Antibiotics for secondary prevention of coronary heart disease (Protocol)

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Antibiotics for secondary prevention of coronary heart disease

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the beneficial and harmful effects of antibiotics for the secondary prevention of coronary heart disease.

As a secondary objective, we plan to assess the effects of individual types of antibiotics for the secondary prevention of coronary heart disease.

BACKGROUND

Description of the condition

Coronary heart disease is the collective term for a group of diseases consisting of stable angina, unstable angina, myocardial infarction, and sudden cardiac death (Wong 2014). Coronary heart disease is estimated to be the leading cause of death worldwide (WHO 2011; WHO 2016), and 15.5 million people in the USA alone suffer from coronary heart disease (Mozaffarian 2016). The World Health Organization (WHO) has estimated that 7.4 million people die each year globally because of coronary heart disease with over three quarters of the deaths occurring in low- and middle-income countries (WHO 2011; WHO 2016). Coronary heart disease also has a significant impact on healthcare costs and accounts for approximately EUR 196 billion in Europe and USD 207.3 billion in the USA (Ferreira-Gonzalez 2014; Mozaffarian 2016).

The pathogenesis of coronary heart disease is related to the narrowing or blockage of the coronary arteries supplying the heart with blood. This process is usually caused by build-up of fatty material and plaque in the walls of the coronary arteries leading to atherosclerosis (Ross 1999; Libby 2010; Libby 2011; Ambrose 2015). Atherosclerosis is a chronic immune-mediated inflammatory disease that usually develops over years, ultimately limiting perfusion to the heart, which may cause shortages of oxygen and glucose, leading to symptoms such as chest pain (angina) and shortness of breath (Ross 1999; Ambrose 2015).

People with established coronary heart disease have a high risk of
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subsequent cardiovascular events including cardiovascular death, myocardial infarction, and stroke (Smith 2011; WHO 2011; Eckel 2014; Piepoli 2016). Therapeutic lifestyle changes (e.g. increased physical activity; weight reduction; dietary modification; smoking cessation; and alcohol intake reduction) and adjunctive drug therapies (e.g. antithrombotic treatment; managing hypertension; diabetes; dyslipidaemia; and chronic kidney disease) are necessary to improve survival and quality of life, and reduce recurrent events and the need for revascularisation procedures (Smith 2011; WHO 2011; Eckel 2014; Piepoli 2016). Nonetheless, even complete adherence to the before-mentioned therapies is reported to not completely eliminate the person’s risk of subsequent cardiovascular events (Bertrand 2016). This residual risk may result, in part, from the failure of current therapies to efficiently address inflammation (Bertrand 2016).

Studies have shown that inflammation seems to be a predictor for the development and progression of atherosclerosis (Libby 2002; Kaptoge 2010; Lawson 2016) and the inflammatory process may be induced by stimuli from infectious agents (Mandell 1996; Rosenfeld 2011; Lawson 2016). The infectious agents might induce the inflammatory process by infecting vascular cells within the atheromatous plaque and consequently activating an innate immune response (Rosenfeld 2011). The activated innate immune response then contributes to the inflammation within the plaque (Rosenfeld 2011). Moreover, infectious agents may induce inflammation at non-vascular places, which might lead to increased secretion of cytokines and other acute-phase proteins. The cytokines and other acute-phase proteins then add to the inflammation within the plaque (Rosenfeld 2011). Hence, an association between coronary heart disease and various infectious agents has been suggested and a number of studies have investigated the validity of this possible association.

Chlamydia pneumoniae has been identified in atheromatous plaques (Shor 1992; Kuo 1993; Muhlestein 1996; Assar 2015; Pigarevskii 2015). Moreover, seroepidemiological studies (Saikkku 1988; Thom 1991; Linnanmaki 1993; Kazar 2005; Romano Carratelli 2006; Sakurai-Komada 2014) and a meta-analysis of seroepidemiological studies (Danesh 1997) have all shown increased levels of C pneumoniae antibodies in people with coronary heart disease. In vivo studies and a meta-analysis of observational studies have shown that C pneumoniae may contribute to atherosclerosis (Burnett 2001; Ezzahiri 2002; Ezzahiri 2003; Fildro 2015). Contrary to these findings, prospective seroepidemiological studies (Ridker 1999; Danesh 2000a; Danesh 2000b; Danesh 2002), retrospective seroepidemiological studies (Prasad 2002; Al-Younes 2016), and meta-analyses of seroepidemiological studies (Danesh 2000a; Danesh 2000b; Danesh 2002; Bloemenkamp 2003) did not show any association between C pneumoniae antibodies and coronary heart disease.

Porphyromonas gingivalis has also been identified in atheromatous plaques (Pucar 2007; Zaremba 2007; Gaetri-Jardim 2009; Mahendra 2009). Moreover, studies have shown increased levels of antibodies or higher amount of oral bacterial burden of P gingivalis in people with coronary heart disease (Pussinen 2004; Renvert 2006; Gotsman 2007; Mahendra 2015). In vivo studies have shown that P gingivalis may contribute to atherosclerosis (Broda 2005; Maekawa 2011). Contrary to these findings, retrospective studies (Spahir 2006; Pesonen 2009; Andrianakia 2011) and a prospective study (De Boer 2014) did not show any association between P gingivalis and coronary heart disease.

Helicobacter pylori is another infectious agent that might induce an inflammatory process and lead to coronary heart disease. The association between coronary heart disease and H pylori has been assessed in seroepidemiological studies (Mendall 1994; Lenzi 2006; Vcev 2007; Shamley 2014; Matsik 2016), a meta-analysis of seroepidemiological studies (Danesh 1997), and meta-analyses of prospective studies (Sun 2016; Jiang 2017). These studies have shown that infection with H pylori increases the risk of coronary heart disease. Contrary to these findings, prospective studies (Whincup 1996; Folsom 1998; Roisviren 2000; Zhu 2001; Zhu 2002; Jin 2007) and a meta-analysis of seroepidemiological studies (Danesh 1998) did not show any association between H pylori and coronary heart disease. A possible association between Escherichia coli and cardiovascular disease has been assessed. However, a cohort study has shown that infection with E coli did not increase the risk of cardiovascular disease in the decade following infection (Hizo-Abes 2013). Further, a seroepidemiological study did not show any association between E coli and coronary heart disease (Mahdi 2002).

