Brandt and colleagues voice a concern about statistical precision, but not statistical bias. We agree that precision, due to a combination of slower disease progression and greater variability than predicted, contributed to low power in the ancillary study. We find little evidence to suggest that the nonfluoroscopic MTP view produced bias.

Contrary to the assertions made by Brandt et al, we did not report trends indicating that any of the agents slowed JSN. Within the context of the study’s limitations, however, the observations we did report are as follows: there was no significant difference in predefined joint space width (JSW) loss between the treatment groups and the placebo group, and regardless of treatment group, knees with K/L grade 2 OA appeared to have less JSW loss and were less likely to progress radiographically than knees with K/L grade 3 OA. In accordance with the hypothesis-generating goals of this ancillary study and the above observations, investigators designing future OA trials evaluating structural modification will need to include planning for a lower rate of progression and a smaller loss in JSW over time than were assumed in past studies.

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No evidence yet to change American Heart Association recommendations for poststreptococcal reactive arthritis: comment on the article by van Bemmel et al

To the Editor:

In the recent article by van Bemmel et al, the authors state that long-term antibiotic prophylaxis is not recommended for adults who have poststreptococcal reactive arthritis (ReA), based on their findings which indicated that there was no increased risk of valvular heart disease in a prospective cohort of white adult patients with poststreptococcal ReA (1). In fact, although the effectiveness of prophylaxis has not been well established, an American Heart Association class II recommendation (level of evidence C) advises secondary prophylaxis for up to 1 year after poststreptococcal ReA onset; then, if no clinical evidence of carditis is observed, prophylaxis can be discontinued (class I recommendation) (2). In our opinion, considering the study design and the methodology utilized by van Bemmel and colleagues (1), some points must be addressed and long-term prophylaxis reconsidered.

First, some inclusion criteria bias might have hampered the results in the study by van Bemmel et al and, therefore, the conclusions. The term “poststreptococcal ReA” has been proposed in an attempt to define a homogeneous group of patients who do not fulfill the revised Jones criteria for acute rheumatic fever (ARF) (3); however, as in cases of ARF, evidence of a recent group A β-hemolytic streptococcal...
infection is mandatory for a diagnosis of poststreptococcal ReA (4). In the 75 adult patients included in van Bemmel and colleagues’ inception cohort, poststreptococcal ReA was diagnosed in patients with recent arthritis who also had fever, cough, or angina preexisting before the development of arthritis and serologic evidence of an antecedent streptococcal infection determined by antistreptolysin O (ASO) titer; however, ASO testing was repeated in only 29 of 75 subjects (39%). Antistreptococcal antibody titers can determine past but not present group A streptococcal infections (2), and therefore cannot be used alone in determining recent infection. To document a recent group A streptococcal infection, antibody tests should be obtained at 2–4-week intervals, thus confirming a rising titer. In fact, patients with diseases other than ARF and/or poststreptococcal ReA may also have increased streptococcal antibody titers (3).

In addition, van Bemmel et al report that 30 patients had arthritis combined with 2 minor Jones criteria. The authors speculate that these subjects, even if they fulfill Jones criteria, present some clinical characteristics that closely resemble poststreptococcal ReA, and therefore they were classified as having the disease. We completely agree with the authors that the updated Jones criteria “are not a substitute for clinical judgment,” but on the other hand, they should not be used to formulate subjective clinical opinions. Therefore for study purposes, if a recent group A streptococcal infection is documented in patients, those patients who fulfill the Jones criteria must be defined as having ARF and should receive appropriate secondary prophylaxis. It would be interesting to know if the 30 patients mentioned above had rising streptococcal antibody titers at the time of disease onset. It is also surprising that the exclusion of these 30 patients did not affect the reported results in patients compared with controls, especially considering that the statistical approach used for a population that is not homogeneous and has no apparent Gauss distribution is a parametric test, such as the Student’s t-test.

