Randomized Secondary Prevention Trial of Azithromycin in Patients With Coronary Artery Disease
Primary Clinical Results of the ACADEMIC Study

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Background—Chlamydia pneumoniae is associated with coronary artery disease (CAD), although its causal role is uncertain. A small preliminary study reported a >50% reduction in ischemic events by azithromycin, an antibiotic effective against C pneumoniae, in seropositive CAD patients. We tested this prospectively in a larger, randomized, double-blind study.

Methods and Results—CAD patients (n=302) seropositive to C pneumoniae (IgG titers $\geq 1:16$) were randomized to placebo or azithromycin 500 mg/d for 3 days and then 500 mg/wk for 3 months. The primary clinical end point included cardiovascular death, resuscitated cardiac arrest, nonfatal myocardial infarction (MI), stroke, unstable angina, and unplanned coronary revascularization at 2 years. Treatment groups were balanced, and azithromycin was generally well tolerated. During the trial, 47 first primary events occurred (cardiovascular death, 9; resuscitated cardiac arrest, 1; MI, 11; stroke, 3; unstable angina, 4; and unplanned coronary revascularization, 19), with 22 events in the azithromycin group and 25 in the placebo group. There was no significant difference in the 1 primary end point between the 2 groups (hazard ratio for azithromycin, 0.89; 95% CI, 0.51 to 1.61; $P=0.74$). Events included 9 versus 7 occurring within 6 months and 13 versus 18 between 6 and 24 months in the azithromycin and placebo groups, respectively.

Conclusions—This study suggests that antibiotic therapy with azithromycin is not associated with marked early reductions ($\geq 50\%$) in ischemic events as suggested by an initial published report. However, a clinically worthwhile benefit (ie, 20% to 30%) is still possible, although it may be delayed. Larger (several thousand patient), longer-term ($\geq 3$ to 5 years) antibiotic studies are therefore indicated. (Circulation. 2000;102:1755-1760.)

Key Words: coronary disease ■ antibiotics ■ Chlamydia pneumoniae

A pathogenic role for local inflammation in atherosclerotic plaque (inflammatory cytokines, macrophages, T lymphocytes) and systemic inflammation (eg, C-reactive protein [CRP]) in coronary artery disease (CAD) is being increasingly recognized.1–3 The stimuli for the inflammatory response are unknown, but they may include modified (oxidized) LDL and mechanical and toxic factors. Also, the possibility that infectious agents may stimulate vascular inflammation has been raised.4 Specifically, cytomegalovirus5 and Chlamydia pneumoniae6 have been identified within atherosclerotic plaque; whether they play a causal role or are innocent commensals in atherogenesis is unknown. However, the possibility that chronic diseases may stimulate vascular inflammation has been raised.4 Specifically, cytomegalovirus5 and Chlamydia pneumoniae6 have been identified within atherosclerotic plaque; whether they play a causal role or are innocent commensals in atherogenesis is unknown. However, the possibility that chronic diseases may stimulate vascular inflammation has been raised.4 Specifically, cytomegalovirus5 and Chlamydia pneumoniae6 have been identified within atherosclerotic plaque; whether they play a causal role or are innocent commensals in atherogenesis is unknown. However, the possibility that chronic diseases may stimulate vascular inflammation has been raised.4 Specifically, cytomegalovirus5 and Chlamydia pneumoniae6 have been identified within atherosclerotic plaque; whether they play a causal role or are innocent commensals in atherogenesis is unknown. However, the possibility that chronic diseases may stimulate vascular inflammation has been raised.4 Specifically, cytomegalovirus5 and Chlamydia pneumoniae6 have been identified within atherosclerotic plaque; whether they play a causal role or are innocent commensals in atherogenesis is unknown. However, the possibility that chronic diseases may stimulate vascular inflammation has been raised.4 Specifically, cytomegalovirus5 and Chlamydia pneumoniae6 have been identified within atherosclerotic plaque; whether they play a causal role or are innocent commensals in atherogenesis is unknown. However, the possibility that chronic diseases may stimulate vascular inflammation has been raised.4 Specifically, cytomegalovirus5 and Chlamydia pneumoniae6 have been identified within atherosclerotic plaque; whether they play a causal role or are innocent commensals in atherogenesis is unknown. However, the possibility that chronic diseases may stimulate vascular inflammation has been raised.4 Specifically, cytomegalovirus5 and Chlamydia pneumoniae6 have been identified within atherosclerotic plaque; whether they play a causal role or are innocent commensals in atherogenesis is unknown. However, the possibility that chronic diseases may stimulate vascular inflammation has been raised.4 Specifically, cytomegalovirus5 and Chlamydia pneumoniae6 have been identified within atherosclerotic plaque; whether they play a causal role or are innocent commensals in atherogenesis is unknown. However, the possibility that chronic diseases may stimulate vascular inflammation has been raised.4 Specifically, cytomegalovirus5 and Chlamydia pneumoniae6 have been identified within atherosclerotic plaque; whether they play a causal role or are innocent commensals in atherogenesis is unknown. However, the possibility that chronic diseases may stimulate vascular inflammation has been raised.4 Specifically, cytomegalovirus5 and Chlamydia pneumoniae6 have been identified within atherosclerotic plaque; whether they play a causal role or are innocent commensals in atherogenesis is unknown. However, the possibility that chronic diseases may stimulate vascular inflammation has been raised.4 Specifically, cytomegalovirus5 and Chlamydia pneumoniae6 have been identified within atherosclerotic plaque; whether they play a causal role or are innocent commensals in atherogenesis is unknown. However, the possibility that chronic diseases may stimulate vascular inflation...
absorbed, is widely distributed, achieves high and persistent tissue concentrations (tissue half-life, \( \approx 72 \) hours), is well tolerated, and has been effective in animal models.\(^2\) Thus, azithromycin and roxithromycin have been selected for human pilot studies and ongoing major clinical coronary prevention trials.\(^2\)\(^5\)\(^6\)