Description of the intervention

Antibiotics are antimicrobial drugs of chemical origin that treat and prevent bacterial infections by either killing or inhibiting the growth of the bacteria (Waksman 1947). Antibiotics can be classified based on their mechanism of action (bactericidal or bacteriostatic), bacterial spectrum (broad or narrow) and chemical structure (e.g. penicillins, macrolides, quinolones, or tetracyclines) (Burkey 2005). The optimal dose and duration of antibiotic therapy depends on various factors (e.g. the patient’s immune status, the infecting agent, and the focus of infection) (Polk 1999).

Macrolides, such as azithromycin, clarithromycin, and erythromycin, have been the primary antibiotic class used to investigate the effects of antibiotics as secondary prevention in people with coronary heart disease, presumably because C pneumoniae and H pylori are known to be sensitive to macrolides (Chirgwin 1989; Mallertheiner 2007). Macrolides’ mechanism of action is to inhibit the protein synthesis through binding to the 50S subunit of the ribosome (Gaynor 2003). However, the use of macrolides has been reported in both observational studies and in a randomised clinical trial to increase the risk of cardiovascular morbidity and mortality (see Why it is important to do this review). The increased risk of cardiovascular morbidity and mortality might be associated with macrolides’ pro-arrhythmic effects (i.e. QT pro-
longation) leading to torsades de pointes (Bril 2010). Further, the use of macrolides might lead to an inflammatory cascade resulting in more vulnerable plaques that over time increases the risk of plaque rupture and, hence, leads to increased risk of cardiovascular events and mortality (Winkel 2011).

**How the intervention might work**
Antibiotics might prevent the development of coronary heart disease through antibacterial activity. In addition, animal studies and in-vitro studies suggest that several classes of antibiotics (e.g. macrolides, tetracyclines, or quinolones) seem to exert anti-inflammatory and anti-oxidative effects, which might slow down the atherogenesis independently of any antibacterial effect (Anderson 1996; Rajagopalan 1996; Dalhoff 2003; Sapadin 2006; Steel 2012). The anti-inflammatory and anti-oxidative effects might stabilise the atherosclerotic plaques.

**Why it is important to do this review**
Coronary heart disease is the leading cause of death worldwide as it leads to 7.4 million deaths each year (WHO 2011; WHO 2016). People with established coronary heart disease have a high risk of subsequent cardiovascular events including cardiovascular death, myocardial infarction, and stroke (Smith 2011; WHO 2011; Eckel 2014; Piepoli 2016). Prevention and management of the common risk factors for coronary heart disease is necessary to improve survival and quality of life, and reduce recurrent events and the need for revascularisation procedures (Smith 2011; WHO 2011; Eckel 2014; Piepoli 2016). Nonetheless, even complete adherence to the before-mentioned therapies may not completely eliminate the person’s risk of subsequent cardiovascular events (Bertrand 2016). The use of antibiotics might play a possible part in the preventive efforts of people with coronary heart disease, and might improve survival and quality of life, and reduce recurrent events and the need for revascularisation procedures.

The use of antibiotics for secondary prevention of coronary heart disease is not mentioned in any guidelines, indicating that it is not conventional therapy (Fihn 2012; Montalescot 2013). However, a very large number of people with coronary heart disease receive antibiotics each year to treat proven or suspected bacterial infections. In the first instance, the antibiotics may help them. In the second instance, any adverse event may be as likely as any benefit. In both instances, we need to know the impact of antibiotic intervention on long-term health.

The first trials that investigated the use of antibiotics for secondary prevention of coronary heart disease were published in the late 1990s. The trials compared macrolide versus placebo in people with coronary heart disease. The trials showed conflicting results and made clear the need for larger trials (Gupta 1997; Anderson 1999; Torgano 1999; Gurfinkel 1999).

Several meta-analyses of randomised trials have assessed the effects of antibiotics for secondary prevention of coronary heart disease (Etminan 2004; Andraws 2005; Baker 2007; Gluud 2008). Etminan 2004 included nine trials with 12,032 participants; Andraws 2005 included 11 trials with 19,217 participants; and Baker 2007 included six trials with 13,778 participants. All of these reviews compared antibiotics versus placebo. None of the reviews showed any benefits or harms of antibiotic therapy for secondary prevention of coronary heart disease. Gluud 2008 included 17 trials with 25,271 participants comparing antibiotics versus placebo, and found a significantly increased risk of all-cause mortality of 10% in the antibiotic group. Moreover, Gluud 2008 did a meta-analysis of the three trials that reported more than two years’ follow-up (i.e. PROVE-IT (Cannon 2005), ACES (Grayston 2005), and CLARICOR (Gluud 2008)) and showed a significantly increased risk of all-cause mortality of 17% in the antibiotic group. Cheng 2015 recently included 33 studies of various designs with 20,779,963 participants in a review comparing macrolides with or to placebo or no intervention. The review included any type of participant and did not focus on a specific infectious agent or disease. The authors of the review found no significant effect of macrolides on all-cause mortality. However, the participants treated with macrolide had a significantly (152%) higher risk of sudden death from cardiac problems and 31% had a higher risk of dying from cardiovascular problems.

