Treatment with Clarithromycin Prior to Coronary Artery Bypass Graft Surgery Does Not Prevent Subsequent Cardiac Events

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Background. Recently, it has been suggested that Chlamydia pneumoniae possibly plays a possible role in the pathogenesis of atherosclerosis. We investigated whether treatment with clarithromycin prior to coronary artery bypass graft (CABG) surgery would prevent subsequent cardiovascular events and mortality.

Methods. Patients who were scheduled for CABG surgery were randomly assigned to receive either clarithromycin or placebo until the day of surgery in a double-blind trial. During the 2 years of follow-up, mortality and cardiovascular events were assessed.

Results. Follow-up at 2 years was achieved for 473 patients. The mean duration of treatment was 16 days. Patient characteristics at baseline were well balanced between the 2 treatment groups. Mortality was equal in the 2 groups: 10 (4.2%) of 238 patients in the clarithromycin group and 9 (3.8%) of 235 patients in the placebo group (relative risk, 1.10; 95% CI, 0.42–2.89; P = 1.0). Also, there were no significant differences in the proportion of patients who experienced cardiovascular events during the follow-up period: 20 (8.4%) of 238 patients in the clarithromycin group and 19 (8.1%) of 235 patients in the placebo group (relative risk, 1.04; 95% CI, 0.55–1.98; P = 1.0). The overall rate of such events was 58 (12.3%) of 473 patients.

Conclusions. Treatment with clarithromycin in patients scheduled for CABG surgery did not reduce the subsequent occurrence of cardiovascular events or mortality during a 2-year follow-up period.

It is generally acknowledged that atherosclerosis can be considered, in part, an inflammatory disease. It may result from an immune response to various inflammatory stimuli that leads to atherogenesis and coronary artery disease (CAD) progression [1]. Common chronic infections caused by viruses and bacteria may contribute to this inflammatory process and interact with classic cardiovascular risk factors, such as smoking, hypercholesterolemia, diabetes mellitus, hypertension, and a family history of CAD [1, 2]. To date, Chlamydia pneumoniae is the infectious agent for which evidence linking infection and atherosclerosis is strongest [3].

Seroepidemiological studies, detection of the organism within atherosclerotic vascular tissue (by culture, electron microscopy, and antigen and DNA detection techniques), in vitro experiments, and animal models have supported the hypothesis that this microorganism has a role in the pathogenesis of atherosclerosis [4, 5]. Recently, studies of the reliability of molecular detection methods have raised serious questions regarding the interpretation of previous data [6]. Therefore, the exact role of C. pneumoniae in atherosclerosis remains to be determined. The chain of evidence could be strengthened by studying the effect of antibiotic treatment on clinical outcome in patients with CAD.

Worldwide interest was generated by the results of 2 small studies published in 1997 [7, 8], which showed a better outcome after treatment of atherosclerosis with a macrolide. The purpose of the present study was to determine the effect of treatment with the macrolide antibiotic clarithromycin prior to coronary artery by-
pass graft (CABG) surgery on clinical outcome and prognosis for patients with severe atherosclerosis in a double-blind, randomized, placebo-controlled study.

**METHODS**

**Study population.** Between July 1999 and July 2001, patients with documented CAD were enrolled in the study. All patients had been scheduled for CABG surgery. Patients who were scheduled for a procedure including valve replacement or reconstruction were not included. Patients were enrolled when they attended the preoperative outpatient clinic at the Department of Thoracic Surgery of the Amphia Hospital (Amsterdam, The Netherlands).

Exclusion criteria were as follows: participation in another study, concomitant treatment with terfenadine, rifabutin, cisapride, or antipyrene, concomitant antibiotic therapy with a macrolide, tetracycline, or quinolone within 3 months prior to enrollment or during the study period, the presence of renal failure (defined as a serum creatinine rate >150 μmol/L), elevated liver function test results (defined as levels of alanine transaminase >55 U/L, aspartate transaminase >45 U/L, total bilirubin >27 μmol/L, and alkaline phosphatase >180 U/L), and being a female capable of child-bearing but not taking adequate birth control precautions. The study was approved by the local Medical Ethics Committee.

