Antibiotics for the Secondary Prevention of Ischemic Heart Disease

A Meta-analysis of Randomized Controlled Trials

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Background: Infections have been suspected in the pathogenesis of ischemic heart disease (IHD) for more than 100 years. *Chlamydia pneumoniae* has been identified in atherosclerotic specimens, and in some studies antibody titers to *C pneumoniae* have been related to the risk of myocardial infarction. The numerous clinical trials that have studied the use of antibiotics in the secondary prevention of IHD have had conflicting results.

Methods: This study is a meta-analysis of the published randomized controlled trials on the secondary prevention of IHD with antibiotics. Studies included in the analysis were limited to those studies that used antibiotics effective against *C pneumoniae*, enrolled patients with known IHD, and examined clinical outcomes related to IHD. Inclusion in the analysis was limited to well-designed randomized controlled trials that met inclusion criteria established by an expert panel.

Results: Nine published studies, with a total of 11,015 participants, were identified that met the criteria for this meta-analysis. Four of the studies reported a benefit from antibiotics, whereas 5 found no effect. A funnel plot of the published studies did not suggest the existence of other unpublished data. The combined effect found no benefit from antibiotics in the prevention of cardiovascular events in subjects with known IHD (relative risk, 0.94 [95% confidence interval, 0.86-1.03]) or mortality (relative risk, 0.94 [95% confidence interval, 0.79-1.12]).

Conclusion: In patients with known IHD, macrolide antibiotics for *C pneumoniae* did not result in a statistically significant reduction in recurrent cardiac events or mortality over 3 months to 3 years.

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Ischemic heart disease (IHD) is the number 1 cause of death in the United States and is projected to become the number 1 cause of disability worldwide by 2020. Current treatments have improved mortality rates for IHD but have not had the impact that was initially envisioned. Recent research has identified a significant inflammatory component in the progression of coronary atherosclerosis. Rudolf Ludwig Karl Virchow first proposed an association between infections and as possible cofactors in the progression of coronary atherosclerosis. Several antibiotics are available that effectively treat *C pneumoniae*. A standardized dose and duration of treatment has not been established for chronic indolent infections with *C pneumoniae*. Randomized controlled trials (RCTs) performed on the use of antibiotics in IHD have had conflicting results. However, these studies have been relatively small and thus lack the statistical power needed to identify any potential benefit. The purpose of this meta-analysis was to evaluate the combined effect of antibiotics on IHD outcomes from all of the completed clinical trials.
Numerous case-control and cross-sectional studies have been published on the use of antibiotics in the secondary prevention of IHD. The results of these studies have been conflicting. In addition, the inherent biases of these types of studies make the evidence that they provide much less powerful than that obtained from well-designed RCTs. Furthermore, the average effect of a new treatment has generally been larger in non-randomized than in randomized studies.

Numerous RCTs have also looked at the effect of antibiotics on various inflammatory markers, such as C-reactive protein, fibrinogen, and interleukin 6 levels. The clinical significance of these indirect measures is still being established, and their heterogeneity makes the estimation of a pooled effect difficult. Therefore, it was decided to limit inclusion to only RCTs that enrolled patients with known IHD and that analyzed IHD outcomes.

### LITERATURE SEARCH

A literature search of the MEDLINE database from 1966 through 2003 was performed to identify all potential clinical trials using antibiotics in IHD. The following terms were searched both with and without matching to the medical search heading (MeSH): cardiovascular diseases or heart diseases or coronary heart disease or coronary arteriosclerosis or coronary disease or arteriosclerosis or myocardial infarction or myocardial ischemia or angina, unstable or coronary artery disease or atherosclerotic heart disease or ischemic heart disease or angina pectoris. These terms were then combined with the terms antibiotics or anti-microbials or anti-infective agents, which were then combined with randomized controlled trials or clinical trials. The search was then limited to trials performed only on humans and written in the English language. In addition, several review articles on the topic were identified, and references were searched to ensure that no studies had been overlooked. The identified studies were then examined to ensure that they were conducted on patients with known IHD and analyzed clinical IHD outcomes. The search and review resulted in the identification of 9 published trials (Table 1).