Currently, no guidelines report whether antibiotics should be used or avoided as secondary prevention of coronary heart disease (Fihn 2012; Montalescot 2013). This might be because the use of antibiotic therapy for secondary prevention of coronary heart disease lost momentum a decade ago, possibly as a consequence of the majority of previous evidence showing no effects - either beneficial or harmful. Nevertheless, the public-health aspect of administration of antibiotics to people with coronary heart disease is not to be neglected. Further, our preliminary literature search has identified several new trials that were not included in the former attempts to systematically review the literature, and more trials may be identified during the literature search. Accordingly, the benefits and harms of antibiotics in people with coronary heart disease seem unclear based on current evidence. Furthermore, antibiotics, including macrole, are commonly used interventions in people with coronary heart disease and any beneficial or harmful effects of administering antibiotics in this group of people is of urgent importance. The CLARICOR trial, as mentioned previously, showed that clarithromycin versus placebo for secondary prevention of coronary heart disease significantly increased the risk of death (Jespersen 2006; Gluud 2008; Winkel 2015). We, therefore, find it very important to investigate whether antibiotics have a beneficial, neutral, or harmful effect for secondary prevention of coronary heart disease.

No former relevant review has taken into account both risks of random errors and risk of systematic errors (Cochrane methodology, Trial Sequential Analysis (TSA), and GRADE assessment)
Therefore, it is still unclear whether antibiotics have a beneficial, neutral, or harmful effect for secondary prevention of coronary heart disease.

**OBJECTIVES**

To assess the beneficial and harmful effects of antibiotics for the secondary prevention of coronary heart disease.

As a secondary objective, we plan to assess the effects of individual types of antibiotics for the secondary prevention of coronary heart disease.

**METHODS**

Criteria for considering studies for this review

**Types of studies**

Randomised clinical trials irrespective of trial design, setting, blinding, publication status, publication year, and language. We will not include quasi-randomised trials and observational studies for the assessment of harms. By focusing on randomised clinical trials, we are aware that the present review will be biased towards focusing on more benefits and less on harms.

**Types of participants**

Participants with any diagnosis of coronary heart disease, that is, acute myocardial infarction, previous myocardial infarction, stable angina, or unstable angina. We will accept the definitions used by the individual trialists. We will include participants irrespective of age, sex, and antibody status (e.g. for *C. pneumoniae, H. pylori, P. gingivalis*, or *E. coli*). We will exclude participants with any other cause of chronic inflammatory disease (e.g. lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, polymyositis/dermatomyositis, and inflammatory bowel disease). We will only include trials that include a subset of eligible participants if separate data for the eligible participants are available or if the majority of participants (i.e. more than 80%) are eligible. We will document difficult decisions in the review, and sensitivity analyses will assess the impact of these decisions on the review’s findings.

**Types of outcomes**

For all outcomes we will use the trial results at maximal follow-up. However, if the trialists report results at multiple time points, we will also assess the results reported at the time point closest to 24 months (plus and minus six months). We chose 24 months’ follow-up based on the Kaplan-Meier made by Winkel 2015. We believe that 24 months’ follow-up is long enough to show any possible secondary prevention effects of antibiotics. Furthermore, 24 months’ follow-up is not so long that other factors, unrelated to the given trial but affecting the outcomes, might decrease the statistical power, that is, that the results are ‘diluted’ by events unrelated to the trial.

**Primary outcomes**

- All-cause mortality
- Serious adverse event. We will define a serious adverse event as any untoward medical occurrence that resulted in death; was life-threatening; required hospitalisation or prolongation of existing hospitalisation; resulted in persistent or significant disability; or jeopardised the patient (ICH-GCP 1997).
Quality of life measured on any valid scale

Secondary outcomes
Definitions for secondary outcomes will be according to the individual trialists.
- Cardiovascular mortality
- Myocardial infarction
- Stroke
- Sudden cardiac death

We will include randomised clinical trials irrespective of whether they report the above outcomes.

Search methods for identification of studies

Electronic searches
We will search the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, LILACS, Science Citation Index Expanded on Web of Science and BIOSIS in order to identify relevant trials. The preliminary search strategy for MEDLINE (Ovid) is given in Appendix 1 and will be adapted for use in the other databases. We will apply the Cochrane sensitivity-maximising randomised clinical trial filter (Lefebvre 2011) to MEDLINE (Ovid) and adaptations of it to the other databases, except CENTRAL.
We will search all databases from their inception to the present and we will impose no restriction on language of publication or publication status. We will assess non-English language papers by asking individuals that fluently speak the language for help. We will not perform a separate search for adverse effects of antibiotics used for the treatment of coronary heart disease. We will only consider adverse effects described in the included trials.

Searching other resources
The reference lists of included randomised clinical trials, previous systematic reviews, and other kinds of reviews will be checked for any unidentified randomised clinical trials. We will contact authors of included randomised clinical trials for further information and we will contact the following major pharmaceutical companies by email asking them for any unpublished randomised clinical trials:
- Merck & Co.;
- Roche Holding AG;
- Pfizer Inc.;
- Novartis AG;
- GlaxoSmithKline Plc;
- AstraZeneca Plc;
- Bristol-Myers Squibb Co.;
- Sanofi-Aventis;
- Abbott Laboratories;
- Taisho Pharmaceutical; and
- Pliva.

Furthermore, we will search for ongoing and unidentified randomised clinical trials on:
- Google Scholar;
- The Turning Research into Practice (TRIP) Database;
- ClinicalTrials.gov;
- EU Clinical Trial Register;
- Chinese Clinical Trial Registry (ChCTR);
- International Standard Randomised Controlled Trial Number (ISRCTN) registry;
- GSK Clinical Study Register;
- Pan African Clinical Trials Registry (PACTR);
- Australian New Zealand Clinical Trials Registry (ANZCTR);
- Clinical Trials Registry - India (CTRI); and
- the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal.
We will also examine relevant retraction statements and errata for included trials.

Data collection and analysis
We will follow Cochrane recommendations to perform the review (Higgins 2011a) and we will use Review Manager 5 (RevMan 5) to perform the analyses (RevMan 2014) and TSA (TSA 2011).

