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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
BACKGROUND	1
OBJECTIVES	4
METHODS	4
ACKNOWLEDGEMENTS	9
REFERENCES	9
APPENDICES	13
CONTRIBUTIONS OF AUTHORS	18
DECLARATIONS OF INTEREST	18
SOURCES OF SUPPORT	18

[Intervention Protocol]

Drug-eluting stents versus bare-metal stents for stable ischaemic heart disease

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ABSTRACT

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

To assess the benefits and harms of drug-eluting stents versus bare-metal stents in participants with stable ischaemic heart disease.

BACKGROUND

Description of the condition

Cardiovascular disease, in which ischaemic heart disease is the largest component, is considered to be the number one cause of death globally (Lloyd-Jones 2010; Nichols 2014; Rosamond 2008). According to the World Health Organization (WHO), 7.4 million people died from ischaemic heart disease in 2012, representing 15% of all global deaths (WHO 2015). Ischaemic heart disease remains increasingly prevalent and costly to treat due to an increase in life expectancy and a decrease in death rates (Cooper 2000; Schmidt 2012).

Ischaemic heart disease has different underlying mechanisms:

1. atherosclerotic plaque-related obstruction of the coronary arteries;
2. focal or diffuse spasms of normal or plaque-diseased arteries;
3. microvascular dysfunction; and
4. left ventricular dysfunction caused by acute myocardial necrosis or ischaemic cardiomyopathy (Montalescot 2013).

Ischaemic heart disease is generally divided into acute coronary syndrome (ACS) and stable ischaemic heart disease (Roffi 2016). Acute coronary syndrome has three different forms:

1. chest pain during rest (unstable angina pectoris);
2. acute non-ST-segment elevation myocardial infarction (NSTEMI); and

3. acute ST-segment elevation myocardial infarction (STEMI) (Roffi 2016). The symptom of chest pain (angina) is usually because of the blockage of a great coronary artery resulting in ischaemia of the myocardium.

Episodes of reversible myocardial demand/supply mismatch, related to ischaemia or hypoxia (a condition where the tissue of the heart is deprived of adequate oxygen supply) of the heart muscle commonly associated with transient chest discomfort, define stable ischaemic heart disease. The symptoms are usually precipitated by, for example, walking, emotion, or stress with none to minimal symptoms at rest and symptom relief with the administration of sublingual nitroglycerin (Montalescot 2013).

Historically, the degree of luminal stenosis (abnormal narrowing of the lumen of the vessel) and the number of coronary arteries involved (single-vessel disease, double-vessel disease, or triple-vessel disease) have defined the severity of ischaemic heart disease (Ringqvist 1983). More recently, researchers have developed more comprehensive scorings systems (Farooq 2013; Gensini 1983; Seizer 1982; Sianos 2005). Coronary angiography score and two additional scores, i.e. vascular scoring and stenosis scoring, determine the Gensini score (Gensini 1983). The SYNTAX score II is used to improve the decision-making in choosing between percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) for a long-term, individualised risk assessment in patients with complex ischaemic heart disease. The SYNTAX score II combines the anatomical-based SYNTAX score (Sianos 2005), as well as seven clinical variables (creatinine clearance, peripheral vascular disease, unprotected left main coronary disease, gender, chronic obstructive pulmonary disease, age, and left ventricular ejection fraction) (Farooq 2013; Sianos 2005).

Description of the intervention

PCI is performed by inserting an access sheath into a peripheral artery (most often the femoral artery or the radial artery); a catheter is advanced, under X-ray screening, through the blood vessels to the aortic root, at the origin of the coronary arteries. Other tools such as balloons and stents can then be advanced down the artery, over a guide wire, to the location of the narrowing or blockage (Cantor 2005; Hamon 2009). Andreas Roland Grüntzig performed the first PCI in 1977 (Grüntzig 1978). PCI has since then evolved to become one of the cornerstones in the treatment of ischaemic heart disease.

PCI in patients with stable ischaemic heart disease is often performed as an elective treatment. This is performed in the following patients:

1. those where coronary artery bypass grafting is not indicated; and
2. those who due to severe angina (Canadian Cardiovascular Society Grade III to IV) are dissatisfied with their quality of life (Montalescot 2013).