### METHODS

#### STUDY TYPES

Numerous case-control and cross-sectional studies have been published on the use of antibiotics in the secondary prevention of IHD. The results of these studies have been conflicting. In addition, the inherent biases of these types of studies make the evidence that they provide much less powerful than that obtained from well-designed RCTs. Furthermore, the average effect of a new treatment has generally been larger in non-randomized than in randomized studies.

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### ANTIMICROBIALS

The randomized trials identified for this meta-analysis used several different types of antibiotics in differing dosages and durations of treatment. There is debate over the dose and duration of antibiotics necessary to treat chronic C. pneumoniae infections. Some experts have hypothesized that a long course of treatment (>1 month) is necessary to eradicate C. pneumoniae from the coronary arteries. However, azithromycin and clarithromycin are recommended for the treatment of pneumonia caused by C. pneumoniae in 5-day and 7- to 14-day courses, respectively. Similarly, roxithromycin has also been shown to be effective in a 10- to 14-day course for C. pneumoniae infections. In addition, Schneider et al. found that azithromycin is taken up by human coronary plaques in therapeutic concentrations after 3 days of oral therapy. Because a universal standard of care has not been established, it was decided to not exclude any study that used azithromycin, clarithromycin, or roxithromycin as the treatment medication.

### CHLAMYDIA TESTING

There is significant controversy about the best method for the identification of a systemic indolent infection with C. pneumoniae. IgG titers have a relatively low positive predictive value and may remain elevated after a clinical cure. The overall prevalence of C. pneumoniae exposure in the general population is estimated at about 30%. Some of the studies in our analysis tested for C. pneumoniae exposure, whereas others did not. Therefore, it was decided to not exclude any study based on the presence or absence of C. pneumoniae testing. A subanalysis of persons with and without positive markers for C. pneumoniae was not performed owing to the low numbers in each of these categories.

### OUTCOMES

There have been several outcomes used in clinical trials as surrogate markers for progression of coronary atherosclerosis. A consistent definition across studies is vital to a well-designed meta-analysis. Although some research has examined the effect of antibiotics on “noncardiac” vascular disease, most research has focused on coronary atherosclerosis. The pathophysiologic features of ischemic cerebrovascular disease and peripheral arterial occlusive disease are somewhat different from those of IHD. There are few data linking C. pneumoniae to cerebrovascular disease. Therefore, our meta-analysis focused solely on studies that enrolled patients with known IHD and used clinical coronary outcomes and death to define “events.” The following were considered coronary events: acute myocardial infarction (as demonstrated by elevated cardiac enzyme level or the presence of new Q waves on electrocardiogram), un-
stable angina (as demonstrated by angina requiring hospitalization), or sudden death (without obvious noncardiac cause).

Experts in clinical trials have argued that multiple end points should be used with caution. Multiple end points can increase power but sometimes falsely inflate or dilute the treatment effect of a drug. Therefore, an analysis that only used the primary end point of death to define outcomes was also performed.

ANALYSIS

A doctor of medicine (B.J.W.), a doctor of pharmacy (L.M.D.), and a doctor of philosophy (A.G.M.) independently reviewed the identified RCTs. The reviewers used a structured spreadsheet to evaluate each of the studies on the following criteria: randomization, blinding, intent to treat, loss to follow-up, outcome measures, and use of placebo. The reviewers then met to discuss the reviews and to compromise on any significant disagreements. Overall, the RCTs were well designed and had few methodological flaws. Specific details about 2 of the trials that raised some concerns are summarized below.

