

Title: Protocol of the systematic review on the cardiovascular risk associated with macrolides

Registration: This protocol has not been registered.

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Introduction

Rationale

In the past decades, it was postulated that antibiotics can be used for the treatment of *Chlamydia pneumoniae* to prevent further cardiovascular events as *C. pneumoniae* was found to be associated with atherosclerosis and coronary heart disease.^{1,2} Several clinical trials were conducted to investigate the association using macrolides as exposure, while most of them were in small sample size.³⁻⁹ Conflicting results were found and there were only limited evidence of the beneficial effect. A meta-analysis including randomised controlled trials only found no evidence that antibiotics could prevent further myocardial infarction events.¹⁰ Surprisingly, one of the macrolides, clarithromycin, was even shown to have higher risk of cardiovascular events versus placebo in a randomised controlled trial (Effect of Clarithromycin on Mortality and Morbidity in Patients with Ischemic Heart Disease trial [CLARICOR trial]).¹¹ Recent observational studies also found an elevated risk of cardiovascular events associated with clarithromycin^{12,13} but the duration of the effects remain unclear. The clinical implications of the risk factors for cardiovascular events associated with clarithromycin have not yet been reported. Current literature suggests statin may have a potential protective effect of cardiovascular mortality associated with clarithromycin¹⁴ as a higher but not statistically significant cardiovascular risk was found among clarithromycin users receiving statins^{12,14}. However, the evidence is limited and has not been summarised and analysed.

Objectives

This review will aim to focus on the evidence of studies on the cardiovascular effects among patients receiving macrolides in terms of duration effects and risk factors. This review will also summarise the current evidence of the suggested protective effect of statin for preventing cardiovascular outcomes associated with clarithromycin.

Methods

Eligibility criteria

We will include published observational studies (such as cohort studies, nested case-control studies, case-control studies, self-controlled case series, case-crossover studies or case-time-control studies) and randomised controlled trials that investigated the association between macrolides and cardiovascular events in adults aged ≥ 18 years old. Studies that did not investigate cardiovascular events as outcome or specify the types of cardiovascular events will be excluded. Studies examining drugs other than macrolides or using other macrolides as comparator only will be excluded. Animal studies or studies in languages other than English or Chinese will also be excluded.

Information sources

We will search electronic databases as the main information source.

Search strategy

PubMed, EMBASE Classic + EMBASE 1947- via Ovid and the Cochrane library will be searched using keywords and/or medical subject headings such as ('sudden death' or 'cardiovascular diseases' or 'cardiac death' or 'cardiac mortality' or 'heart diseases' or 'heart infarct*' or 'myocardial infarct*' or 'coronary disease' or 'coronary artery disease' or 'heart attack' or 'out-of-hospital cardiac arrest' or 'myocardial ischemia' or 'angina' or 'angina pectoris' or 'arrhythmia' or 'ventricular fibrillation' or 'brain ischemia' or 'stroke') AND ('clarithromycin or azithromycin or erythromycin or roxithromycin'). Potential studies will be retrieved after the screening of title and abstract. A reference list of the retrieved studies will also be reviewed for further identification of potential eligible studies.

Study records

After searching the electronic databases, Endnote X7 will be used to store all the citations of identified articles. Data for outcomes will be extracted independently by two reviewers. Data extraction form will be compiled to record PICO items such as (but not limiting to) the number of study subjects, study place, duration of treatment, follow-up time, outcomes of interest and risk factors of cardiovascular risks associated with macrolides. Review manager 5.3 will be used for data analysis.

Outcomes and prioritization

For clinical relevance, the risk of cardiac/cardiovascular mortality will be selected as primary outcome. Other cardiovascular outcomes such as myocardial infarction, arrhythmia, heart failure and stroke will be selected as secondary outcomes. The risk of cardiovascular mortality among concomitant use of statin and macrolide users and risk factors of cardiovascular risk will be the tertiary outcome.

Risk of bias in individual studies

The included observational studies will be assessed for methodological quality using the Newcastle-Ottawa scale. The risk of bias of the identified randomised controlled trials will be assessed using the Cochrane Collaboration's tool.

Data synthesis

Measures of effect including relative risk, hazard ratios, odds ratio and 95% confidence interval will be retrieved and pooled using the generic inverse variance method. Where the actual measure of effect is not available, it will be calculated by inputting data into a 2x2 contingency table using Review Manager 5.3. Studies with similar follow up time will be analysed using a random-effect model. We will assess the heterogeneity using the I² statistic. Sensitivity analyses will be performed by removing studies that resulted in high heterogeneity or other possible reasons. Subgroup analyses will be performed among users who had concomitant use of statins with clarithromycin and dose response relationship will also be examined if data is available in the current literature.

Meta-bias(es)

As a rule of thumb, the publication bias will be assessed using the funnel plot when there are at least 10 studies included for each outcome in the meta-analysis.

Confidence in cumulative evidence

We will assess the body of evidence according to Grading of Recommendations Assessment, Development, and Evaluation (GRADE) guidelines.¹⁵⁻¹⁸

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