The first PCI was performed by inflating a balloon at the blockage of the coronary artery to dilate the artery ('balloon angioplasty') (Grüntzig 1978; Grüntzig 1979). The healing properties of the treatment seem to be related to the PCI expanding the outer diameter of the blocked coronary artery and not by decompression of the arterial plaque (Düber 1986). Balloon angioplasty however generally did not seem to achieve a long-lasting result, with restenosis occurring over time (Puel 1988). In an attempt to keep the lumen open for longer, the next development was a small metallic scaffold called a "stent". These tubular devices are expanded over a balloon and press against the walls of the artery to keep it open (Puel 1988). These first devices were subsequently termed "bare-metal stents" (after the later introduction of "drug-eluting stents") and improved outcomes over balloon angioplasty, but still had high rates of restenosis over time (Erbel 1998; Fischman 1994; Macaya 1996; Puel 1988; Serruys 1994; Serruys 1998).

Newer drug-eluting stents have decreased strut thickness and are meant to have improved flexibility/deliverability, enhanced polymer biocompatibility/drug-eluting profiles, and superior re-endothelialisation kinetics (Serruys 2010; Stone 2010). They typically use everolimus or zotarolimus as their antiproliferative drug (Serruys 2010; Stone 2010).

The polymer-coating of the drug-eluting stents has been linked with adverse events, such as stent thrombosis (Chen 2015). Therefore, both drug-eluting stents with a biodegradable polymer as well as polymer-free drug-eluting stents have been developed. Polymer-free drug-eluting stents use the same antiproliferative drugs (such as paclitaxel or sirolimus) as the polymer drug-eluting stents (Abizaid 2010; Chen 2015).

In an attempt to further reduce the risk of restenosis, bioresorbable (also called biodegradable) stents were developed. The principal components of the bioresorbable stent are the same as the drug-eluting stents; however, in most cases, a polylactic acid mesh replaces the metal mesh (Haude 2013; Puricel 2015). The polylactic acid mesh is broken down and removed over time (Tamai 2000). The same types of drugs (everolimus, paclitaxel, sirolimus) used in drug-eluting stents along with biolimus are used in bioresorbable stents (Haude 2013; Haude 2016; Puricel 2015).

Bare-metal stents, drug-eluting stents, and bioresorbable stents are used in modern PCIs, with drug-eluting stents generally being the first choice (Windecker 2014). Guidelines recommend that acute coronary syndrome patients receive 12 months of antiplatelet therapy (aspirin and a P2Y₁₂ receptor blocker) regardless of whether PCI is performed (Windecker 2014). The minimum length of duration for the implant of the bare-metal stents and drug-eluting stents is recommended to be one month and six months, respectively (Windecker 2014).

Adverse events associated with PCI include death, coronary artery complications (such as perforation of the artery, distal embolisation (passage of an intravascular mass, which is capable of clogging capillaries), or stent thrombosis), myocardial infarction (type four myocardial infarction) (Thygesen 2012), vascular complications

(such as bleeding or infection at the access site, retroperitoneal bleeding, or atheroembolism), stroke, and acute kidney failure (Baim 1996; Cantor 1998; Stankovic 2004).

How the intervention might work

PCI aims to decrease the stenosis of the coronary artery resulting in increased blood flow to the myocardium of the heart, which is thought to limit ischaemia and potentially reinfarction. Drug-eluting stents may be more beneficial than bare-metal stents because they release antiproliferative drugs, which cause less neointimal growth (Holmes 2004; Stone 2004; Serruys 2010; Stone 2010). The new bioresorbable stents as well as the polymer-free drug-eluting stents may be even more beneficial since they remove material that has been associated with adverse events (Abizaid 2010; Chen 2015; Haude 2013; Puricel 2015).

Why it is important to do this review

The prevalence of ischaemic heart disease is considerable and causes one third of all deaths in patients over the age of 35 years (Lloyd-Jones 2010; Nichols 2014; Rosamond 2008). Beneficial treatments can therefore alleviate a considerable disease burden and healthcare cost.

