Effects of Antibiotic Therapy on Outcomes of Patients With Coronary Artery Disease
A Meta-analysis of Randomized Controlled Trials

Richard Andraws, MD
Jeffrey S. Berger, MD
David L. Brown, MD

Infection with Chlamydia pneumoniae has been serologically, pathologically, and clinically associated with the initiation and progression of atherosclerosis as well as the development of coronary heart disease.1-18 Given the prevalence of C pneumoniae infection19 and the considerable global burden of coronary artery disease (CAD), a causal link between the 2 may have important public health implications. Specifically, the use of antibiotics effective against this pathogen could become an important treatment option.20-23

Numerous clinical trials have examined whether treatment of C pneumoniae is beneficial in the secondary prevention of events in patients with stable and unstable CAD, but results have been inconsistent. We therefore conducted a systematic review and meta-analysis of all published randomized clinical trials that evaluated the effect of antichlamydial antibiotic treatment on outcomes of patients with CAD.

METHODS
Search Strategy
Comprehensive searches of the MEDLINE and Cochrane Central Register of Controlled Trials databases were performed using Web-based search engines (OVID, PubMed) for human studies published in English between 1966 and April 2005. Search terms included antibacterial agents, myocardial infarction, unstable angina, and coronary arteriosclerosis.

Study Selection
Eligible studies were prospective, randomized, placebo-controlled trials of antichlamydial antibiotic therapy in patients with CAD that reported all-cause mortality, myocardial infarction (MI), or unstable angina. Of the 110 potentially relevant articles identified, 11 reports enrolling 19,217 patients were included.

Data Extraction
Included studies were reviewed to determine the number of patients randomized, mean duration of follow-up, and end points. End points of interest included all-cause mortality, myocardial infarction (MI), and a combined end point of MI and unstable angina.

Data Synthesis
Event rates were combined using a random-effects model. Antibiotic therapy had no impact on all-cause mortality among treated vs untreated patients (4.7% vs 4.6%; odds ratio [OR], 1.02; 95% confidence interval [CI], 0.89-1.16; P = .83), on the rates of MI (5.0% vs 5.4%; OR, 0.92; 95% CI, 0.81-1.04; P = .19), or on the combined end point of MI and unstable angina (9.2% vs 9.6%; OR, 0.91; 95% CI, 0.76-1.07; P = .22).

Conclusion
Evidence available to date does not demonstrate an overall benefit of antibiotic therapy in reducing mortality or cardiovascular events in patients with CAD.

Context
Although Chlamydia pneumoniae infection has been associated with the initiation and progression of atherosclerosis, results of clinical trials investigating antichlamydial antibiotics as adjuncts to standard therapy in patients with coronary artery disease (CAD) have been inconsistent.

Objective
To conduct a meta-analysis of clinical trials of antichlamydial antibiotic therapy in patients with CAD.

Data Sources
The MEDLINE and Cochrane Central Register of Controlled Trials databases were searched from 1966 to April 2005 for English-language trials of antibiotic therapy in patients with CAD. Bibliographies of retrieved articles were searched for further studies. Presentations at major scientific meetings (2003-2004) were also reviewed. Search terms included antibacterial agents, myocardial infarction, unstable angina, and coronary arteriosclerosis.

©2005 American Medical Association. All rights reserved.
(Reprinted) JAMA, June 1, 2005—Vol 293, No. 21 2641
were pilot studies were excluded

tization, were not placebo controlled, or
antibiotics as an adjunct to revascular-
the randomized trials, 9 clinical trials that
letters to the editor, case reports, case-
clinical trials (reviews, editorials,
articles because they were not random-
identified 110 studies. We excluded 90
was previously published includ-
therapy in patients with established CAD.

For inclusion, studies had to be prospec-
tive, randomized, placebo-controlled
trials of antichlamydial antibiotic treat-
ment as an adjunct to standard medical
therapy in patients with established CAD.
We assessed quality using criteria that
have been previously published includ-
ing adequate binding of randomiza-
tion, binding of treatment assignment,
completeness of follow-up, and objec-
tivity of the outcome assessment.24,25 We
identified 110 studies. We excluded 90
articles because they were not random-
ized clinical trials (reviews, editorials,
letters to the editor, case reports, case-
control studies, and meta-analyses). Of
the randomized trials, 9 clinical trials that
did not report clinical end points, used
antibiotics as an adjunct to revascular-
ization, were not placebo controlled, or
were pilot studies were excluded (FIGURE 1).