Selection of studies
Two authors (NJS, SS) will independently screen titles and abstracts. We will retrieve all relevant full-text study reports/publications and two review authors (NJS, SS) will independently screen the full text and identify and record reasons for exclusion of the ineligible studies. We will resolve disagreements through discussion or, if required, by consulting with a third author (JCJ). We will display trial selection in a flow diagram as per the PRISMA statement (Moher 2009).
We will record the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table.

Data extraction and management
Three authors (NJS, SS, SKK) will extract data independently from included trials. We will resolve any disagreements by discussion with a fourth author (JCJ). We will assess duplicate publications and companion papers of a trial together in order to evaluate all available data simultaneously (maximise data extraction, correct bias assessment). We will contact the authors of the trials...
by email to specify any of the data, had they not been reported sufficiently in the publication.

**Trial characteristics**

Bias risk components (as defined below); trial design (parallel, factorial, or cross-over); number of intervention arms; length of follow-up; estimation of sample size; inclusion and exclusion criteria.

**Participant characteristics and diagnosis**

Number of randomised participants; number of analysed participants; number of participants lost to follow-up/withdrawals/cross over; age range (mean or median) and sex ratio; presence of cardiovascular risk factors (i.e. diabetes mellitus, hypertension, hyperlipidaemia, or smoking); antibody status (i.e. for *C pneumoniae, H pylori, P gingivalis*, or *E coli*).

**Intervention characteristics**

Type of antibiotic; dose of antibiotic; duration of antibiotic therapy; and mode of administration.

**Control characteristics**

Placebo or no-intervention.

**Co-intervention characteristics**

Type of co-intervention; dose of co-intervention; duration of co-intervention; and mode of administration.

**Outcomes**

We will extract all outcomes listed above from each randomised clinical trial, and we will identify whether outcomes are incomplete or selectively reported according to the criteria described in Table 1.

**Notes**

We will extract details on funding of the trial and notable conflicts of interest of trial authors, if available.

We will note in the 'Characteristics of included studies' table if outcome data were not reported in a usable way. Two review authors (NJ, SS) will independently transfer data into the RevMan 5 file (RevMan 2014). We will resolve any disagreements through discussion or, if required, by consulting a third author (JCJ).

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**Assessment of risk of bias in included studies**

We will use the instructions given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017) in our evaluation of the methodology and hence the risk of bias of the included trials. We will evaluate the methodology in respect of:

- random sequence generation;
- allocation concealment;
- blinding of participants and personnel;
- blinding of outcome assessment;
- incomplete outcome data;
- selective outcome reporting;
- other risks of bias;
- overall risk of bias.

These domains enable classification of randomised trials with low risk of bias and high risk of bias. The latter trials tend to overestimate positive intervention effects (benefits) and underestimate negative effects (harms) (Schulz 1995; Moher 1998; Kjaergard 2001; Gluud 2006; Wood 2008; Savovic 2012; Lundh 2017).

We will classify the trials according to the criteria described in Table 1. We will assess the domains 'blinding of outcome assessment', 'incomplete outcome data', and 'selective outcome reporting' for each outcome result. Thus, we will be able to assess the bias risk for each outcome assessed in addition to each trial.

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**Assessment of bias in conducting the systematic review**

We will conduct the review according to this published protocol and report any deviations from it in the 'Differences between protocol and review' section of the systematic review.

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**Measures of treatment effect**

**Dichotomous outcomes**

We will calculate risk ratios (RRs) with 95% confidence interval (CI) for dichotomous outcomes, as well as the TSA-adjusted CIs (see below).

**Continuous outcomes**

We will calculate the mean differences (MDs) and the standardised mean difference (SMD) with 95% CI for continuous outcomes, as well as the TSA-adjusted CIs (see below). We will consider using the SMD approach when all the trials assess the same outcome but measure it in a variety of ways, but only as a hypothesis-generating analysis (Deeks 2017).
Unit of analysis issues
We will only include randomised clinical trials. For trials using cross-over design, we will only include data from the first period (Elbourne 2002; Deeks 2017). There will, therefore, not be any unit of analysis issues.

Dealing with missing data
We will, as a first option, contact all trial authors to obtain missing data (i.e. for data extraction and for assessment of risk of bias, as specified above).

Dichotomous outcomes
We will not impute missing values for any outcomes in our primary analysis. In two of our sensitivity analyses (see paragraph below), we will impute data.

Continuous outcomes
We will primarily analyse scores assessed at single time points. If only change from baseline scores are reported, we will analyse the results together with follow-up scores (Higgins 2011b). If standard deviations (SDs) are not reported, we will calculate the SDs using trial data if possible. We will not use intention-to-treat data if the original report did not contain such data. We will not impute missing values for any outcomes in our primary analysis. In two of our sensitivity analyses (see paragraph below), we will impute data.

Assessment of heterogeneity
We will primarily investigate forest plots to visually assess any sign of heterogeneity. We will secondly assess the presence of statistical heterogeneity by Chi² test (threshold P < 0.10) and measure the quantities of heterogeneity by the I² statistic (Higgins 2002; Higgins 2003).
We will follow the recommendations for thresholds in the Cochrane Handbook for Systematic Reviews of Interventions (Deeks 2017):
- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: may represent considerable heterogeneity.
We will investigate possible heterogeneity through subgroup analyses. Ultimately, we may decide that a meta-analysis should be avoided (Deeks 2017).

Assessment of reporting biases
We will use a funnel plot to assess reporting bias if we include 10 or more trials. We will visually inspect funnel plots to assess the risk of bias. We are aware of the limitations of a funnel plot (i.e. a funnel plot assesses bias due to small sample size. From this information, we will assess possible reporting bias). For dichotomous outcomes, we will test asymmetry with the Harbord test (Harbord 2006). For continuous outcomes, we will use the regression asymmetry test (Egger 1997) and the adjusted rank correlation (Begg 1994).