The research physician (H.F.B.) saw all patients during their visits to the preoperative outpatient clinic, examined their patient files, interviewed them, and asked for informed consent. Patients were randomized in a double-blind, placebo-controlled study. The study medication consisted of either a daily dose of 500 mg slow-release tablet of clarithromycin or a matching placebo tablet (both obtained from Abbott Laboratories). The

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**Figure 1.** Flow chart summarizing the enrollment and randomization of patients in the trial and listing reasons for exclusion or withdrawal from the study. All values are no. of patients.
Table 1. Demographic and clinical characteristics and medical history of patients at baseline.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Clarithromycin group (n = 238)</th>
<th>Placebo group (n = 235)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of treatment in days</td>
<td>15.7 ± 8.0</td>
<td>16.4 ± 7.8</td>
</tr>
<tr>
<td>Age in years</td>
<td>64.9 ± 8.7</td>
<td>63.8 ± 10.8</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>81.8 ± 13.3</td>
<td>81.3 ± 14.2</td>
</tr>
<tr>
<td>Height, cm</td>
<td>171.9 ± 11.2</td>
<td>171.1 ± 11.0</td>
</tr>
<tr>
<td>Male sex</td>
<td>188 (79.0)</td>
<td>186 (79.1)</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angina pectoralis scorea</td>
<td>2.85 ± 0.8</td>
<td>2.85 ± 0.8</td>
</tr>
<tr>
<td>Current smoker</td>
<td>49 (20.6)</td>
<td>43 (18.2)</td>
</tr>
<tr>
<td>Smoker in past</td>
<td>133 (55.9)</td>
<td>135 (57.4)</td>
</tr>
<tr>
<td>COPD</td>
<td>26 (10.9)</td>
<td>23 (9.8)</td>
</tr>
<tr>
<td>Diabetes mellitus type I</td>
<td>14 (5.9)</td>
<td>13 (5.5)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>135 (56.7)</td>
<td>143 (60.9)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10 (4.2)</td>
<td>7 (3.0)</td>
</tr>
<tr>
<td>Stroke</td>
<td>21 (8.8)</td>
<td>18 (7.7)</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>225 (94.5)</td>
<td>223 (94.9)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>116 (48.7)</td>
<td>109 (46.4)</td>
</tr>
<tr>
<td>Heart valve insufficiency</td>
<td>9 (3.8)</td>
<td>4 (1.7)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>10 (4.2)</td>
<td>7 (3.0)</td>
</tr>
<tr>
<td>Family medical history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>179 (75.2)</td>
<td>163 (69.4)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>33 (13.9)</td>
<td>34 (14.5)</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td>141 (59.2)</td>
<td>151 (64.3)</td>
</tr>
<tr>
<td>Anti-hypertension drugs</td>
<td>237 (99.6)</td>
<td>234 (99.6)</td>
</tr>
</tbody>
</table>

NOTE. Data are no. (%) of patients or mean value ± SD. For all characteristics, mean values at baseline for the two groups were not significantly different. COPD, chronic obstructive pulmonary disease.

An independent pharmacist dispensed either clarithromycin or placebo tablets, according to a computer-generated randomization table that stratified patients into groups of 10 patients. The research physician was responsible for enrolling patients and making sure they were assigned the next available number on entry into the trial. Each patient received the corresponding tablets directly from the researcher. The randomization code was revealed to the researcher after the 2.5 years of follow-up was completed.

Outcome data. Data on clinical outcomes and cardiovascular events were collected by the research physician by telephone interview of each patient at 6 and 12 months after cardiac surgery and by interview of the general practitioner at the end of the 2 years of follow-up. The Dutch general practitioner is the central authority in medical care in The Netherlands and is aware when a serious event occurs. The primary end point was overall mortality. Secondary end points included reappearance of angina pectoris, myocardial reinfarction, and additional percutaneous coronary intervention or coronary artery bypass surgery, stroke, and peripheral artery disease that required bypass or percutaneous intervention.

Statistical analysis. An intention-to-treat analysis was performed. All baseline characteristics were analyzed with $\chi^2$-test or a student’s $t$ test, as appropriate. Statistical analysis was performed using SPSS software, version 11.0 (SPSS). Statistical significance was set at $P < .05$.

RESULTS

Between July 1999 and July 2001, there were 641 patients seen at the preoperative outpatient clinic. The trial profile (figure 1) shows that 473 patients were enrolled in the study. Complete follow-up data were obtained for all 473 patients because of an intention-to-treat analysis.