Several systematic reviews and meta-analysis have previously assessed the effects of PCI for stable ischaemic heart disease. However, none of these reviews have exclusively assessed people with stable ischaemic heart disease.

Former evidence on drug-eluting stents versus bare-metal stents for stable ischaemic heart disease

A 2010 Cochrane Review compared drug-eluting stents with bare-metal stents in participants with both acute coronary syndrome and stable ischaemic heart disease (Greenhalgh 2010). It found no significant when comparing drug-eluting stents and bare-metal stents on mortality, incidence of acute myocardial infarction, and thrombosis. However, the review showed indications of beneficial effect of drug-eluting stents on target lesion revascularisation, target vessel revascularisation, and a composite outcome of cardiac events compared with bare-metal stents.

Three meta-analyses have assessed the effects of drug-eluting stents versus bare-metal stents (Kastrati 2007; Roukoz 2009; Stettler 2007). Of the three meta-analyses, two compared sirolimus stents and paclitaxel stents with bare-metal stents (Roukoz 2009; Stettler 2007), while one compared only sirolimus stents with bare-metal stents (Kastrati 2007). All three meta-analyses found no effect on mortality of sirolimus and paclitaxel stents compared with bare-metal stents. Stettler 2007 found a beneficial effect in favour of the drug-eluting stents using sirolimus on myocardial

infarction, it found no effect for drug-eluting stents using paclitaxel. Kastrati 2007 and Roukoz 2009 found no difference between drug-eluting stents versus bare metal stents on myocardial infarction. All three meta-analyses found a beneficial effect favouring drug-eluting stents on target vessel revascularisation (Kastrati 2007; Roukoz 2009; Stettler 2007).

Current guidelines on drug-eluting stents versus bare-metal stents for stable ischaemic heart disease

The American College of Cardiology Foundation/American Heart Association/Society for Cardiovascular Angiography and Interventions guideline (ACCF/AHA/SCAI) (Levine 2011) have assessed the effects of drug-eluting stents versus bare-metal stents.

The ACCF/AHA/SCAI recommend drug-eluting stents as an alternative to bare-metal stents to prevent restenosis in cases where there is an increased risk of restenosis, and the patient is likely to be able to tolerate and comply with prolonged dual antiplatelet therapy. The clinical situations associated with increased risk of restenosis are left main disease, small vessels, in-stent restenosis, bifurcations, diabetes, long lesions, multiple lesions, and saphenous vein grafts (Levine 2011). The guideline also states that bare-metal stents should be used in patients with a high risk of bleeding, inability to comply with one year of dual antiplatelet therapy, or anticipated invasive or surgical procedures in the next year.

The National Institute for Health and Care Excellence (NICE) has assessed the effects of drug-eluting stents (NICE 2008). NICE recommends drug-eluting stents in cases where the target artery for treatment has less than a 3 mm calibre or the lesion is longer than 15 mm, and the price difference between drug-eluting stents and bare-metal stents is no more than £300 (GBP).

Problems with major adverse cardiac events (MACE) as an outcome

In recent years, two major reports have described and analysed several issues regarding the cardiac composite outcome MACE (Cutlip 2007; Kip 2008). The main issues regarding MACE concern the variability and lack of consistency in which outcomes are included in the composite outcome (Cutlip 2007; Kip 2008). This may lead to misleading conclusions. The main issue with MACE in this particular review is the problem with using target vessel revascularisation or target lesion revascularisation as components of MACE. There are several reasons for this being problematic. First, it is important to remember that the decision of whether or not target vessel revascularisation will be performed is based on a subjective opinion. Since both treatment providers and participants will presumably not be blinded to treatment allocation in the included trials, target vessel revascularisation and target lesion revascularisation may introduce bias. Secondly, using a composite outcome consisting of safety endpoints (death and myocardial infarction) and outcomes presumed to be a measure of procedural effectiveness (target vessel revascularisation and target lesion

revascularisation) could lead to erroneous conclusions (Kip 2008). Therefore, we have decided not to use MACE as a composite outcome. Instead, we will use a composite cardiovascular outcome consisting of cardiovascular mortality and myocardial infarction. This review is an update of a 2010 Cochrane Review that has now been divided into two reviews (Greenhalgh 2010): a review including ACS participants and a review including stable ischaemic heart disease participants. To our knowledge, no former review has assessed the effect of drug-eluting stents versus bare-metal stents only in patients with stable ischaemic heart disease. Additionally, no review assessing the effect of drug-eluting stents versus bare-metal stents in patients with ischaemic heart disease is up-to-date with the latest trials. The present review will also be the first to do the following:

1. take full account of the risk of systematic errors ('bias'), design errors, and risks of random errors ('play of chance') (Higgins 2011; Jakobsen 2014; Keus 2010; Thorlund 2011; Wetterslev 2008);
2. include trials irrespective of outcome, follow-up duration, and number of participants;
3. assess outcomes at several time points and take into account the variability of the follow-up period; and
4. include all types of drug-eluting stents, including polymer-free stents and bioresorbable stents.

OBJECTIVES

To assess the benefits and harms of drug-eluting stents versus bare-metal stents in participants with stable ischaemic heart disease.

METHODS

Criteria for considering studies for this review

Types of studies

We will search for randomised clinical trials (both individual and cluster-randomised trials) irrespective of publication type, publication status, publication date, and language.

Types of participants

We will include participants of any age with a diagnosis of stable ischaemic heart disease (according to the definition of the trialists). If we identify trials where only a subset of participants are eligible for our review, we will only include these data if the trialists report separate valid data for the specific participants relevant for our

review according to our predefined inclusion and exclusion criteria or we are able to obtain such data from the authors.

Types of interventions

We will include any type of drug-eluting stents, including bioresorbable stents and polymer-free drug-eluting stents. We will accept any type of medical therapy as a co-intervention to percutaneous coronary intervention (PCI). We will include any type of bare-metal stent as a control intervention.

Types of outcome measures

Primary outcomes

1. All-cause mortality.
2. Serious adverse events defined as any untoward medical occurrence that resulted in death, was life-threatening, was persistent, or led to significant disability; prolonged hospitalisation; or any medical event that had jeopardised the participant or required intervention to prevent it (ICH-GCP 1997).
3. Major cardiovascular event defined as a composite outcome consisting of cardiovascular mortality and myocardial infarction.
4. Quality of life measured on any valid scale, such as the Seattle Angina Questionnaire or 36-Item Short Form Survey (SF-36) (Ware 1992; Wyrwich 2004)

Secondary outcomes

1. Cardiovascular mortality (defined by the trialists).
2. Myocardial infarction (defined by the trialists).
3. Angina on a continuous scale, such as 'angina stability' and 'angina frequency' used in the Seattle Angina Questionnaire (Wyrwich 2004).

Exploratory outcomes

1. Stent thrombosis.
2. Target vessel revascularisation (defined by the trialists). In general, target vessel revascularisation is any repeat percutaneous intervention or surgical bypass of any segment of the target vessel (Hicks 2010). We will narratively report adverse events, presenting them in a table. We will conduct meta-analyses when possible of all dichotomous and continuous outcomes at the following two time points:
 - outcomes assessed at maximal follow-up (this will be the time point of primary interest); and
 - outcomes assessed at three months or earlier.

Search methods for identification of studies

Electronic searches

We will identify trials through systematic searches of the following bibliographic databases:

- the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library;
- MEDLINE Ovid;
- Embase Ovid;
- LILACS (Latin American and Caribbean Health Science Information Database) (BIREME);
- Science Citation Index Expanded (Thomson Reuters Web of Science);
- BIOSIS Citation Index (Thomson Reuters Web of Science).

The preliminary search strategy for MEDLINE Ovid will be adapted for use in the other databases (Appendix 1). The Cochrane sensitivity-maximising RCT filter, Lefebvre 2011, will be applied to MEDLINE Ovid, and adaptations of it will be applied to the other databases, except CENTRAL.

We will also conduct a search of the US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization International Clinical Trials Registry Platform (ICTRP) (www.apps.who.int/trialsearch). We will also search Google Scholar manually for trials not found in the preliminary search (Lefebvre 2011).