NOTE FOR THE STUDY BY GUPTA ET AL

In the study by Gupta et al,23 220 consecutive male survivors of myocardial infarction were tested for antibodies to C. pneumoniae. Eighty participants had elevated antibody levels on 2 separate occasions and were eligible to be enrolled in the treatment phase of the study. Sixty of these individuals were randomized to a control group (n = 20) or 1 of 2 treatment groups. Treatment group 1 (n = 28) received 1 course of oral azithromycin, 500 mg/d for 3 days. Treatment group 2 (n = 12) received 2 courses of oral azithromycin, 500 mg/d for 3 days, which were given 3 months apart. The biggest concern of this study surrounds the data analysis. There were 20 patients who had persistently elevated antibodies to C. pneumoniae but who were not randomized for the treatment phase of this study. However, the authors concluded that the characteristics of these nonrandomized patients were similar to those of the control group and thus included the nonrandomized patients in their final analysis. We decided to include this study but only analyzed data from the 60 individuals who were included in the randomization. Data from the nonrandomized subjects were ignored.

STATISTICAL ANALYSIS

Meta-analysis calculations were made using Review Manager software (RevMan 4.2.2; the Cochrane Collaboration, Oxford, England, 2003). Data were entered for the number of events and total number of participants in the treatment and control.

Table 2. Analysis of Published Studies

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Patients</th>
<th>Loss to Follow-up, No. (%)</th>
<th>Randomized?</th>
<th>Placebo?</th>
<th>Double Blinded?</th>
<th>Intent to Treat?</th>
<th>Outcomes</th>
<th>Decisions</th>
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<td>0</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>CV death, unstable angina, AMI, cardiac arrest, unplanned revascularization*</td>
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<tr>
<td>ROXIS</td>
<td>202</td>
<td>14 (6.9)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Severe recurrent ischemia, AMI, death</td>
<td>Include</td>
</tr>
<tr>
<td>Gupta et al</td>
<td>60</td>
<td>0</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Not†</td>
<td>Death, unstable angina, AMI, hospitalization for angina, cardiac death</td>
<td>Include‡</td>
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<tr>
<td>STAMINA</td>
<td>325</td>
<td>3 (0.01)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Death, AMI, unstable angina, critical peripheral ischemia, ischemic strokes*</td>
<td>Include</td>
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<tr>
<td>CLARIFY</td>
<td>148</td>
<td>0</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Death, AMI, hospitalization for angina or CHF, revascularization procedure**</td>
<td>Include</td>
</tr>
<tr>
<td>AZACS</td>
<td>1439</td>
<td>27 (0.02)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>AMI, hospitalization for unstable angina</td>
<td>Include</td>
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<tr>
<td>ANTIBIO</td>
<td>872</td>
<td>4 (0.005)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Death, reinfarction, resuscitation, stroke, postinfection angina until discharge, PTCA, or CABG*</td>
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<tr>
<td>Leowattana et al</td>
<td>84</td>
<td>§</td>
<td>Yes</td>
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<td>Death, PTCA, CABG, recurrent angina, myocardial infarction</td>
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<td>WIZARD</td>
<td>7723</td>
<td>32 (0.004)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Death, AMI, revascularization, hospitalization for angina</td>
<td>Include</td>
</tr>
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</table>

Abbreviations: AMI, acute myocardial infarction; CABG, coronary artery bypass graft; CHF, congestive heart failure; CVD, cardiovascular disease; PTCA, percutaneous transluminal coronary angioplasty.

*AMI, unstable angina, and death were the only outcomes included in pooled analysis.
†Patients who were not enrolled in the study (not randomized) were included in the final analysis in the control group.
‡Data were only included from the 60 patients who were randomized.
§Data were only included from the 60 individuals who were randomized.
¶Patients who were not enrolled in the study (not randomized) were included in the control group.
**Hospitalization for CHF included hospitalization for unstable angina.
††Loss to follow-up was not specifically mentioned in the study.
** Intent to treat was not specifically mentioned in this study; however, all randomized participants were analyzed.
groups for each study. Data input was double-checked for accuracy. The total sample size for each study represents the number of patients who completed the entire follow-up for that study. In the case of multiple follow-up points, the numbers were calculated from those who finished the entire length of the study. The period of event-free intervals (expressed as hazard ratios in some of the studies) was not considered in the calculations. The number of events over the course of the study was simply entered into a standard 2×2 table for each study.