Data synthesis
We will undertake this meta-analysis according to the recommendations stated in the Cochrane Handbook for Systematic Reviews of Interventions (Deeks 2017), by Keus and colleagues (Keus 2010), and according to the eight-step assessment suggested by Jakobsen and colleagues (Jakobsen 2014). We will use the Cochrane statistical software RevMan 5 (RevMan 2014) to analyse data.
We will assess our intervention effects with both random-effects meta-analyses (DerSimonian 1986) and fixed-effect meta-analyses (DeMets 1987). We will use the more conservative point estimate of the two (Jakobsen 2014). The more conservative point estimate is the estimate closest to zero effect. If the two estimates are similar, we will use the estimate with the widest CI. We will conduct sensitivity analyses and subgroup analyses to explore the reasons for substantial statistical heterogeneity (see Assessment of heterogeneity). We will assess the risk of publication bias in meta-analyses consisting of 10 trials or more by visual inspection of funnel plots and statistical tests for funnel plot asymmetry (see Assessment of reporting biases). We will adjust our thresholds for statistical significance when there are problems with multiplicity (family-wise error rate), by dividing the pre-specified P value threshold with the value halfway between 1 (no adjustment) and the number of primary or secondary outcome comparisons (Bonferroni adjustment) (Jakobsen 2014; Jakobsen 2016). There are three primary outcomes in this review, therefore, we will consider a P value of 0.025 or less as the threshold for statistical significance for these outcomes (Jakobsen 2014), and there are four secondary outcomes, therefore, we will consider a P value of 0.02 or less as the threshold for statistical significance for these outcomes (Jakobsen 2014; Jakobsen 2016). We will use the eight-step procedure to assess whether the thresholds for significance are crossed (Jakobsen 2014). We will include all trials in our analyses and conduct a sensitivity analysis excluding trials with high risk of bias. If the results are similar, we will base our primary conclusions on the overall analysis. If they differ, we will base our primary conclusions on trials at low risk of bias.
Where multiple trial intervention groups are reported in a single trial, we will include only the relevant groups. If two comparisons are combined in the same meta-analysis, we will halve the control group to avoid double-counting (Deeks 2017).
**Trial Sequential Analysis**

Cumulative meta-analyses are at risk of producing random errors due to sparse data and multiple testing of accumulating data (Brok 2008; Wettrelev 2008; Brok 2009; Thorlund 2009; Wettrelev 2009; Thorlund 2010; Thorlund 2011; TSA 2011; Imberger 2015; Imberger 2016; Wettrelev 2017), therefore, TSA (TSA 2011) can be applied to control these risks (www.ctu.dk/tsa/) (Thorlund 2011). Similar to a sample size calculation in a randomised clinical trial, TSA calculates the required information size (that is, the number of participants needed in a meta-analysis to detect or reject a certain intervention effect) in order to minimise random errors (Wettrelev 2009). The required information size takes into account the anticipated intervention effect, the variance of the anticipated difference in intervention effects, the acceptable risk of falsely rejecting the null hypothesis (alpha), the acceptable risk of falsely confirming the null hypothesis (beta), and the variance of the intervention effect estimates between trials (Wettrelev 2009; Turner 2013; Jakobsen 2014). To determine and predefine the anticipated intervention effects, we searched for suitable empirical data (Jakobsen 2014). However, no suitable data could be found. Instead, we pragmatically hypothesise the anticipated intervention effects:

- When analysing dichotomous outcomes, we pragmatically anticipate an intervention effect equal to a relative risk reduction of 15%.
- When analysing continuous outcomes, we pragmatically anticipate an intervention effect equal to the mean difference of the observed SD/2 (Norman 2003).

TSA enables testing for significance to be conducted each time a new trial is included in the meta-analysis. On the basis of the required information size, trial sequential monitoring boundaries are constructed. This enables one to determine the statistical inference concerning cumulative meta-analysis that has not yet reached the diversity-adjusted required information size (Wettrelev 2008; Wettrelev 2009).

Firm evidence for benefit or harm may be established if a trial sequential monitoring boundary is crossed before reaching the diversity-adjusted required information size, in which case further trials may turn out to be superfluous. In contrast, if a boundary is not surpassed one may conclude that it is necessary to continue with further trials before a certain intervention effect can be detected or rejected. Firm evidence for lack of the postulated intervention effect can also be assessed with TSA. This occurs when the cumulative Z-score crosses the trial sequential boundaries for futility.

For dichotomous outcomes, we will estimate the required information size based on a relative risk reduction of 15%, the observed proportion of participants with an outcome in the control group, an alpha of 2.5% for our primary outcomes and 2.0% for our secondary outcomes (see ‘Meta-analysis’ above), a beta of 10%, and a diversity as suggested by the trials in the meta-analysis (diversity-adjusted required information size) (Wettrelev 2009; Jakobsen 2014). In case there is some evidence or effect of the intervention, a supplementary TSA will use the limit of the CI closest to 1.00 as the anticipated intervention effect (Jakobsen 2014). Additionally, we will calculate TSA-adjusted CIs.

For continuous outcomes, we will estimate the required information size based on a minimal clinically important difference of SD/2, the standard deviation observed in the control group, an alpha of 2.5% for our primary outcomes and 2.0% for our secondary outcomes (see 'Meta-analysis' above), a beta of 10%, and a diversity as suggested by the trials in the meta-analysis (diversity-adjusted required information size) (Wettrelev 2009; Jakobsen 2014). In case there is some evidence of effect of the intervention, a supplementary TSA will use the limit of the CI closest to 0.00 as the anticipated intervention effect (Jakobsen 2014). Additionally, we will calculate TSA-adjusted CIs.