We will search all databases from their inception to the present, and we will impose no restriction on language of publication. If we identify any papers in a language not known by the author group, we will seek professional assistance, which we will acknowledge in the Acknowledgements section.

Searching other resources

We will identify additional trials from the reference lists of review articles and identified trials.

Data collection and analysis

We will perform the review following the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will perform the analyses using Review Manager 5 (RevMan 2014), Stata 14 (Stata 2015), and trial sequential analysis (CTU 2011).

Selection of studies

Two review authors (EEN and JF) will independently screen titles and abstracts of all of the potentially eligible trials for inclusion. We will code all of these studies as 'retrieve' (eligible or potentially

eligible/unclear) or 'do not retrieve'. If there are any disagreements, we will ask a third author to arbitrate (JCJ). We will retrieve the full-text trial reports/publications, and two review authors will independently screen the full texts and identify trials for inclusion. We will report reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion, or if required, we will consult a third person (JCJ). We will identify and exclude duplicates and collate multiple reports of the same trial so that each trial, rather than each report, is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' tables.

Data extraction and management

We will use a data collection form, which we have piloted on at least one trial in the review, to collect trial characteristics and outcome data. Two review authors (JF and EEN) will extract trial characteristics from included trials. We will extract the following trial characteristics.

1. Methods: duration of the trial, details of any 'run-in' period, and date of publication.
2. Participants: number randomised, number analysed, mean age, sex, inclusion criteria, and exclusion criteria.
3. Interventions: intervention, comparison, concomitant medications, and excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected and time points reported.
5. Notes: trial funding and notable conflicts of interest of the trial authors.

Two review authors (EEN and JF) will independently extract outcome data from included studies. We will resolve disagreements by consensus or by involving a third person (JCJ). One review author (EEN) will transfer data into the Review Manager 5 file (RevMan 2014). We will double-check that data is entered correctly by comparing the data presented in the systematic review with the study reports. A second review author will spot-check study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

We will use the instructions given in the *Cochrane Handbook for Systematic Reviews of Interventions* in our evaluation of the methodology and the risk of bias of the included trials (Higgins 2011). Two review authors will independently assess the included trials. We will evaluate the risk of bias in random sequence generation; allocation sequence concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective outcome reporting, including industry funding; and other bias sources. This is done because these components enable classification of randomised trials with a bias assessment of low, high, or unclear. The latter trials overestimate benefits and underestimate harms (Gluud 2006; Hróbjartsson 2012;

Hróbjartsson 2013; Kjaergard 2001; Lundh 2012; Moher 1998; Savovic 2012; Schulz 1995; Wood 2008). For additional details on how we will assess risk of bias, see [Appendix 2](#).

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 review.

Measures of treatment effect

Dichotomous outcomes

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

Continuous outcomes

We will include both end scores and change scores in our analyses. We will use end scores in the analyses if both are reported. We will calculate the mean differences (MDs) and the standardised mean differences (SMDs) with 95% CIs for continuous outcomes. We will use the standardised mean difference when the trials all assess the same outcome but measure it in a variety of ways, e.g. with different scales ([Higgins 2011](#)).

Dealing with missing data

We will contact investigators or study sponsors to obtain any missing data.

Dichotomous outcomes

We will not impute missing values for any outcomes in our primary analysis. In two of our sensitivity analyses, we will impute data (see [Sensitivity analysis](#)).

Continuous outcomes

We will not impute missing values for any outcomes in our primary analysis. In our sensitivity analysis for dichotomous and continuous outcomes, we will impute data (see [Sensitivity analysis](#)). If studies do not report standard deviations (SD), we will calculate them using data from the trial if possible.

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* ([Higgins 2011](#)):

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity; and
- 75% to 100%: may represent considerable heterogeneity.

We will investigate possible heterogeneity through subgroup analyses. Ultimately, we may decide that we should avoid a meta-analysis ([Higgins 2011](#)).

Assessment of reporting biases

We will assess publication bias and other reporting biases by visual inspection of funnel plots for primary outcomes if we include at least 10 trials ([Higgins 2011](#)). Using the asymmetry of the funnel plot, we will assess the risk of bias.