End Points and Definitions
End point definitions were those used
in the individual trials. All-cause mor-
tality was death from any cause (car-
diac or noncardiac). Myocardial infarction
(MI) was defined as elevation of serum markers of myocardial injury along with electrocardiographic changes. Unstable angina (UA) was defined as a change in typical anginal pat-
tern including increases in anginal fre-
quency, intensity, or duration, with or
without electrocardiographic changes,
requiring hospitalization. These 3 end
points were extracted from each trial.

The composite rate of MI and UA was also analyzed to investigate the possible
impact of treatment on the sub-
sequent development of acute coro-
nary syndromes (ACS). Event rates at
the end of the follow-up period for each
study were used for the analysis.

Statistical Analysis
Because patient-level data from each trial
were not available, meta-analyses of sum-
mary statistics from individual trials were
performed using Comprehensive Meta
Analysis software (Bios tat, Englewood,
NJ). Data were analyzed according to the
intention-to-treat principle. Methods
based on odds ratios (ORs) (Mantel-
Haenszel and Peto methods) were used.
The Q statistic failed to indicate statisti-
cal heterogeneity. However, because the
lack of heterogeneity does not necessar-
ily imply homogeneity, a summary OR
was calculated using a random-effects
model from the ORs and 95% confi-
dence intervals (CIs) for each end point
in each study. Sensitivity analyses were
performed for each outcome to assess the
contribution of each study to the pooled
estimate by excluding individual trials 1
at a time and recalculating the com-
bined OR for the remaining studies. To
assess publication bias, we generated a
funnel plot of the logarithm of effect size
vs the standard error for each trial.

RESULTS

Search Results
Our search identified a total of 11 ran-
domized controlled trials for inclusion
in the meta-analysis.26-30 These trials ran-
domized a total of 19 217 patients (9613
treated, 9604 placebo). Four studies26-28,30
randomized patients with stable
CAD whereas 7 trials29,34,36 randomized
patients presenting with ACS.

Qualitative Findings
Trial details are summarized in TABLE 1.
Baseline characteristics of the patients
are presented in TABLE 2. Patients were
predominately men with mean ages be-
tween 60 and 66 years. The study by
Gupta et al,26 the Randomized Second-
ary Prevention Trial of Azithromycin
in Patients with Coronary Artery Dis-
ease (ACADEMIC),27 and the Weekly
Intervention with Zithromax for Atherosclerosis and Its Related Disorders
(WIZARD) trial28 only randomized pa-
tients with positive titers to C. pneumo-
niae. Follow-up ranged from 3 months
to 4 years.

Treatment
Treatment was most commonly with a
single macrolide antibiotic using (1) rox-
ithromycin in the Treatment with the
Antibiotic Roxithromycin in Patients
with Acute Non-Q-Wave Coronary Syn-
dromes (ROXIS) trial,29 the trial by Leo-
wattana et al,31 and the Antibiotic
Therapy after Acute Myocardial Infarc-
tion (ANTIBIO) trial32; (2) azithro-
mycin in WIZARD, ACADEMIC, the Effect
of Short-Term Treatment with Azithro-
mycin on Recurrent Ischaemic Events in
Patients with Acute Coronary Syn-
dromes (AZACS) trial,33 the trial by
Gupta et al, and the Azithromycin and
Coronary Events Study (ACES)34; and (3)
clarithromycin in the Clarithromycin in
Acute Coronary Syndrome Patients in
Finland (CLARIFY) trial.30 In the South
Thames Trial of Antibiotics in Myocar-
dial Infarction and Unstable Angina
(STAMINA),32 a regimen that included
metronidazole and a proton pump inhibi-
tor (omeprazole) along with azithro-
mycin was used. In addition, there was
a third study group designed to evalu-
ate the potential benefit of Helicobacter
pylori eradication in which patients were
treated with amoxicillin, metronida-
zone, and omeprazole. We included only
the macrolide treatment group of
STAMINA in this analysis. The antibiotic group of the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT-TIMI 22) trial assessed gatifloxacin. Courses of treatment ranged from 5 days to 2 years. Seven studies reported the pharmacologic regimen the patients were receiving in addition to treatment or placebo. In these trials, rates of use of β-blockers, antiplatelet agents, and statins exceeded 50%.