**Subgroup analysis and investigation of heterogeneity**

We will perform the following subgroup analyses when assessing each outcome (all-cause mortality, serious adverse event, quality of life, cardiovascular mortality, myocardial infarction, stroke, and sudden cardiac death) both at the time point closest to 24 months’ follow-up and at maximal follow-up.

- Comparison of the effects between trials with different types of antibiotic (e.g. azithromycin, clarithromycin, erythromycin, doxycycline, tetracycline hydrochloride, digoxin, levofloxacin, moxifloxacin, telithromycin, penicillin, amoxicillin, or metronidazole).
- Antibody status (i.e. people with identified C pneumoniae, H pylori, P gingivalis, or E coli antibodies compared to people without any identified C pneumoniae, H pylori, P gingivalis, or E coli antibodies).
- Comparison of participants on statins at entry compared to participants not on statins at entry (Jensen 2010).
- Comparison of the mean age of participants (0 to 59 years, 60 to 79 years, 80 years and over).
- Comparison of the effects between trials with different clinical trial registration status (pre-registration, post-registration or no registration).

Additionally, we will perform the following subgroup analysis when assessing each outcome (all-cause mortality, serious adverse event, quality of life, cardiovascular mortality, myocardial infarction, stroke, and sudden cardiac death) at maximal follow-up.

- Comparison of trials with less than 12 months’ follow-up with trials equal to or longer than 12 months’ follow-up.

We will use the formal test for subgroup differences in RevMan 5 (RevMan 2014).

**Sensitivity analysis**

To assess the potential impact of bias, we will perform a sensitivity analysis in which we exclude trials at overall high risk of bias.
To assess the potential impact of the missing data for dichotomous outcomes, we will perform the following four sensitivity analyses when assessing each dichotomous outcome (all-cause mortality, serious adverse event, cardiovascular mortality, myocardial infarction, stroke, and sudden cardiac death).

1. **Best-worst-case** scenario: we will assume that all participants lost to follow-up in the experimental group have survived, had no serious adverse event, had no cardiovascular death, had no myocardial infarction, had no stroke, and had no sudden cardiac death; and all those participants lost to follow-up in the control group have not survived, had a serious adverse event, had a cardiovascular death, had a myocardial infarction, had a stroke, and had a sudden cardiac death.

2. **Worst-best-case** scenario: we will assume that all participants lost to follow-up in the experimental group have not survived, had a serious adverse event, had a cardiovascular death, had a myocardial infarction, had a stroke, and had a sudden cardiac death; and all those participants lost to follow-up in the control group have survived, had no serious adverse event, had no cardiovascular death, had no myocardial infarction, had no stroke, and had no sudden cardiac death.

3. A modified 'best-worst-case' scenario: we will assume that half of the participants lost to follow-up in the experimental group have survived, had no serious adverse event, had no cardiovascular death, had no myocardial infarction, had no stroke, and had no sudden cardiac death; and that half of the participants lost to follow-up in the control group have not survived, had a serious adverse event, had a cardiovascular death, had a myocardial infarction, had a stroke, and had a sudden cardiac death.

4. A modified 'worst-best-case' scenario: we will assume that half of the participants lost to follow-up in the experimental group have not survived, had a serious adverse event, had a cardiovascular death, had a myocardial infarction, had a stroke, and had a sudden cardiac death; and that half of the participants lost to follow-up in the control group have survived, had no serious adverse event, had no cardiovascular death, had no myocardial infarction, had no stroke, and had no sudden cardiac death.

We will present results of all four scenarios in our review. When analysing quality of life, a 'beneficial outcome' will be the group mean plus two standard deviations (SDs) (we will then use one SD in another sensitivity analysis) of the group mean (Jakobsen 2014). To assess the potential impact of missing SDs for continuous outcomes, we will perform the following sensitivity analysis.

- Where SDs are missing and it is not possible to calculate them, we will impute SDs from trials with similar populations and low risk of bias. If we find no such trials, we will impute SDs from trials with a similar population. As the final option, we will impute SDs from all trials.

We will present results of this scenario in our review. Other post-hoc sensitivity analyses might be warranted if unexpected clinical or statistical heterogeneity is identified during the analysis of the review results (Jakobsen 2014).

### 'Summary of Findings' table

We will create a Summary of Findings table using each of the primary (all-cause mortality, serious adverse event, and quality of life) and secondary outcomes (cardiovascular mortality, myocardial infarction, stroke, and sudden cardiac death). We will use the five GRADE considerations (trial limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence as it relates to the studies that contribute data to the meta-analyses for the prespecified outcomes (Schunemann 2003; Guyatt 2008; Guyatt 2011; Jakobsen 2014). We will use methods and recommendations described in chapter 8 (Section 8.5) (Higgins 2011b) and Chapter 12 (Schünemann 2017) of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011a) using GRADEpro GDT software (GRADEpro GDT 2015; Schunemann 2013). We will justify all decisions to downgrade the quality of studies using footnotes and we will make comments to aid the reader's understanding of the review where necessary.

We will include all trials in our analyses, and conduct a sensitivity analysis excluding trials at high risk of bias. If the results are similar, we will base our primary 'Summary of Findings' tables and primary conclusions on the overall analysis. If they differ, we will base our primary 'Summary of Findings' tables and primary conclusions on trials at low risk of bias.