Stimulated by these considerations, our own observational and animal data,\(^6\)\(^2\)\(^3\) and a small pilot antibiotic study in patients with CAD from Great Britain,\(^2\)\(^5\) we undertook a larger prospective, randomized, secondary prevention study. We have reported the 6-month laboratory results (showing a reduction in the global inflammatory marker index).\(^2\) Here, we report the 2-year primary clinical end-point results.

**Methods**

**Study Design and Objectives**

The study was designed as a randomized, double-blind, secondary prevention trial of azithromycin (3-month course) versus placebo in patients with documented CAD and seropositivity to *C pneumoniae* to test both laboratory and clinical objectives. The primary laboratory hypothesis was that compared with placebo, azithromycin therapy would reduce a global measure of systemic levels of the cluster of inflammatory markers C-reactive protein (CRP), interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-\(\alpha\) at 3 (end of therapy) and 6 months. The secondary laboratory hypothesis was that antibiotic therapy would reduce anti-Chlamydia IgG and IgA antibody levels at 6 months. Methods and results of the laboratory hypotheses have been reported previously.\(^2\)

The clinical hypothesis was that at 2 years (primary end point), cardiovascular events would be reduced in the azithromycin compared with placebo groups. End-point events were defined as cardiovascular death (sudden death of unknown cause or death resulting from myocardial infarction [MI], congestive heart failure, stroke, or arrhythmia), resuscitated cardiac arrest, nonfatal MI (abnormal cardiac enzymes or new q-waves), stroke, unstable angina requiring hospitalization, and unplanned coronary interventions (catheter based or surgical). All primary end-point events were adjudicated by a blinded end-point committee. Other clinical objectives included the comparison by treatment group of all deaths, other cardiovascular hospitalizations or procedures, adverse experiences and drug discontinuations, and clinical infections. On the basis of the observation in our earlier report that inflammation markers decreased gradually, first becoming evident at 6 months, we hypothesized that at 6 months, we hypothesized at our interim (6-month) analysis\(^2\) that subsequent (6- to 12-month) events would favor the azithromycin group.