There are other methodologic issues that should also be discussed. Van Bemmel and colleagues claim their study was prospective, but the echocardiographic studies (the main outcome measure) seem to have been completed using a cross-sectional method. In fact, the tables that the authors included report patient characteristics and ventricular measurements at echocardiography, as well as valve morphology and function, compared with controls, after a median followup of 8.9 years. We can suppose, even if van Bemmel et al did not specifically report it, that patients underwent echocardiography at baseline and did not exhibit evidence of cardiac involvement; otherwise, ARF, and not poststreptococcal ReA, would be the final diagnosis. However, the authors did not specify whether echocardiographic values obtained in patients at followup were significantly different from those obtained at baseline. A prospective, paired comparative study design with evaluation at onset, after 1 year, and at the final followup might have been more suitable for the study, which was designed to assess the development of valvular heart disease over time in a poststreptococcal ReA cohort without prophylaxis.

The authors state, “considering the different clinical and genetic characteristics of poststreptococcal ReA and ARF,” could be reductive and possibly confounding (5). Nonetheless, van Bemmel and colleagues speculate that some cases of poststreptococcal ReA closely resemble ARF, although their clinical judgment prompted them to consider these patients as having poststreptococcal ReA, which means the patients did not receive antibiotic prophylaxis. It is still not clear whether poststreptococcal ReA represents a distinct syndrome or is a manifestation of ARF, and as far as we know, the debate is still open (2).

In our own rheumatology units, we are monitoring the cases of 52 children with poststreptococcal ReA identified according to previously published criteria (4), who have been described in part in a previous report (6). None of the patients with poststreptococcal ReA enrolled in that study fulfilled the updated Jones criteria for the diagnosis of ARF (3); they did not show major manifestations of ARF other than arthritis, and only one possible minor criterion, an increase of acute-phase reactant levels, was observed. All children with poststreptococcal ReA were followed up for a median of 8 years (range 6 years, 4 months–10 years, 3 months), and presented with an initial episode of arthritis, with evidence of an antecedent group A streptococcal infection. Streptococcal antibody tests (ASO and anti–D-Nase B) were performed on the serum of all patients at the time of initial presentation, and were subsequently repeated 3 weeks after the onset of arthritis. In all patients, the level of at least 1 antibody was significantly elevated (at least 2.5 times above the upper limit of normal), and in 49 of the 52 patients, levels of both antibodies were elevated. The clinical and laboratory findings of the patients are summarized in Table 1. All patients underwent a complete cardiac evaluation, with electrocardiography and color Doppler echocardiography performed by a pediatric cardiologist at the time of disease onset, at followup at 1 year, and at the final recorded followup. None of the patients developed clinical or echocardiographic evidence of valvular disease or cardiac involvement at the time of disease onset or during followup. As recommended (2), all children received intramuscular benz-

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### Table 1. Clinical and laboratory characteristics of the 52 children with poststreptococcal ReA

<table>
<thead>
<tr>
<th></th>
<th>Median (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, no. female/male</td>
<td>23/29</td>
</tr>
<tr>
<td>Age at disease onset, years</td>
<td>9.17 (4.83–15.33)</td>
</tr>
<tr>
<td>Preceding sore throat, no.</td>
<td>36</td>
</tr>
<tr>
<td>Onset of arthritis after pharyngitis, days</td>
<td>9 (4–12)</td>
</tr>
<tr>
<td>Duration of arthritis from onset to resolution of symptoms, days</td>
<td>54 (7–153)</td>
</tr>
<tr>
<td>No. of swollen joints</td>
<td>2 (1–5)</td>
</tr>
<tr>
<td>Distribution of involved joints, no.</td>
<td>19</td>
</tr>
<tr>
<td>Arthritis involving 1 large joint (knee, ankle, or hip)</td>
<td>29</td>
</tr>
<tr>
<td>Arthritis involving &gt;3 joints</td>
<td>4</td>
</tr>
<tr>
<td>Arthritis, no. migratory/nonmigratory</td>
<td>15/37</td>
</tr>
<tr>
<td>ASO, mean ± SEM IU/ml</td>
<td>1,280 ± 205</td>
</tr>
<tr>
<td>Anti-DNase B, mean ± SEM IU/ml</td>
<td>1,020 ± 125</td>
</tr>
<tr>
<td>ESR, mm/hour (normal &gt;25)</td>
<td>42 (28–57)</td>
</tr>
<tr>
<td>CRP, mg/dl (normal &lt;0.35)</td>
<td>3.4 (1.8–5.4)</td>
</tr>
</tbody>
</table>