All trials were randomized, double-blinded, and placebo-controlled and were of comparable quality. Randomization protocols were available for 10 of the 11 studies. One study did not provide details of the randomization scheme. Nine trials reported the use of a blinded end points committee for the adjudication of outcome events. This information was unavailable from 2 studies. All analyses were conducted by intention-to-treat. Follow-up was 100% in 6 studies and greater than 98% in the remaining 5 studies. Full or partial funding was provided by the company whose drug was used for the study in 7 of 11 trials.

Quantitative Findings

Mortality. Mortality outcomes were presented in 11 trials that enrolled 19,217 patients. A nonsignificant reduction in mortality was observed in 6 trials. Figure 2 presents the mortality rates for each of the 11 studies as well as for the pooled data. The combined mortality rate was 4.7% among 9,613 treated patients vs 4.6% of 9,604 participants in the placebo group (OR, 1.02; 95% CI, 0.89-1.16; P = .83). There was minimal quantitative heterogeneity of results (P = .75). However, we performed a sensitivity analysis to assess the potential impact of qualitative differences in study design and patient selection. Exclusion of any single trial from the analysis did not alter the overall finding of this analysis. Furthermore, inclusion of only those studies that enrolled patients with positive serology (n = 4,524) revealed a nonsignificant trend toward increased mortality with antibiotic treatment (OR, 1.27; 95% CI, 0.89-1.82; P = .19).

Myocardial Infarction. Nine trials randomizing a total of 18,939 patients, reported rates of MI. A nonsignificant reduction in MI was demonstrated in 7 trials and a significant reduction in MI was observed in 1 study. The combined MI rate was 5.0% among 9,462 patients treated with antibiotics vs 5.4% in 9,477 placebo-treated patients (OR, 0.92; 95% CI, 0.81-1.04; P = .19; Figure 3). There was minimal heterogeneity of results with this analysis (P = .54). A sensitivity analysis revealed that exclusion of any single trial from the analysis did not alter the overall finding.

Acute Coronary Syndromes. Of the 10 trials reporting data on ACS (n = 17,778), eight studies reported nonsignificant reductions in ACS event rates. The pooled event rate was 9.2% among 8,897 participants in the antibiotic-treated group vs 9.6% in 8,881 placebo-treated subjects (OR, 0.91; 95% CI, 0.76-1.07; P = .25; Figure 4). There was a trend toward heterogeneity in this analysis (P = .09). However, exclusion of any single trial from the analysis did not alter

The table below presents the mortality rates in patients with coronary artery disease (CAD) who received antibiotic therapy, compared to placebo:

<table>
<thead>
<tr>
<th>Source</th>
<th>Population</th>
<th>Intervention</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gupta et al, 1997</td>
<td>60 Male patients at least 6 mo from documented MI and with titers to Chlamydia pneumoniae &gt; 1:164</td>
<td>Azithromycin 500 mg/d for 3 d (28 received 1 course, 12 received 2 courses 3 mo apart) or placebo</td>
<td>18 mo</td>
</tr>
<tr>
<td>ACADEMIC, 1999</td>
<td>302 Patients with CAD and C pneumoniae titers of &gt; 1:116. Patients were at least 5 d from an MI</td>
<td>Azithromycin 500 mg/d for 3 d then 500 mg/wk for 3 mo or placebo</td>
<td>2 y</td>
</tr>
<tr>
<td>WIZARD, 2003</td>
<td>7722 Patients with a history of MI of more than 6 weeks before and with C pneumoniae titers of &gt; 1:116</td>
<td>Azithromycin 600 mg/d for 3 d then 1 wk for 11 wk or placebo</td>
<td>14 mo</td>
</tr>
<tr>
<td>ACESS, 2005</td>
<td>4012 Patients with stable CAD</td>
<td>Azithromycin 600 mg/wk for 1 y or placebo</td>
<td>4 y</td>
</tr>
<tr>
<td>ROXIS, 1999</td>
<td>202 Patients with documented history of CAD and ACS</td>
<td>Roxithromycin 150 mg 2/d for 30 d or placebo</td>
<td>6 mo</td>
</tr>
<tr>
<td>CLARIFY, 2001</td>
<td>148 Patients with ACS</td>
<td>Clarithromycin 500 mg/d for 85 d or placebo</td>
<td>1 y</td>
</tr>
<tr>
<td>Leowattana et al, 2001</td>
<td>84 Patients with ACS</td>
<td>Roxithromycin 150 mg/d for 30 d or placebo</td>
<td>3 mo</td>
</tr>
<tr>
<td>STAMINA, 2002</td>
<td>218 Patients with ACS</td>
<td>Azithromycin 500 mg/d for 3 d plus metronidazole 20 mg 2/d for 1 wk plus metronidazole 400 mg 2/d for 1 wk or placebo</td>
<td>1 y</td>
</tr>
<tr>
<td>ANTIBIO, 2003</td>
<td>868 Patients with unstable angina or MI</td>
<td>Roxithromycin 300 mg/d for 6 wk or placebo</td>
<td>1 y</td>
</tr>
<tr>
<td>AZACS, 2003</td>
<td>1439 Patients with ACS</td>
<td>Azithromycin 500 mg on day 1 followed by 250 mg/d for 4 d or placebo</td>
<td>6 mo</td>
</tr>
<tr>
<td>PROVE-IT, 2005</td>
<td>4162 Patients hospitalized with ACS in the preceding 10 d</td>
<td>Gatifloxacin 400 mg/d for 10 d/mo for 2 y or placebo</td>
<td>24 mo</td>
</tr>
</tbody>
</table>

Abbreviations: ACADEMIC, Randomized Secondary Prevention Trial of Azithromycin in Patients with Coronary Artery Disease; ACES, Azithromycin and Coronary Events Study; ACS, acute coronary syndromes; ANITBIO, Antibiotic Therapy after Acute Myocardial Infarction; AZACS, Azithromycin on Recurrent Ischaemic Events in Patients with Acute Coronary Syndromes; CAD, coronary artery disease; CLARIFY, Clarithromycin in Acute Coronary Syndrome Patients in Finland; MI, myocardial infarction; PROVE-IT, Pravastatin or Atorvastatin Evaluation and Infection Therapy; ROXIS, Antibiotic Roxithromycin in Patients with Acute Non-Q-Wave Coronary Syndrome; STAMINA, South Thames Trial of Antibiotics in Myocardial Infarction and Unstable Angina; WIZARD, Weekly Intervention with Zithromax for Atherosclerosis and Its Related Disorders.

©2005 American Medical Association. All rights reserved.
the overall finding. Analysis of the 3 trials that enrolled only patients with positive antichlamydial titers (n=4548) found no impact of antibiotic treatment on the development of ACS (OR, 0.92; 95% CI, 0.77-1.11; P=.40).

Publication Bias. To assess publication bias, we generated a funnel plot of the logarithm of effect size vs the standard error for each trial. There was no evidence of significant publication bias.

COMMENT
To date, 11 randomized trials have examined the effects of antichlamydial antibiotic therapy on cardiovascular events in patients with established CAD. This meta-analysis was designed to examine and synthesize the disparate results of these trials to gain a clearer understanding of the role of antimicrobials in this patient population. We examined the pooled effects of antibiotic therapy on total mortality, MI, and ACS and found that, based on available data, there was no significant benefit on any of these end points.

It is well recognized that traditional risk factors do not identify many patients with coronary events.37 Furthermore, measurement of markers of inflammation provides prognostic value beyond traditional risk factors in risk assessment. The recognition that bacteria and other pathogens are avid inducers of inflammation along with the demonstration of a causal relationship between H pylori and peptic ulcer disease provided a theoretical template to consider infectious agents as an etiology of common, important chronic diseases, including CAD.41

C pneumoniae was first associated with CAD and MI in 1988 by Saikku et al. In a retrospective study, 68% of patients with acute MI and 50% of patients chronic CAD had positive titers to C pneumoniae, a significantly greater preva-