Table 1 shows that demographic and clinical characteristics were well balanced between the 2 treatment groups; no significant differences were found. Patients were treated for an average of 16 days (the total number of tablets received ranged from 1–42 for the clarithromycin treatment group and 0–42 for the placebo group). There were no significant differences in the rates of clinical events during the follow-up period, which are shown in table 2. Overall mortality was almost the same for both treatment groups: 10 (4.2%) of 238 patients in the clarithromycin group died, and 9 (3.8%) of 235 patients in the placebo group died (relative risk, 1.10; 95% CI, 0.42–2.89; $P = 1.0$). Subgroup analysis was performed on 3 groups of patients: patients who had been treated for $\geq$21 days (138 patients); patients who had diabetes mellitus (74 patients); and patients who were active smokers or who had a history of smoking (92 patients). In all 3 subgroups, rates of clinical events were not significantly different between the treatment groups (results not shown).

DISCUSSION

Treatment of patients with CAD with a daily dose of 500 mg of clarithromycin SR for a mean duration of 16 days prior to CABG surgery did not reduce rates of mortality or cardiovascular events during the 2 years after surgery. A course of clarithromycin appears, therefore, to be of no clinical value to patients with severe atherosclerosis who undergo CABG surgery.

Randomized controlled trials have been performed to analyze whether treatment with antibiotics active against C. pneumoniae demonstrates an effect in patients with CAD and its associated complications. These trials were undertaken after several in-
vestigators found an association between C. pneumoniae infection and CAD. This association was first noted in 1988 by Saikku et al. [9] in Finland. Further interest in the association was mainly based on the results of seroepidemiological studies, although not all studies have found a significant relationship after correcting for confounding factors [10]. More evidence of the association was the demonstration of C. pneumoniae in some atherosclerotic lesions. Also, animal model experiments suggested that C. pneumoniae induced atherogenesis [4, 5, 11].

Since the publication of promising results from 2 smaller clinical treatment studies in 1997 [7, 8], several larger intervention trials have been performed (table 3). So far, the significant effects of antibiotic therapy in some small clinical trials [7, 8, 12, 13] have not been confirmed by large randomized trials [14–20, 28], including our study. Antibiotic treatment regimes and duration of follow-up varied significantly between the studies, as well as the size and type of the study populations (table 3). Nevertheless, the majority of randomized, controlled trials did not show any beneficial effects on outcome after a course of macrolides in patients with established CAD.

There are several possible explanations for why we did not detect a significant difference in outcomes between the 2 study groups. The duration of treatment in our study might have been too short and therefore not effective enough. In the clarithromycin in acute coronary syndrome patients in Finland (CLARIFY) study, Sinisalo et al. [12] administered clarithromycin for 3 months to patients with acute non–Q-wave infarction or unstable angina, and this reduced the risk of subsequent cardiac events by 41% [12]. Other trials have not indicated that the duration of treatment is an important factor (table 3). In particular, the weekly intervention with zithromax for atherosclerosis and its related disorders (WIZARD) study—by far the largest study with 7747 patients—used 77 days of treatment and did not find a significant effect [19]. In our study, a subgroup of patients who had been treated for ≥21 days before surgery was analyzed, but no difference in outcomes was found, compared with patients treated for a mean of 16 days. Therefore, it is unlikely that the duration of treatment played an important role.

The statistical power of the study could also be a point of discussion. However, there was no trend towards a better or worse outcome as a result of treatment. The values for the most important variables—mortality and rates of all cardiac events—were nearly equal in both study groups. Also, other large studies such as the azithromycin in acute coronary syndrome (AZACS) trial [18], which included 1439 patients, and WIZARD [19], which included 7747 patients, did not detect a reduction in cardiovascular events as a result of treatment.

Duration of follow-up and type of antibiotic received also seem to have had no significant influence, as indicated by comparison of the outcomes of these clinical trials (table 3). It is remarkable that the positive results of smaller clinical trials have not been duplicated in the larger ones. Of course, this could be explained by the fact that such findings are coincidences. Smaller trials may have studied a more selected population, and their findings might indicate that certain groups of individuals could benefit from antibiotics. In the WIZARD trial [19], analysis of subpopulations showed trends toward a favorable effect of antibiotic therapy for men who smoke or who have diabetes or hypercholesterolemia. In a post hoc analysis of the intracoronary-stenting-and-antibiotic-regimen (ISAR)–3 trial data [21], patients with the highest titers of C. pneumoniae antibodies had a reduced rate of restenosis if treated with roxithromycin rather than placebo. In our study, the effect of treatment with clarithromycin did not differ for patients with and without diabetes, or for those who smoked and those who did not.