**Patient Qualification, Enrollment, and Randomization**

Patients were qualified for the study if they had CAD documented by a previous MI, bypass surgery, or >50% angiographic stenosis of \( \geq 1 \) major coronary artery; were \( \geq 18 \) years of age; had a life expectancy of >2 years; and gave written informed consent. Exclusion criteria included the following: female patient capable of childbearing without adequate birth control; NYHA functional class III or IV congestive heart failure or left ventricular ejection fraction <25%; MI within 5 days or bypass surgery within 4 weeks or percutaneous coronary intervention (any technique) within 3 months; planned CABG or coronary intervention; significant comorbid illnesses, including active malignancy, ongoing drug or alcohol abuse, renal failure requiring dialysis, liver failure, etc, with a projected life expectancy of <2 years; known intolerance to azithromycin; and chronic macrolide (eg, erythromycin) or tetracycline use.

Patients were screened for *C pneumoniae* serum antibody titers to provide \( \approx 300 \) patients for enrollment with anti-Chlamydia IgG titers of \( \geq 1:16 \) by micromunnofluorescence (MIF) who met all study criteria and gave informed consent. Enrolled patients were randomized 1:1 to the 2 treatment groups of azithromycin or placebo an unblinded, independent party (pharmacist) uninvolved in clinical management except for provision of blinded drug supplies who opened an envelope containing the drug assignment. The order of randomization followed a permuted block design (alternating blocks of 4 and 6).

**Supplies and Dosing of Drug and Placebo**

Azithromycin, as 250-mg red capsules (Pfizer Laboratories), was purchased from LDS Hospital Pharmacy. Matching placebo capsules were purchased from Jolley’s Corner Pharmacy. Enrolled patients were to initiate therapy with 2 capsules 500 mg/d for 3 days and then maintain therapy with 2 capsules (500 mg) per week (Mondays) for 3 months, to be taken \( \geq 1 \) hour before or \( \geq 2 \) hours after food.

**Study Flow**

Eligibility was determined during a screening visit. Eligible, consenting patients had venous blood drawn and tested by MIF for *C pneumoniae* antibodies. Patients with titers \( \geq 1:16 \) were seen \( \approx 1 \) week later for randomization; baseline history and physical examinations were completed, blood was drawn, a 12-lead ECG was obtained, and study drug was dispensed. At 3, 6, and 12 months, patients returned to review clinical status and drug compliance; blood was sampled and an ECG was obtained. At 18 months and 2 years, clinical follow-up was accomplished by telephone contact. Blinded adjudication of all primary end points was performed by an end-points committee. Each end point was reviewed by \( \geq 2 \) cardiologists, and in cases of differing opinions, the entire end-points committee discussed the case until a consensus was obtained.

**Laboratory Testing**

Screening for anti-*C pneumoniae* antibody (IgG) used a standard MIF test (MRL Diagnostics) on 1:16 diluted serum. Other test methods have been previously described.\(^2\)

**Statistical Analysis**

Clinical event rate estimates were based on the pilot study of Gupta et al\(^2\) who reported a reduction in events from 28% to 8% by 18 months in treated patients with falling antibody titers versus control subjects (ie, placebo-treated or untreated patients with persistently elevated titers). Assuming a placebo event rate of 28%, 150 patients per group provide \( \approx 90\% \) power to detect a reduction in event rate caused by the study drug to 14.5% at 2 years (primary clinical end point). The primary (null) hypothesis was that there would be no difference between the azithromycin and placebo groups in events; the alternate hypothesis was that changes would favor antibiotic therapy. Assessment of clinical events used the intention-to-treat approach. Groups were compared through the use of survival methods (Kaplan-Meier) and the log-rank statistic. Cox regression was used to determine univariate and multiple variable hazard ratios and CIs. Categorical variables in the 2 groups were compared by \( \chi^2 \) testing; continuous variables, by Student’s *t* or Mann-Whitney testing as appropriate.

