Chlamydia pneumoniae in Coronary Artery Disease

To the Editor:

In a recent issue of Circulation, Anderson et al.1 reported the 6-month results of the ACADEMIC trial. In this interesting study, the authors intended to answer the question whether Chlamydia pneumoniae plays a critical role in coronary artery disease, in order to justify antibiotic therapy.

Beyond the final results of this work, it seems to us that the methodological approach used deserves some comment. First, the investigators based the sample size and the clinical event rate estimates on prior data from a small study that used the same compound.2 For this purpose, the authors did not include unstable or subacute cases but rather included only stable coronary patients. Similarly, the British study selected postmyocardial infarction patients in the quiescent phase, thus making the present study statistically underpowered, as stated in the editorial comment by Dr Grayston.3

Second, the authors analyzed some particular and common markers of inflammation, because infection increases their plasmonic levels. These markers decreased at 6 months but interestingly not at 3 months. It is hard to explain why these markers were practically neutral at 90 days, when 39 patients experienced new clinical infections over the 3-month treatment period. Furthermore, the authors compared their study with our ROXIS (Roxithromycin Ischemic Syndromes) trial, stating that we randomized patients with a poor characterization. At the present time, the only study conducted in uniformly unstable patients is the ROXIS, in which we clearly defined the entry criteria to select a standard population with acute coronary events, as shown in the original article.4 In the final report of the study,5 we showed that the beneficial effect of roxithromycin was sustained until 90 days. Beyond this point, the P value was no longer statistically significant. The potential reasons for this were presented in March 1998 (American College of Cardiology meeting) and published elsewhere.5

Finally, the authors speculate in their conclusion that the ACADEMIC trial tested C pneumoniae as an additional risk factor. The authors should clarify how a marker of chronic infection may be regarded as a risk factor, in light of the sample size, the clinical event rates estimated, the serology cutoff point at 1:16, and the immunological basis of this and other infective disease hypotheses.6

Enrique Gurfinkel, MD, PhD
Gerardo Bozovich, MD
Branko Mautner, MD
Coronary Care Unit
Favaloro Foundation
Buenos Aires, Argentina


Response

We appreciate Gurfinkel et al’s interest in our 6-month report of the ACADEMIC study,1 which found significantly reduced (P=0.011, P=0.027) global indexes of inflammation in coronary artery disease (CAD) patients given azithromycin versus those given placebo.2 ACADEMIC was designed to have high power to evaluate inflammatory markers. Its primary clinical end point at 2 years has not yet been reported, but its 7248 patient-months of follow-up will constitute the largest database of the 3 reported studies (2022 and 10803 patient-months, respectively).

We agree with Gurfinkel et al that ROXIS2 studied a different (unstable) stage of CAD; we1 excluded unstable angina or acute myocardial infarction (MI). The British study3 enrolled stable patients an average of 43 months after MI. Similarly, most of our patients (60%) had a history of MI; the others had undergone bypass surgery or coronary intervention.

Our 2-year clinical event rates will be of interest, but both we1 and Grayston4 emphasize the need for larger, longer-term studies, well-powered to detect worthwhile event reductions of 20% to 30%. Our 6-month events number too few to exclude an important treatment effect and should be viewed as exploratory.

We also were surprised to find that differences between groups in inflammatory markers did not develop until after 3 months. This was due to transient falls in marker values in the placebo (as well as active) group at 3 months. We can only speculate as to the cause; it may relate to better general care (eg, aspirin use, treatment of infections and lipids) during the 3-month treatment phase. If differences in inflammatory markers precede reductions in clinical events, then treatment for >3 months, as proposed for ACES (Azithromycin and Coronary Events Study),4 may be required.

We stress the importance of ROXIS,3 which tested antibiotics for unstable coronary syndromes. We should have better characterized ROXIS as enrolling patients whose seropositivity (rather than clinical characteristics) was unrestricted. As we discussed,1 the inclusion of seronegative patients2 will help to determine whether treatment effects are specifically antichlamydial.

We agree that Chlamydia pneumoniae seropositivity is an imperfect marker of persistent infection; it may be associated with substantial false-positive and -negative rates. However, the high rate (79%) of coronary antigen positivity in our patients suggests a high prevalence of persistent chlamydial arteritis.

Our findings should stimulate further research on the infection-inflammation hypothesis of atherosclerosis, including larger and longer-term trials.1,4 Previous reports of dramatic benefit, based on limited experience, may have been overly enthusiastic.

Jeffrey L. Anderson, MD
Joseph B. Muhlestein, MD
John Carlquist, PhD
Ann Allen, BS
Sanjeev Trehan, MD
Cindy Nielson, PharmD
Staci Hall
John Brady, BS


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Enrique Gurfinkel, Gerardo Bozovich and Branco Mautner

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