Azithromycin for the secondary prevention of coronary artery disease: a meta-analysis
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CRD summary
The authors’ cautious conclusion that azithromycin does not appear to reduce the frequency or occurrence of cardiac events in patients with coronary artery disease appears to reflect the results reported. However, it is possible that relevant studies might have been missed.

Authors’ objectives
To evaluate the effect of the macrolide antimicrobial azithromycin on clinical outcomes in patients with coronary artery disease (CAD).

Searching
MEDLINE (1966 to September 2006), EMBASE (1990 to September 2006), Web of Science (1994 to September 2006) and the Cochrane Database of Systematic Reviews (Issue 3, 2006) were searched; the search terms were reported. The references of all retrieved articles were also checked. Only articles published in the English language were included.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion. All of the included studies were double-blind. In the included studies, the duration of follow-up ranged from 6 months to 3.9 years.

Specific interventions included in the review
Studies that compared azithromycin with placebo were eligible for inclusion. Treatment regimens varied between studies (doses and concurrent medications were reported). The duration of treatment ranged from 3 days to 1 year.

Participants included in the review
Studies conducted in secondary CAD patients were eligible for inclusion. The participants in half of the included studies were post-acute myocardial infarction (MI) and were either seropositive for Chlamydia pneumoniae (C. pneumoniae) or had unstable angina; the participants in the other studies had unstable angina and documented CAD (with or without seropositivity for C. pneumoniae).

Outcomes assessed in the review
Studies that reported clinical cardiac end points including mortality were eligible for inclusion. The included studies reported mortality rates, nonfatal MI, rate of hospitalisation and a composite cardiovascular end point.

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

Assessment of study quality
Two reviewers assessed the methodological quality of the included studies using the Jadad scale. Any disagreements were resolved by a third party. Studies were assessed for reported randomisation, random allocation concealment, masking of treatment allocation, blinding and withdrawals.

Data extraction
Two reviewers independently extracted the data from the included studies using a standardised data abstraction tool. Any disagreements were resolved by a third reviewer.

Methods of synthesis
How were the studies combined?
The studies were combined in a meta-analysis using a random-effects model. Summary estimates were reported as odds
ratios (ORs) with their corresponding 95% confidence intervals (CIs). Publication bias was assessed through visual inspection of a L'Abbe plot and using Egger's statistic.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the I-squared test. Sensitivity analyses were performed by removing trials with a treatment course of less than 7 days and studies that did not include participants seropositive for C. pneumoniae.

**Results of the review**
Six RCTs (n=13,778) were included in the review.

No statistically significant between-group differences were found for mortality (OR 0.91, 95% CI: 0.77, 1.09; 6 RCTs, n=13,778), nonfatal MI (OR 0.95, 95% CI: 0.80, 1.13; 4 RCTs, n=13,500), hospitalisation (OR 0.97, 95% CI: 0.80, 1.17; 5 RCTs, n=13,718), or a composite of cardiovascular events (OR 0.93, 95% CI: 0.84, 1.03). No evidence of statistical heterogeneity was found. The removal of trials with a treatment course of less than 7 days or trials that did not include participants seropositive for C. pneumoniae did not significantly change the results.

Plots and statistical tests showed a low probability of publication bias.

**Authors' conclusions**
Azithromycin does not appear to reduce the frequency or occurrence of cardiac events in patients with CAD.

**CRD commentary**
The review question was supported by clear inclusion criteria. Several relevant sources were searched for English language publications, which may mean that relevant studies were not included; the authors acknowledged this possibility. Publication bias was assessed, but the small number of studies limited its assessment. Methodology undertaken to assess validity and extract the data was likely to have minimised reviewer error or bias, but it is not known whether similar procedures were undertaken to select the primary studies. Although individual results of the validity assessment were not reported, each study was described as being randomised, double-blind and placebo-controlled. The analysis was appropriate, and the authors assessed statistical heterogeneity and performed sensitivity analyses. The authors’ cautious conclusion appears to reflect the results reported.

**Implications of the review for practice and research**
Practice: The authors stated that the management of patients with CAD should include established interventions.

Research: The authors stated that results from ongoing trials may clarify the role of azithromycin in the secondary prevention of coronary events.

**Funding**
Not stated.

**Bibliographic details**

**PubMedID**
17420199

**DOI**
10.2146/ajhp060539

**Indexing Status**
Subject indexing assigned by NLM
MeSH
Anti-Bacterial Agents /therapeutic use; Azithromycin /therapeutic use; Chlamydia Infections /drug therapy; Chlamydia pneumoniae /drug effects; Coronary Artery Disease /prevention & control; Hospitalization; Humans; Models, Statistical; Myocardial Infarction /drug therapy; Randomized Controlled Trials as Topic

AccessionNumber
12007005717

Date bibliographic record published
10/03/2008

Date abstract record published
03/11/2008

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.