---

**Table 2. Baseline Characteristics**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Gupta et al</th>
<th>ACADEMIC</th>
<th>ROXIS</th>
<th>CLARIFY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics (n = 40)</td>
<td>Placebo (n = 20)</td>
<td>Antibiotics (n = 150)</td>
<td>Placebo (n = 152)</td>
<td>Antibiotics (n = 102)</td>
</tr>
<tr>
<td>Male, No. (%)</td>
<td>40 (100)</td>
<td>20 (100)</td>
<td>129 (86)</td>
<td>138 (91)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>60 (9)</td>
<td>58 (7)</td>
<td>64 (10)</td>
<td>63 (11)</td>
</tr>
<tr>
<td>Risk factors, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>7 (18)</td>
<td>4 (20)</td>
<td>59 (39)</td>
<td>68 (45)</td>
</tr>
<tr>
<td>Previous MI</td>
<td>40 (100)</td>
<td>20 (100)</td>
<td>95 (63)</td>
<td>88 (58)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>12 (30)</td>
<td>8 (40)</td>
<td>17 (11)</td>
<td>17 (11)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>18 (45)</td>
<td>7 (35)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Smoking (current or past)</td>
<td>35 (88)</td>
<td>15 (75)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Previous CAGB</td>
<td>12 (30)*</td>
<td>6 (30)*</td>
<td>98 (65)</td>
<td>93 (61)</td>
</tr>
<tr>
<td>Previous PTCA</td>
<td></td>
<td></td>
<td>63 (42)</td>
<td>74 (49)</td>
</tr>
</tbody>
</table>

| Medications, No. (%) | | | | | | | | |
| NR | NR | NR | NR | 60 (81) | 66 (89) | 15 (20) | 14 (19) |
| NR | NR | NR | NR | 65 (64) | 57 (57) | 72 (97) | 69 (93) |
| NR | NR | NR | NR | 29 (39) | 32 (43) | | |

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Leowattana et al</th>
<th>STAMINA</th>
<th>ANTIBIO</th>
<th>AZACS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic (n = 43)</td>
<td>Placebo (n = 41)</td>
<td>Antibiotic (n = 111)</td>
<td>Placebo (n = 107)</td>
<td>Antibiotic (n = 431)</td>
</tr>
<tr>
<td>Male, No. (%)</td>
<td>29 (67)</td>
<td>24 (59)</td>
<td>78 (70)</td>
<td>68 (64)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>63 (10)</td>
<td>60 (13)</td>
<td>66 (9)</td>
<td>66 (9)</td>
</tr>
<tr>
<td>Risk factors, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>24 (56)</td>
<td>20 (49)</td>
<td>26 (24)</td>
<td>21 (20)</td>
</tr>
<tr>
<td>Previous MI</td>
<td>NR</td>
<td>NR</td>
<td>12 (11)</td>
<td>17 (16)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>22 (51)</td>
<td>15 (37)</td>
<td>11 (10)</td>
<td>14 (13)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>25 (58)</td>
<td>28 (68)</td>
<td>20 (18)</td>
<td>17 (16)</td>
</tr>
<tr>
<td>Smoking (current or past)</td>
<td>19 (44)</td>
<td>25 (61)</td>
<td>36 (32)</td>
<td>37 (35)</td>
</tr>
<tr>
<td>Previous CAGB</td>
<td>NR</td>
<td>NR</td>
<td>7 (6)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Previous PTCA</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

| Medications, No. (%) | | | | | | | | |
| NR | NR | NR | NR | NR | NR | NR | NR |
| NR | NR | NR | NR | NR | NR | NR | NR |

| β-Blockers | 391 (92) | 392 (91) | 500 (70) | 505 (70) |
| NR | NR | NR | NR |

(continued)
lence than among matched controls. Moreover, a significant number of those with acute MI had evidence of acute seroconversion. Since this initial epidemiological observation, C pneumoniae has been shown to infect all of the cells involved in atherosclerosis and to induce inflammation within plaques.14-18 In addition, in a recent prospective study, chlamydial antigens were identified by immunofluorescence in 73% of atheromas.42 Furthermore, treatment of chlamydial infection has been shown to improve endothelial function, halt plaque progression, and reduce inflammation.10-13 The 60-patient study by Gupta et al26 was the first to examine the effects of antibiotic treatment on clinical end points and showed a 68% reduction in cardiovascular events, including mortality. This initial observation stimulated investigations seeking to extend the findings to different cohorts.