**Results**

**Baseline Patient Characteristics**

A total of 430 patients were screened, 333 (77%) had positive *C pneumoniae* serology, and 302 consented and were enrolled in the study, with 150 randomly assigned to receive azithromycin and 152 to receive placebo. Overall, patients were 64±10 (mean±SD) years of age (range, 30 to 88 years); 89% were male; and 60% had suffered a previous MI, 46% had undergone bypass surgery, and 46% had had percutaneous coronary interventions. Patient characteristics on admission were well balanced in the randomly assigned treatment groups (Table 1).
Drug Tolerance and Compliance
These data have been reported previously. Compliance was good to excellent: 89% of active and 85% of placebo patients followed the treatment plan without deviation. Drug was well tolerated. Only 2 active therapy and 3 placebo patients permanently discontinued therapy 2 weeks early. Overall, 36 (24%) of azithromycin and 17 (11%) of placebo patients experienced some adverse effect during the 3-month treatment period ($P = 0.003$). Adverse effects were believed to be possibly or probably drug related in 25 active (17%) and 11 placebo (7%) patients ($P = 0.011$). They were usually mild, occasionally moderate, and most frequently gastrointestinal (31 active, 12 placebo patients; $P = 0.002$), including nausea, diarrhea, or flatulence.

Clinical Cardiovascular Events
A total of 47 patients (15.6%) experienced ≥1 primary event over the course of the trial; 22 patients were in the azithromycin group, and 25 were in the placebo group. Event-free survival plots for the 2 treatment groups are shown in the Figure. There was no significant difference in the combined primary end point between the 2 groups (hazard ratio for azithromycin, 0.89; 95% CI, 0.51 to 1.61; $P = 0.74$). The distribution of events was 9 versus 7 events within 6 months and 13 versus 18 events between 6 and 24 months in the azithromycin and placebo groups, respectively.

The frequency of individual first primary events in the 2 treatment groups was generally similar (Table 2). A total of 63 events were noted during the study, including multiple events in the same patient. These included 9 cardiovascular deaths, 1 resuscitated cardiac arrest, 10 MIs, 4 strokes, 15 unstable anginal episodes, and 24 unplanned coronary revascularizations. A nonsignificant reduction in total events was noted in the azithromycin group (28 compared with 35 in the placebo group, $P = 0.35$). The frequency of each event type by treatment group is shown in Table 3. For none of the event types was there a significant difference, although fewer unplanned coronary revascularizations were performed in the azithromycin group.

**Discussion**

**Summary of Study Results**
This double-blind, randomized, secondary prevention study of moderately large size in CAD patients with serologic evidence of prior *C pneumoniae* exposure did not show a significant reduction in events by antibiotic (azithromycin) therapy at 2 years and is adequately powered to exclude a marked (>50%) early reduction in events, as reported in a previous study. Our earlier report of a gradual reduction in inflammatory markers with azithromycin, first appearing at 6 months, is consistent with the possibility that clinical effects (ie, reduced ischemic events) might be delayed until after the onset of the anti-inflammatory effect. This again contrasts with 2 smaller studies in which large early apparent benefits were reported. The reports based on these earlier, smaller studies thus appear to be overly enthusiastic; however, we believe our results should encourage rather than discourage additional studies based on more realistic expectations.

**Pathophysiological Considerations**
Our results are consistent with 3 possibilities: (1) a noncausal role of *C pneumoniae* in CAD pathogenesis, (2) a smaller benefit for antibiotic therapy (eg, 20% to 30% beneficial effect), or (3) a causal role for *C pneumoniae* with the present negative results explained by inefficiency of the antibiotic regimen used. Additional studies (some underway) will be necessary to distinguish among these possibilities. In our previous report, 3 months of azithromycin therapy led to a gradual reduction in the inflammatory marker index (com-

![Kaplan-Meier primary event-free survival curves during 2 years of follow-up for patients randomized to azithromycin or placebo.](image)

**Table 1. Baseline Patient Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Azithromycin Group (n=150)</th>
<th>Placebo Group (n=152)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atherosclerotic risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (mean±SD), y</td>
<td>64±10</td>
<td>63±11</td>
<td>0.60</td>
</tr>
<tr>
<td>Male, %</td>
<td>86</td>
<td>91</td>
<td>0.19</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>39</td>
<td>45</td>
<td>0.34</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>11</td>
<td>11</td>
<td>0.97</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>38</td>
<td>36</td>
<td>0.85</td>
</tr>
<tr>
<td>Family history of CAD, %</td>
<td>69</td>
<td>73</td>
<td>0.43</td>
</tr>
</tbody>
</table>