To assess for possible publication bias, a funnel plot was prepared as initially described by Light and Pillemer in 1984. Funnel plots are based on the assumption that the results of different studies on a specific treatment will be distributed equally above and below the “true” effect size. Larger studies are given more emphasis than smaller studies, and an asymmetrical funnel plot indicates that the results of some studies may be missing. The funnel plot was constructed by plotting the size of the effect found in the published studies on the horizontal axis and the precision of these effect sizes on the vertical axis. Because this analysis involved studies that reported results on a ratio scale, the measure of effect was transformed by taking the log of the effect. This transformation ensures that negative and positive effects are equally spaced.16

A test for heterogeneity was performed on all of the identified studies using an inverse variance method. The studies were not significantly heterogeneous (cardiovascular events as outcome, χ² = 12.31 [P = .14]; death as outcome, χ² = 4.33 [P = .038]); consequently, the pooled analysis was performed using fixed effects. Study weights were calculated by the Review Manager software, taking into account both total sample size and number of events in each study. The confidence intervals and P values for statistical significance are reported using a 2-tailed method. P ≤ .05 was considered statistically significant.

### RESULTS

In an analysis of the overall data, a funnel plot was constructed with death as the outcome (Figure 1). The funnel plot appears symmetrical, and hence there does not appear to be unpublished data that would significantly affect the results.

Demographic data were compiled from all of the patients enrolled in the 9 published studies (Table 3). The combined demographics illustrate that there is an over-representation of men in the 6 studies. Information was not available from all of the studies to display a racial breakdown of the participants.

### COMMENT

A fixed-effects method was used to calculate the combined outcomes of antibiotics on coronary events from all of the published studies (Figure 2). As expected by sample size, the Weekly Intervention With Zithromax for Atherosclerosis and Its Related Disorders (WIZARD) trial provides the majority of weight for the pooled coronary events analysis. Although they have significantly different sample sizes, the Antibiotic Therapy After an Acute Myocardial Infarction (ANTIBIO) and the Azithromycin in Acute Coronary Syndrome (AZACS) trials both account for approximately 14% of the pooled result because they had very similar numbers of events (130 and 112, respectively). The confidence interval for the combined effect crosses 1.0 and indicates that there is no evidence for a reduction in recurrent cardiac events in individuals with known IHD who were treated with antibiotics. A fixed-effects method was also used to calculate a pooled risk of death from the published studies. The WIZARD trial accounts for more than 72% of the pooled result with death as the outcome. CI indicates confidence interval; RR, relative risk.

![Funnel plot of published studies with death as the outcome. RR indicates relative risk.](image1)

![Table 3. Characteristics of All Patients in Published Trials](image2)
tion in recurrent cardiac events or mortality over 3 months to 3 years. The previous studies that reported a significant reduction in cardiac events likely had methodological flaws and type I error owing to small sample sizes. In addition, some of the reported benefit may have been due to the analyses of multiple heterogeneous end points. Four of the studies examined in this analysis reported significant results in their conclusions. When these studies were analyzed using the end point definitions from this meta-analysis, only the Clarithromycin in Acute Coronary Syndrome Patients (CROAATS (Effects of Azithromycin in other segments of vascular disease. Some research is currently ongoing to test the role of antibiotics in secondary prevention of IHD

