Antibiotics for the secondary prevention of ischemic heart disease: a meta-analysis of randomized controlled trials

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CRD summary
This review examined the effect of antibiotics on Chlamydia pneumoniae (C. pneumoniae) for the secondary prevention of ischaemic heart disease (IHD). The authors concluded that macrolide antibiotics for C. pneumoniae do not significantly reduce recurrent cardiac events or mortality in people with known IHD. Overall, this was generally a well-conducted review and the authors' conclusions are likely to be reliable.

Authors' objectives
To determine the effect of antibiotics on Chlamydia pneumoniae (C. pneumoniae) for the secondary prevention of ischaemic heart disease (IHD).

Searching
MEDLINE was searched from 1966 to 2003 for studies written in English; the search terms were reported. In addition, the reference lists of several review articles were checked for relevant studies. An attempt was made to contact authors and/or supporters of studies that had been presented at scientific meetings and had not yet been published, and to contact authors of the included studies to ask if they knew of any relevant unpublished data.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were included in the review.

Specific interventions included in the review
All trials using antibiotics effective against C. pneumoniae for the secondary prevention of IHD were eligible for inclusion. The antibiotics azithromycin, roxithromycin, metronidazole, omeprazole and clarithromycin, in varying doses, were included in the review. Studies were not excluded based on the presence or absence of C. pneumoniae testing.

Participants included in the review
Studies of patients with known IHD were eligible for inclusion. The included trials were of patients with known IHD and seropositivity to C. pneumoniae, unstable angina or acute myocardial infarction (MI) (non-Q wave), acute MI, acute coronary syndrome (ACS), or a history of MI and seropositivity to C. pneumoniae; patients admitted for acute MI or ACS; and male survivors of acute MI with seropositivity to C. pneumoniae. There appeared to have been an over-representation of men in the included studies (80.1%).

Outcomes assessed in the review
Studies that analysed IHD outcomes were eligible for inclusion. Clinical coronary events and death were included. Coronary events included acute MI, unstable angina, or sudden death.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Validity was assessed on the basis of the following criteria: randomisation, blinding, intention-to-treat, loss to follow-up, outcome measures and use of placebo. Three independent reviewers assessed quality using a structured spreadsheet. Any disagreements were resolved through discussion.
Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. The total number of participants and total number of events were extracted for each treatment arm of each study. The total sample size was considered to be the number of patients who completed follow-up. Where studies had multiple follow-up points, numbers were calculated from the number of patients who finished the entire length of the study. The data entered into a statistical computer package were double-checked for accuracy.

Methods of synthesis
How were the studies combined?
All studies were pooled using a fixed-effect model and confidence intervals (CIs) were calculated. A similar analysis was carried out using only the end point of death. The studies were weighted, taking into account sample size and number of events in each study. Publication bias was visually assessed using a funnel plot.

How were differences between studies investigated?
Statistical heterogeneity was assessed for all the studies using an inverse variance method.

Results of the review
Nine double-blind RCTs (n=11,015) were included in the review.

Patients receiving antibiotics showed no statistically significant reduction in cardiac events or mortality relative to those on placebo; the relative risks were 0.94 (95% CI: 0.86, 1.03) and 0.94 (95% CI: 0.79, 1.12) for cardiac events and mortality, respectively. No publication bias was detected for the outcome death. The studies were not statistically significantly heterogeneous for either outcome.

Authors' conclusions
Macrolide antibiotics for C. pneumoniae did not produce a statistically significant reduction in recurrent cardiac events or mortality over 3 months to 3 years in people with known IHD.

CRD commentary
The authors set out a clear objective and the inclusion criteria were clearly defined. Only one database was searched and only studies written in English were included. This increases the risk of language bias, and relevant studies might have been missed. However, an attempt was made to obtain unpublished data and publication bias was assessed. It was unclear how many reviewers selected the studies or how the data were extracted. Quality was assessed on appropriate criteria by three independent reviewers, which helps to reduce the risk of bias. Adequate details of each of the included studies were provided. Despite some differences in the interventions and study populations, no statistical heterogeneity between the studies was detected, and the statistical pooling of the studies seemed appropriate. Overall, this was generally a well-conducted review and the authors' conclusions are likely to be reliable.

Implications of the review for practice and research
Practice: The authors stated that the findings of this meta-analysis do not support the use of antibiotics in the secondary prevention of IHD.

Research: The authors stated that ongoing research will evaluate further the use of antibiotics for IHD and other specific areas of vascular disease.

Funding
Health Resources and Services Administration, grant number 1 D14HP 00161-02.
Bibliographic details

PubMedID
15505130

DOI
10.1001/archinte.164.19.2156

Original Paper URL
http://archinte.ama-assn.org

Indexing Status
Subject indexing assigned by NLM

MeSH
Anti-Bacterial Agents /therapeutic use; Chlamydophila Infections /complications /drug therapy; Chlamydophila pneumoniae; Humans; Macrolides /therapeutic use; Myocardial Ischemia /etiology /prevention & control; Randomized Controlled Trials as Topic; Treatment Outcome

AccessionNumber
12004008762

Date bibliographic record published
30/06/2006

Date abstract record published
30/06/2006

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.