### Acknowledgements

We thank Cochrane Heart for their expert assistance in creating the search strategy and the provision of a template protocol.
Antibiotics for secondary prevention of coronary heart disease (Protocol)

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Dalhoff 2003

Danesh 1997

Danesh 1998

Danesh 2000a

Danesh 2000b

Danesh 2002

De Boer 2014

Deeks 2017

DeMets 1987

DerSimonian 1986

Eckle 2014

Egger 1997

Elbourne 2002

Etminan 2004

Ezzahiri 2002

Ezzahiri 2003

Ferreira-Gonzalez 2014

Fihn 2012

Filardo 2015

Folsom 1998
Antibiotics for secondary prevention of coronary heart disease (Protocol)

Guyatt 2006


Higgins 2002


Higgins 2003


Higgins 2011a


Higgins 2011b


Higgin 2017


Hizo-Abes 2013


ICH-GCP 1997


Imberger 2015


Imberger 2016

Imberger G, Thorlund K, Gluud C, Weterslev J. False-positive findings in Cochrane meta-analyses with and
Antibiotics for secondary prevention of coronary heart disease (Protocol)

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Mahendra 2015

Malferttheiner 2007

Matusiak 2016

Mendall 1994

Mendall 1996

Moher 1998

Moher 2009

Montalescot 2013

Mozaffarian 2016

Muhlestein 1996

Norman 2003

Pesonen 2009

Piepoli 2016

Pigarevskii 2015

Polk 1999

Prasad 2002

Pucar 2007

Pussinen 2004
heart diseases.


Ridker 2006


Roivainen 2000


Romano Carratelli 2006


Rosenfeld 2011


Ross 1999


Saikku 1988


Sakurai-Komada 2014


Sapadin 2006


Savovic 2012


Schulz 1995


Schunemann 2003


Schunemann 2013


Schnuennemann 2017


Shmuel 2014


Shor 1992


Smith 2011

Spahr 2006

Steel 2012

Sun 2016

Thom 1991

Thorlund 2009

Thorlund 2011

Torgano 1999

TSA 2011 [Computer program]
Copenhagen Trial Unit. Trial Sequential Analysis. Version 0.9 beta. Copenhagen: Copenhagen Trial Unit, 2011.

Turner 2013

Vcev 2007

Waksman 1947

Wetterslev 2008

Wetterslev 2009

Wetterslev 2017

Whincup 1996

WHO 2011

WHO 2016

Winkel 2011

Winkel 2015

Wong 2014

Wood 2008

**Zaremba 2007**

**Zhu 2001**

**Zhu 2002**

* Indicates the major publication for the study

**ADDITIONAL TABLES**

Table 1. The Cochrane tool for assessing risk of bias

<table>
<thead>
<tr>
<th>Domain</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Random sequence generation</strong></td>
<td>• Low risk: if sequence generation was achieved using computer random number generator or a random numbers table. Drawing lots, tossing a coin, shuffling cards, and throwing dice were also considered adequate if performed by an independent adjudicator.</td>
</tr>
<tr>
<td></td>
<td>• Unclear risk: if the method of randomisation was not specified, but the trial was still presented as being randomised.</td>
</tr>
<tr>
<td></td>
<td>• High risk: if the allocation sequence was not randomised or only quasi-randomised. We will exclude these trials.</td>
</tr>
<tr>
<td><strong>Allocation concealment</strong></td>
<td>• Low risk: if the allocation of participants was performed by a central independent unit, on-site locked computer, identical-looking numbered sealed envelopes, drug bottles, or containers prepared by an independent pharmacist or investigator.</td>
</tr>
<tr>
<td></td>
<td>• Uncertain risk: if the trial was classified as randomised but the allocation concealment process was not described.</td>
</tr>
<tr>
<td></td>
<td>• High risk: if the allocation sequence was familiar to the investigators who assigned participants.</td>
</tr>
<tr>
<td><strong>Blinding of participants and personnel</strong></td>
<td>• Low risk: if the participants and the personnel were blinded to intervention allocation and this was described.</td>
</tr>
<tr>
<td></td>
<td>• Uncertain risk: if the procedure of blinding was insufficiently described.</td>
</tr>
<tr>
<td></td>
<td>• High risk: if blinding of participants and the personnel was not performed.</td>
</tr>
<tr>
<td><strong>Blinding of outcome assessment</strong></td>
<td>• Low risk of bias: if it was mentioned that outcome assessors were blinded and this was described.</td>
</tr>
<tr>
<td></td>
<td>• Uncertain risk of bias: if it was not mentioned if the outcome assessors in the trial were blinded, or the extent of blinding was insufficiently described.</td>
</tr>
<tr>
<td></td>
<td>• High risk of bias: if no blinding or incomplete blinding of outcome assessors was performed.</td>
</tr>
<tr>
<td><strong>Incomplete outcome data</strong></td>
<td>• Low risk of bias: if missing data were unlikely to make treatment effects depart from plausible values. This could either be: 1) there were no drop-outs or withdrawals for all outcomes, or 2) the numbers and reasons for the withdrawals and drop-outs for all outcomes were clearly stated and could be described as being similar in both groups.</td>
</tr>
</tbody>
</table>
Table 1. The Cochrane tool for assessing risk of bias  (Continued)