Subsequent trials have been unable to consistently reproduce these findings possibly because of differences in patient populations, trial designs, and antibiotic regimens. For example, only 3 trials (all involving patients with stable CAD) used seropositivity for Chlamydia as an inclusion criterion.36-38 Treating both patients with and without evidence of prior Chlamydia infection may reduce the ability to demonstrate a benefit on clinical end points. There is evidence that increasing “pathogen burden,” as defined by serum levels of immunoglobulins to various infectious agents, correlates with an increased risk of adverse outcomes.2,3 Patients with higher pathogen burden may benefit from treatment with antibiotics more robustly than those with lower burdens.10 However, this analysis, as well as a subgroup analysis of the PROVE-IT trial,36 found no improvement in outcomes among patients with positive C pneumoniae titers.
The duration of treatment differs significantly between studies and early trends toward benefit have been lost on longer follow-up. For example, WIZARD demonstrated that patients treated for 3 months had a statistically significant 33% decrease in death and MI at 6 months, which was not apparent at 12 months. ACES and PROVE-IT were designed, in part, to test the hypothesis that longer therapy would improve clinical outcomes. Both enrolled more than 4000 patients but neither trial showed benefits on any clinical end point. Thus, longer treatment duration is unlikely to be beneficial.

Figure 3. Effect of Antibiotic Treatment on Myocardial Infarction

<table>
<thead>
<tr>
<th>Source</th>
<th>Antibiotic</th>
<th>Placebo</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACADEMIC</td>
<td>4/150</td>
<td>6/152</td>
<td>0.67 (0.18-2.41)</td>
</tr>
<tr>
<td>ROXIS</td>
<td>0/102</td>
<td>2/100</td>
<td>0.19 (0.01-4.05)</td>
</tr>
<tr>
<td>CLARIFY</td>
<td>5/74</td>
<td>14/74</td>
<td>0.31 (0.12-0.91)</td>
</tr>
<tr>
<td>Leowattana et al</td>
<td>4/43</td>
<td>6/41</td>
<td>0.60 (0.16-2.30)</td>
</tr>
<tr>
<td>ANTIBIO</td>
<td>21/431</td>
<td>24/437</td>
<td>0.88 (0.48-1.61)</td>
</tr>
<tr>
<td>AZACS</td>
<td>17/716</td>
<td>22/723</td>
<td>0.78 (0.41-1.47)</td>
</tr>
<tr>
<td>WIZARD</td>
<td>145/3866</td>
<td>153/3856</td>
<td>0.94 (0.75-1.19)</td>
</tr>
<tr>
<td>ACES</td>
<td>136/2004</td>
<td>131/2008</td>
<td>1.04 (0.82-1.34)</td>
</tr>
<tr>
<td>PROVE-IT</td>
<td>137/2076</td>
<td>154/2086</td>
<td>0.89 (0.70-1.13)</td>
</tr>
<tr>
<td>Total*</td>
<td>469/9462</td>
<td>512/9477</td>
<td>0.92 (0.81-1.04)</td>
</tr>
</tbody>
</table>

*Test of Heterogeneity P = .54

Data are based on event rates at the end of follow-up for each study. For fully expanded study names see the footnote in Table 1. CI indicates confidence interval; OR, odds ratio. The sizes of the data markers are proportional to the square root of the number of patients in the study.

Figure 4. Effect of Antibiotic Treatment on Acute Coronary Syndromes (Myocardial Infarction and Unstable Angina)