However, this does not mean that infections do not play a role in the progression of coronary atherosclerosis. Moreover, it should not be concluded that antimicrobial agents will never have a role in the prevention of IHD. Perhaps different types or timing of antimicrobial agents will eventually prove beneficial. Chlamydia pneumoniae is capable of producing a dormant infection that may be difficult to eradicate. This study could not assess whether macrolide antibiotics penetrate atherosclerotic lesions in adequate concentrations to be effective. In addition, this study says nothing about the use of antibiotics for the primary prevention of IHD. It is possible that treatment with antibiotics earlier in life may be effective in the prevention of coronary atherosclerosis. Furthermore, it is also possible that significant subsets of patients in these studies had a benefit from the antibiotics that they were given. Data obtained from the WIZARD study indicated that patients with diabetes may benefit more from antibiotics than those without diabetes. There are also other pathogens such as herpes simplex virus and cytomegalovirus that have been implicated in the development of IHD, which would not have been effectively treated by the drugs used in these trials.

There are several limitations to this meta-analysis. One criticism of all meta-analyses is that studies that are included in the analysis tend to show positive results owing to what has been termed publication bias. Easterbrook et al reviewed the publication status of 285 medical studies and found that more than 60% of the studies with significant results were published, whereas less than 35% of the studies without significant findings were published. To limit this bias, we attempted to contact the authors and/or supporters of studies that have been presented at scientific meetings but have not yet been published. In addition, an attempt was made to contact the primary authors of all 9 published trials in the meta-analysis to determine if they knew of any other unpublished data in this area. No new trials were revealed. It is unlikely that data exist that would significantly affect the results, especially since the funnel plot does not suggest the presence of unpublished contradictory data. Second, there is the potential for selection bias, because the studies were diverse in the types of patients enrolled and types of antibiotics used. There were more men in these studies than women, and the CLARIFY study included only white patients. Third, the outcomes analyzed in this analysis were over a relatively short time frame. The possibility exists that these patients would have seen a benefit if they were followed for a longer period.

Further research is ongoing. The MARBLE (Might Azithromycin Reduce Bypass List Events?), ACES (Azithromycin and Coronary Events Study), CLARICOR (Intervention With Clarithromycin in Patients With Stable Coronary Heart Disease), PROVE-IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy), and CROAATS (Effects of Azithromycin in Chlamydia pneumoniae–Positive Postmyocardial Infarction Patients) studies are all scheduled to be published in the next 2 years and will further evaluate antibiotics for IHD. Additional research is currently ongoing to test the role of antibiotics in other specific segments of vascular disease. Some data suggest that antibiotics may help slow the expansion of abdominal aortic aneurysms and slow the progression of peripheral arterial occlusive disease and carotid atherosclerosis.

In summary, this meta-analysis did not find a reduction in recurrent cardiac events or mortality in patients with known IHD. The use of macrolide antibiotics for C pneumoniae in the prevention of IHD is not supported by this meta-analysis.

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REFERENCES


<table>
<thead>
<tr>
<th>Source</th>
<th>RR (Fixed) (95% CI)</th>
<th>Weight, %</th>
<th>RR (Fixed) (95% CI)</th>
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<tr>
<td>CLARIFY</td>
<td>0.19 (0.49-164.25)</td>
<td>9.00</td>
<td>0.94 (0.79-1.12)</td>
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<td>Leowattana et al</td>
<td>0.39 (0.66-14.75)</td>
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<td>0.95 (0.66-14.75)</td>
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<td>Gupta et al</td>
<td>0.51 (0.03-7.59)</td>
<td>0.50</td>
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<td>1.27 (0.35-6.43)</td>
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<td>0.43 (0.09-2.15)</td>
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<td>0.96 (0.29-3.24)</td>
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<td>ANTIBIOTIC</td>
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<tr>
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<td>11.11 (0.47-1.37)</td>
<td>0.80</td>
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<tr>
<td>WIZARD</td>
<td>72.49 (0.76-1.14)</td>
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<td>0.93 (0.76-1.14)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>100.00</td>
<td>0.94</td>
<td>0.94 (0.79-1.12)</td>
</tr>
</tbody>
</table>

Figure 3. Pooled effect of antibiotics on death in published studies. CI indicates confidence interval; RR, relative risk.