It must be noted that patients in our study underwent CABG...
Table 3. Summary of randomized controlled intervention trials that have investigated the association between *Chlamydia pneumoniae* and coronary artery disease.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study name</th>
<th>Study population</th>
<th>Antibiotic used</th>
<th>Duration of treatment, days</th>
<th>Duration of follow-up, months</th>
<th>End points</th>
<th>Results</th>
<th>Relative risk</th>
<th>(95% CI)</th>
<th>associated with cardiac events after treatmenta</th>
</tr>
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<tbody>
<tr>
<td>[7]</td>
<td>St George’s Hospital trial</td>
<td>220 Male survivors of MI</td>
<td>Roxithromycin</td>
<td>3–6</td>
<td>18 ± 4b</td>
<td>Nonfatal MI, unstable angina, death due to cardiovascular disease</td>
<td>Anti- C. pneumoniae titer</td>
<td>4-fold decreased risk of cardiovascular events in patients with an anti-C. pneumoniae titer of ≥ 1/64</td>
<td>0.27 (0.06– 0.95)</td>
<td></td>
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<td>[8]</td>
<td>ROXISc</td>
<td>202 patients with unstable angina or non–Q-wave MI</td>
<td>Roxithromycin</td>
<td>30</td>
<td>1</td>
<td>Death due to cardiac ischemia, MI, severe recurrent ischemia</td>
<td>Anti- C. pneumoniae titer, CRP</td>
<td>Significant reduction in the primary composite triple end point rates in the treatment group</td>
<td>0.11 (0.01– 0.82)</td>
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<td>[14]</td>
<td>ROXISd</td>
<td>202 Patients with unstable angina or non–Q-wave MI</td>
<td>Roxithromycin</td>
<td>30</td>
<td>6</td>
<td>Anti- C. pneumoniae titer, CRP, Death due to cardiac ischemia, MI, severe recurrent ischemia</td>
<td>Combined rate of 3 secondary events was not significantly different at 6 months</td>
<td>0.60 (0.24– 1.44)</td>
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<td>[28]</td>
<td>ACADEMICd</td>
<td>302 Patients with coronary artery disease with anti-C. pneumoniae titer</td>
<td>Azithromycin</td>
<td>90</td>
<td>6</td>
<td>Cardiovascular events: death due to cardiac disease, MI, stroke, hospitalization for unstable angina, cardiac arrest, and resuscitation, and/or revascularization</td>
<td>Inflammatory markers</td>
<td>No significant difference in rates for the primary end point between the 2 groups</td>
<td>1.12 (0.45– 2.76)</td>
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<tr>
<td>[15]</td>
<td>ACADEMICd</td>
<td>302 Patients with coronary artery disease with anti-C. pneumoniae titer</td>
<td>Azithromycin</td>
<td>90</td>
<td>24</td>
<td>Inflammatory markers</td>
<td>Cardiovascular events: death due to cardiac disease, MI, stroke, hospitalization for unstable angina, resuscitated cardiac arrest with resuscitation, revascularization</td>
<td>No significant difference in rates for the primary end point between the 2 groups</td>
<td>0.89 (0.51– 1.57)</td>
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<td>[20]</td>
<td>Siriraj Hospital trial</td>
<td>84 Patients with acute coronary syndrome</td>
<td>Roxithromycin</td>
<td>30</td>
<td>3</td>
<td>Death due to cardiac disease, unplanned revascularization, recurrent angina, MI</td>
<td>Anti-C. pneumoniae titer</td>
<td>No significant difference in rates of cardiac events</td>
<td>1.01 (0.56– 1.84)</td>
<td></td>
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<tr>
<td>Study</td>
<td>Design</td>
<td>Participants</td>
<td>Antibiotics</td>
<td>Outcome Measures</td>
<td>Relative Risk (95% CI)</td>
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<td>STAMINA</td>
<td>325 patients with acute MI or unstable angina (acute coronary syndromes)</td>
<td>Azithromycin or Amoxicillin 7 12 Unstable angina, MI Antitibodies to C. pneumoniae and H. pylori</td>
<td>36% Reduction in rates of all end points in patients who received antibiotics</td>
<td>0.61 (0.41–0.93)</td>
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<tr>
<td>CLARIFY</td>
<td>148 patients with acute non-Q-wave infarction or unstable angina</td>
<td>Clarithromycin 90 18 ± 12 Death, MI, angina Death, MI, unstable angina, ischemic stroke, critical limb ischemia</td>
<td>Significant reduction in rates of cardiovascular events during mean follow-up period</td>
<td>0.49 (0.26–0.92)</td>
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<td>WIZARD</td>
<td>7747 patients with a &gt;6-week history of MI</td>
<td>Azithromycin 77 48 Death from any cause, nonfatal recurrent MI, coronary revascularization, hospitalization for angina Anti–C. pneumoniae titer, CRP, TNF-α, fibrinogen</td>
<td>No significant difference in end points. Baseline titer of IgG antibodies against C. pneumoniae had no effect on outcome</td>
<td>0.93 (0.83–1.05)</td>
<td></td>
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<tr>
<td>ANTIBIO</td>
<td>872 Patients with acute MI</td>
<td>Roxithromycin 42 12 Total mortality Death, recurrent infarction, resuscitation, stroke, postinfarction angina until hospital discharge, unstable angina leading to hospitalization, rate of PTCA or CABG intervention</td>
<td>No difference in rates of clinical events. Rates of death, MI, resuscitation, stroke, and unstable angina were not significantly different at 12 month follow-up</td>
<td>1.21 (0.95–1.53)</td>
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<tr>
<td>AZACS</td>
<td>1439 Patients with unstable angina or acute MI</td>
<td>Azithromycin 5 6 Death, recurrent MI, revascularization Unstable angina, congestive heart failure requiring hospital admission</td>
<td>No difference in rates of events at 6 month follow-up</td>
<td>1.03 (0.82–1.29)</td>
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<tr>
<td>This study, 2005</td>
<td>Amphia Hospital trial 473 Patients with angina or a history of MI scheduled for CABG surgery</td>
<td>Clarithromycin 16 24 Overall mortality Reappearance of angina, recurrence of MI, PTCA or CABG, stroke, peripheral vascular surgery</td>
<td>No difference in rates of events at 24 month follow-up</td>
<td>1.04 (0.55–1.98)</td>
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**NOTE.** CABG, coronary artery bypass graft; MI, myocardial infarction; CRP, c-reactive protein; PTCA, percutaneous transluminal coronary angioplasty.