<table>
<thead>
<tr>
<th>Source</th>
<th>Antibiotic</th>
<th>Placebo</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gupta et al</td>
<td>4/43</td>
<td>6/41</td>
<td>0.60 (0.16-2.30)</td>
</tr>
<tr>
<td>ACADEMIC</td>
<td>12/150</td>
<td>13/152</td>
<td>0.90 (0.41-2.11)</td>
</tr>
<tr>
<td>ROXIS</td>
<td>6/102</td>
<td>9/100</td>
<td>0.63 (0.22-1.85)</td>
</tr>
<tr>
<td>CLARIFY</td>
<td>10/74</td>
<td>25/74</td>
<td>0.31 (0.14-0.70)</td>
</tr>
<tr>
<td>Leowattana et al</td>
<td>2/40</td>
<td>4/20</td>
<td>0.21 (0.02-1.27)</td>
</tr>
<tr>
<td>STAMINA</td>
<td>23/111</td>
<td>31/107</td>
<td>0.64 (0.34-1.19)</td>
</tr>
<tr>
<td>ANTIBIO</td>
<td>94/431</td>
<td>82/437</td>
<td>1.21 (0.87-1.68)</td>
</tr>
<tr>
<td>WIZARD</td>
<td>250/3866</td>
<td>256/3856</td>
<td>0.97 (0.81-1.16)</td>
</tr>
<tr>
<td>ACES</td>
<td>186/2004</td>
<td>185/2008</td>
<td>1.01 (0.81-1.25)</td>
</tr>
<tr>
<td>PROVE-IT</td>
<td>230/2076</td>
<td>246/2086</td>
<td>0.93 (0.77-1.13)</td>
</tr>
<tr>
<td>Total*</td>
<td>817/8897</td>
<td>857/8881</td>
<td>0.91 (0.76-1.07)</td>
</tr>
</tbody>
</table>

*Test of Heterogeneity P = .09

Data are based on event rates at the end of follow-up for each study. For fully expanded study names see the footnote in Table 1. CI indicates confidence interval; OR, odds ratio. The sizes of the data markers are proportional to the square root of the number of patients in the study.

Studies performed from 1997-2002 were modestly sized, analyzed composite end points, and were inadequately powered to detect differences in individual end points. STAMINA was actually designed to detect changes in serologic markers as its primary outcome. ANTIBIO, the first of the larger studies, had several post hoc flaws. Although designed adequately, it enrolled only 22% of its intended cohort due to poor accrual. More patients in the roxithromycin group had anterior wall MIs; thus, the treatment group may have been sicker at baseline. Moreover, significantly fewer patients were compliant with antibiotic treatment than were compliant with placebo. Since ANTIBIO, there have been 4 large, well-designed trials with adequate power to investigate the effects of antibiotics on events. None of these demonstrated improvements in clinical outcome nor did the pooled analysis. Thus, it appears unlikely that larger trials will yield different results.

The failure to improve clinical outcomes by treatment with antichlamydial antibiotics does not exclude C pneumoniae infection as a potential etiology of acute coronary events. Rather the negative results of this analysis may be related to the pathobiology of chlamydial infection. Eradication of C pneumoniae in vivo is extremely difficult, if not impossible, to achieve, even with long courses of antibiotics. Infected monocytes may provide a treatment sanctuary for the organisms. In addition, while under immune stress, chlamydiae enter a persistent phase in their life cycle that renders them resistant to treatment yet capable of inciting inflammation. Furthermore, the ability of antimicrobials to effectively penetrate atheroscleras has also been questioned. Finally, reinfection with C pneumoniae is common, rendering a single course of treatment potentially ineffective over the lifetime of a patient.

Limitations

Our study must be viewed in the context of its potential limitations. First, this meta-analysis only extracted data from
randomized clinical trials. Patients enrolled in such trials may not be representative of patients actually seen in clinical practice. Second, only macrolides and a fluoroquinolone were used in these studies, so the effect of treatment of additional pathogens that may be involved in atherosclerosis but are not in the spectrum of activity of these drugs was not evaluated. Third, our pooled analysis combines studies performed during a time of rapid improvements in medical therapy for patients with CAD. It is possible that the treatment effect observed with antibiotic therapy in earlier studies was masked in later trials because of a greater impact of the improved medical therapy on enhancing survival and reducing adverse events.

Conclusion

Despite these limitations, this systematic review and meta-analysis demonstrates that, based on evidence available to date, antichlamydial antibiotic therapy does not significantly improve major clinical outcomes in patients with CAD. Management of patients with CAD should focus on optimization of proven lifestyle interventions (exercise, weight loss, smoking cessation) and medical therapies (aspirin, β-blockers, angiotensin-converting enzyme inhibitors, and statins).


Financial Disclosures: None reported.

REFERENCES