<table>
<thead>
<tr>
<th>Risk of bias</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generally, the trial is</td>
<td>judged as at a low risk of bias due to incomplete outcome data if drop-outs are less than 5%.</td>
</tr>
<tr>
<td>judged as at a low risk of</td>
<td>However, the 5% cut-off is not definitive.</td>
</tr>
<tr>
<td>bias due to incomplete</td>
<td>• Uncertain risk of bias: if there was insufficient information to assess whether missing</td>
</tr>
<tr>
<td>outcome data</td>
<td>data were likely to induce bias on the results.</td>
</tr>
<tr>
<td></td>
<td>• High risk of bias: if the results were likely to be biased due to missing data either</td>
</tr>
<tr>
<td></td>
<td>because the pattern of drop-outs could be described as being different in the two</td>
</tr>
<tr>
<td></td>
<td>intervention groups or the trial used improper methods in dealing with the missing data</td>
</tr>
<tr>
<td></td>
<td>(e.g. last observation carried forward).</td>
</tr>
<tr>
<td>Selective outcome</td>
<td>reporting</td>
</tr>
<tr>
<td></td>
<td>• Low risk of bias: if a protocol was published before or at the time the trial was</td>
</tr>
<tr>
<td></td>
<td>begun and the outcomes specified in the protocol were reported on.</td>
</tr>
<tr>
<td></td>
<td>If there is no protocol or the protocol was published after the trial has begun, reporting</td>
</tr>
<tr>
<td></td>
<td>of all-cause mortality and serious adverse events will grant the trial a grade of low risk</td>
</tr>
<tr>
<td></td>
<td>of bias.</td>
</tr>
<tr>
<td></td>
<td>• Uncertain risk of bias: if no protocol was published and the outcomes all-cause mortality</td>
</tr>
<tr>
<td></td>
<td>and serious adverse events were not reported on.</td>
</tr>
<tr>
<td></td>
<td>• High risk of bias: if the outcomes in the protocol were not reported on.</td>
</tr>
<tr>
<td>Other risks of bias</td>
<td>• Low risk of bias: if the trial appears to be free of other components (for example, academic</td>
</tr>
<tr>
<td></td>
<td>bias or for-profit bias) that could put it at risk of bias.</td>
</tr>
<tr>
<td></td>
<td>• Unclear risk of bias: if the trial may or may not be free of other components that could put</td>
</tr>
<tr>
<td></td>
<td>it at risk of bias.</td>
</tr>
<tr>
<td></td>
<td>• High risk of bias: if there are other factors in the trial that could put it at risk of bias</td>
</tr>
<tr>
<td></td>
<td>(for example, authors have conducted trials on the same topic, for-profit bias etc).</td>
</tr>
<tr>
<td>Overall risk of bias</td>
<td>• Low risk of bias: the trial will be classified as overall 'low risk of bias' only if all of</td>
</tr>
<tr>
<td></td>
<td>the bias domains described in the above paragraphs are classified as 'low risk of bias'.</td>
</tr>
<tr>
<td></td>
<td>• High risk of bias: the outcome result will be classified 'high risk of bias' if any of the</td>
</tr>
<tr>
<td></td>
<td>bias risk domains described in the above are classified as 'unclear' or 'high risk of bias'.</td>
</tr>
</tbody>
</table>

APPENDICES

Appendix 1. MEDLINE preliminary search strategy

1. exp Coronary Disease/
2. exp Myocardial Ischemia/
3. (myocard* adj3 infarct*).tw.
4. (coronary adj3 disease*).tw.
5. (myocard* adj3 ischemi*).tw.
6. (myocard* adj3 ischaem*).tw.
7. (ischemic adj3 heart).tw.
8. (ischaemic adj3 heart).tw.
9. exp Atherosclerosis/
10. atheroscleropenici*.tw.
11. angina*.tw.
12. or/1-11
13. Anti-Bacterial Agents/
15. cephalosporin*.tw.
16. carbapenem*.tw.
17. monobactam*.tw.
18. beta-lactam*.tw.
19. aminoglycoside*.tw.
20. macrolide*.tw.
22. exp Penicillins/
23. exp lactams/ or beta-lactams/
24. exp Tetracyclines/
25. exp Aminoglycosides/
26. exp Macrolides/
27. exp Clindamycin/
28. exp Chloramphenicol/
29. Fusidic Acid/
30. Vancomycin/
31. Daptomycin/
32. exp Polymyxins/
33. (antibiotic* or anti-bacterial* or anti-infective*).tw.
34. or/13-33
35. 12 and 34
36. randomized controlled trial.pt.
37. controlled clinical trial.pt.
38. randomized.ab.
39. placebo.ab.
40. drug therapy.fs.
41. randomly.ab.
42. trial.ab.
43. groups.ab.
44. 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43
45. exp animals/ not humans.sh.
46. 44 not 45
47. 35 and 46

**WHAT'S NEW**

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>12 July 2017</td>
<td>New citation required and major changes</td>
<td>Authorship changed with new author and new contact person. The methods have been updated in line with more recent Collaboration guidelines</td>
</tr>
</tbody>
</table>
**HISTORY**

Protocol first published: Issue 2, 2002

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>11 August 2008</td>
<td>Amended</td>
<td>Authorship changed with new author and new contact person.</td>
</tr>
<tr>
<td>12 June 2008</td>
<td>Amended</td>
<td>Converted to new review format.</td>
</tr>
</tbody>
</table>

**CONTRIBUTIONS OF AUTHORS**

Naqash Javaid Sethi drafted the protocol, based on a previous version authored by Maria Skoog, Berit Grevstad, Asbjørn Hróbjartsson, Jørn Weterslev, and Christian Gluud.

Janus Christian Jakobsen, Sanam Safi, Steven Kwasi Korang, Asbjørn Hróbjartsson, Maria Skoog, and Christian Gluud amended the protocol. All the authors read and approved the final manuscript.

**DECLARATIONS OF INTEREST**

The performance of this review is free of any real or perceived bias introduced by receipt of any benefit in cash or kind, or any subsidy derived from any source that may have or be perceived to have an interest in the outcomes of the review.

Naqash J. Sethi (NJS): no conflict on interest.
Sanam Safi (SS): no conflict of interest.
Steven Kwasi Korang (SKK): no conflict of interest.
Maria Skoog (MS): Involved in a randomised trial (CLARICOR) in which the intervention drug (Klacid Uno®) and placebo were donated by Abbott.
Asbjørn Hróbjartsson (AH): no conflict of interest.
Christian Gluud (CG): member of The Copenhagen Trial Unit task force for developing TSA methods, manual, and software. Involved in a randomised trial (CLARICOR) in which the intervention drug (Klacid Uno®) and placebo were donated by Abbott.
Januc C. Jakobsen (JCJ): no conflict of interest.

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External sources

- The 1991 Pharmacy Foundation, Denmark.
- The Danish Medical Research Council, Denmark.

NOTES

This is a re-publication of a protocol (DOI: 10.1002/14651858.CD003610.pub2) due to changes in authorship and methods.