a Relative risk of combined cardiovascular end points.

b Results of this study were published twice, after 1 and 6 months of follow-up.

c Results of this study were published twice, after 6 and 24 months of follow-up.

d Mean value ± SD.
surgery. Cardiac events may well have been attributable to other factors, such as thrombosis of the graft, in addition to a possible infection with *C. pneumoniae*. However, treatment with clarithromycin had no additional effect on clinical outcomes for these patients.

The negative results of the majority of recent trials, including ours, challenge the hypothesis that viable *C. pneumoniae* plays a causal role in the pathogenesis of atherosclerosis. This doubt is confirmed by other evidence in the research field. In more recent studies, many investigators have failed to detect *C. pneumoniae* DNA in vascular specimens from patients with atherosclerosis [22–26]. Major interlaboratory differences exist, especially concerning false-positive results. Moreover, there is no established reference method for detection of *C. pneumoniae*, which makes it almost impossible to draw clear conclusions about its presence in vascular tissue and its association with atherosclerosis [6]. In addition, the results of a recent meta-analysis appear to indicate that there is no clear relation between the presence of chlamydial IgG and atherogenesis [10]. Therefore, whether infection with *C. pneumoniae* plays a role in the development of atherosclerosis needs to be questioned. As shown in all studies included in table 3, macrolide treatment did not show a significant effect on pooled cardiac events (relative risk, 0.97; 95% CI, 0.89–1.06) or pooled data on mortality (relative risk, 0.97; 95% CI, 0.82–1.16). The results of our study are in line with these pooled data. Therefore, at present, no recommendation can be made for the use of antibiotic therapy for secondary prevention of atherosclerosis.

In addition to their ability to treat *C. pneumoniae* infection and to reduce the vasotropic infectious burden, macrolide antibiotics are often noted to have an anti-inflammatory effect. However, an anti-inflammatory effect of clarithromycin, as measured by the levels of cytokines and the levels of proteins in acute phase blood samples, was not detected in our study patients, as has been published elsewhere [27].

In conclusion, this study shows that treatment with macrolide antibiotics has no beneficial effect on the rates of mortality, cardiac events, and surgical site infection in patients with severe atherosclerosis who undergo CABG surgery. Our findings provide further evidence against the hypothesis that *C. pneumoniae* has a causative role in the development of atherosclerosis. The relationship between *C. pneumoniae* and atherosclerosis should be studied in more detail before new therapeutic trials are to be performed.

**Acknowledgment**

**Potential conflicts of interest.** All authors: no conflicts.

**References**