*Except where otherwise indicated, values are the median (range). ReA = reactive arthritis; ASO = antistreptolysin O; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein.
thine penicillin prophylaxis, which was discontinued after 1 year, since evidence of carditis was not detected.

We agree with van Bemmel et al that abnormal cardiac findings following poststreptococcal ReA are extremely rare, although it has been previously reported that a small proportion of patients with poststreptococcal ReA may subsequently develop carditis (4,7,8), making poststreptococcal ReA part of the spectrum of ARF. In children with arthritis following a group A streptococcal infection, who did not fulfill the revised Jones criteria at the time of disease onset, we do not consider it crucial to differentiate poststreptococcal ReA from ARF, but it does seem judicious to follow the recommendations of the American Heart Association and administer secondary prophylaxis to patients with poststreptococcal ReA for a period of 1 year (2). If carditis develops, the patient should be reclassified as having ARF and should continue to receive secondary prophylaxis. If carditis does not develop, prophylaxis can be discontinued in the patient, who was correctly classified as having poststreptococcal ReA.

Notably, the study by van Bemmel et al was completed using adult patients, while most of our recommendations derive from observations in pediatric studies. However, we do not think that there are major differences between populations of adults and children, apart from a different group A streptococcal infection rate seen in children. We believe that the main question, i.e., whether to use prophylaxis in patients with poststreptococcal ReA, can be answered only in a controlled study, and that until such time, there is no evidence to suggest that the recommendations of the American Heart Association should be changed.

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Reply

To the Editor:

We congratulate Dr. Simonini and colleagues on their study, in which they used serial echocardiography to investigate poststreptococcal ReA in 52 children. Those patients were treated with benzylpenicillin, and during followup, no echocardiographic evidence of valvular disease was observed. Therefore, these data suggest that treatment with benzylpenicillin effectively reduces the risk of carditis in children.

The aim of our study was not to examine the efficacy of benzylpenicillin in preventing carditis. Our goal was to determine the increased risk of carditis (previously unknown) in adult patients with poststreptococcal ReA. Studies on ARF have shown that the risk of carditis in adults is lower than in children (33% versus 50%) (1–3). In children with poststreptococcal ReA, the risk of carditis is ~8% (1–3), and in adults, as mentioned above, the risk had yet to be determined.

This led us to study the frequency of valvular heart disease in an unselected cohort of adult patients with poststreptococcal ReA, with a median followup of 8.9 years. Since none of these patients were treated with benzylpenicillin, the data presented in our report were an estimation of the natural course of the disease. As such, the aim of our study was different than that of the study by Simonini and colleagues. We observed no increased frequency of valvular heart disease in patients, compared with matched controls.

We completely agree with Simonini et al that it would have been more convenient to have serial ASO and anti-DNase B measurements. Unfortunately, serial serologic measurements, as well as throat cultures, had not been performed in all cases at the time of enrollment, which began in 1993. In our study, 2 patients were diagnosed as having ARF because they each fulfilled 2 major Jones criteria; these patients were treated with antibiotic prophylaxis and excluded from the study. Additionally, 30 patients with poststreptococcal ReA could have been classified, according to the Jones criteria, as having ARF, based on the fact that they fulfilled 1 major Jones criterion (arthritis, although not strictly a polyarthritis in our study) and 2 minor criteria (fever, increased erythrocyte sedimentation rate/C-reactive protein). These 30 patients had an arthritis that was atypical in its time of onset and duration and in its localization and that did not exhibit a dramatic response to antiinflammatory agents. Therefore, we catego-