**Table 2. Effect of Therapy on First Primary Clinical Events**

<table>
<thead>
<tr>
<th>Event</th>
<th>Azithromycin, n</th>
<th>Placebo, n</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>22</td>
<td>25</td>
<td>0.67</td>
</tr>
<tr>
<td>CV death</td>
<td>5</td>
<td>4</td>
<td>0.72</td>
</tr>
<tr>
<td>Resuscitated cardiac arrest</td>
<td>1</td>
<td>0</td>
<td>0.31</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>4</td>
<td>6</td>
<td>0.53</td>
</tr>
<tr>
<td>Hospitalization for unstable angina</td>
<td>3</td>
<td>2</td>
<td>0.64</td>
</tr>
<tr>
<td>Unplanned revascularization</td>
<td>8</td>
<td>11</td>
<td>0.50</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>1</td>
<td>2</td>
<td>0.57</td>
</tr>
</tbody>
</table>

CV indicates cardiovascular.
The study of Gurfinkel et al was of intermediate size (200 patients) and used roxithromycin; their report of a trend in adverse events reduction (2 versus 9) at 1 month also stands in contrast to our study. It should be stressed, however, that Gurfinkel et al studied acute coronary syndrome patients and a different antibiotic regimen, so differences in outcome could occur on the basis of differences in the patient population and treatment. Between 1 and 6 months, no further separation of event curves was observed (differences no
longer nominally significant); longer-term follow-up has not been reported.

Although not definitive, these pilot trials offer the hope that antibiotic therapy targeted against C pneumoniae might be useful in the secondary prevention of cardiovascular disease and that this deserves further testing. In this regard, 2 large antibiotic secondary trials are underway that are adequately powered to determine a clinically important effect on cardiovascular events. Each uses once-a-week azithromycin. The Weekly Intervention With Zithromax Against Atherosclerotic-Related Disorders (WIZARD) trial, sponsored by Pfizer, is enrolling >7000 patients with prior MI and C pneumoniae seropositivity, treating them for 3 months, and observing events over 2.5 years. The Azithromycin Coronary Events Study (ACES) trial, sponsored by the NHLBI, is enrolling >4000 patients with CAD regardless of antibody status, treating them for 1 year, and following them up for 4 years. These trials should provide more definitive answers about the infectious hypothesis of CAD and treatment opportunities.

Study Strengths, Limitations, and Implications
This study adds substantially to the small amount of previous work relating C pneumoniae to atherosclerosis in humans and antibiotic therapy directed at chlamydia in patients with CAD manifestations.25–26 The validity of the statistical inferences of the study is bolstered by its prospective, randomized, double-blind design and moderately large size. However, the power of the study was adequate only for large changes in clinical end points (ie, for ≥50% reductions) over 2 years. We have excluded such large effects with confidence but have left open the possibility of more modest, clinically worthwhile benefits (eg, 20% to 30% reductions).

The optimal dose and duration of therapy are unknown. C pneumoniae in a persistent, metabolically inactive state might be resistant to short-term and nonbacteriocidal antibiotic therapy. Longer-term and/or intermittent (eg, monthly) treatment with azithromycin or another agent may be required to achieve worthwhile benefit. Beneficial effects, if seen, may be due to either a specific antichlamydial action or a more general anti-infectious or anti-inflammatory effect. Consequently, it is not expected that this study or any other single antibiotic-related clinical trial can definitively confirm or reject the hypothesis that atherosclerosis, an inflammatory disease, also contains an infectious component. It does, however, add to the growing body of knowledge regarding this hypothesis.

Conclusions
In a study of 302 CAD patients followed up for 2 years, a 3-month course of azithromycin was not associated with an overall reduction in cardiovascular events compared with placebo. Larger, longer-term studies are needed to assess the potential of worthwhile but more modest and delayed benefits of antibiotic therapy in CAD than previously reported. The role of infectious agents in CAD is a legitimate area of research, but a causal role for infection remains a hypothesis to be proved, and antibiotic therapy for patients with CAD is not yet indicated.

Acknowledgments
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