For dichotomous outcomes, we will test asymmetry with the Harbord test, [Harbord 2006](#), if τ^2 is less than 0.1 and with the Rucker test, [Rucker 2008](#), if τ^2 is more than 0.1.

For continuous outcomes, we will use the regression asymmetry test ([Egger 1997](#)).

Data synthesis

Meta-analysis

We will undertake this systematic review according to the recommendations stated in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)), according to [Keus 2010](#), and according to the eight-step assessment suggested by [Jakobsen 2014](#). We will use the statistical software Review Manager 5, provided by Cochrane, to meta-analyse data ([RevMan 2014](#)).

We will use Stata, [Stata 2015](#), in case of zero-event trials where Review Manager 5's zero-event handling (replacing zero with a constant of 0.5) is not sufficient, e.g. in cases with a skewed number of participants between groups, which we will handle with reciprocal zero-event handling according to [Sweeting 2004](#), and in case we need to undertake meta-regression (post hoc).

We will use trial sequential analysis (TSA) to assess and control the risk of random error. If the review does not reach the required information size, we will present TSA-adjusted confidence intervals to account for the lack of information.

If the included studies report both end scores and change-from-baseline scores, meta-analysing continuous outcomes, we will use

end scores. If they report only change, we will analyse the results together with end scores (Higgins 2011a).

We will include all studies in our initial analyses and conduct a sensitivity analysis of studies at low 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 studies at low risk of bias.

However, we do not expect to identify any trials performing adequate blinding of participants and personnel because of the nature of the PCI procedure. Under these circumstances, we will instead conduct a sensitivity analysis of the results at low risk of bias in all bias risk domains except 'blinding of participants and personnel'. If the results differ from the overall analysis, we will base our primary conclusions on the results of the analyses of the primary outcomes with low risk of bias in all bias risk domains except 'blinding of participants and personnel' and the trial sequential analysis-adjusted CIs (see below). We will discuss in the final review the limitations of the expected lack of 'blinding of participants and personnel' for conclusions (Hróbjartsson 2014; Pocock 2015).

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; Brok 2009; Higgins 2011a; Pogue 1997; Thorlund 2009; Wetterslev 2008); therefore, trial sequential analysis (TSA) can be applied to control this risk (CTU 2011; www.ctu.dk/tsa) (Thorlund 2011). The required information size (that is the number of participants needed in a meta-analysis to detect or reject a certain intervention effect) can be calculated in order to minimise random errors (Wetterslev 2008; Wetterslev 2009). The required information size takes into account the event proportion in the control group, the assumption of a plausible relative risk reduction, and the heterogeneity of the meta-analysis (Turner 2013; Wetterslev 2008; Wetterslev 2009). TSA enables testing for significance each time a meta-analysis includes a new trial. On the basis of the required information size, trial sequential monitoring boundaries can be constructed. This enables one to determine the statistical inference concerning cumulative meta-analysis that has not yet reached the required information size (Wetterslev 2008). Firm evidence for benefit or harms may be established if the trial sequential monitoring boundary is crossed before reaching the required information size, in which case further trials may turn out to be superfluous. In contrast, if the boundaries for benefit or harm are 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 monitoring boundaries for futility.

To control the risks of random errors, we have used relatively conservative estimations of the anticipated intervention effect esti-

mates (Jakobsen 2014). Large anticipated intervention effects lead to small required information sizes, and the thresholds for significance will be less strict after the information size has been reached (Jakobsen 2014).

We will analyse all primary and secondary outcomes with TSA. We will use the following assumptions.

Primary outcomes

We will estimate the diversity-adjusted required information size based on the proportion of patients with an outcome in the control group (Wetterslev 2009). We will use an alpha of 2% (Jakobsen 2014), a beta of 20%, and the diversity suggested by the trials in the meta-analysis (Jakobsen 2014).

As anticipated intervention effects for the primary outcomes in the trial sequential analysis, we will use the following relative risk reductions or increases because they seem to be the maximum realistic intervention effect estimates based on former studies, trials, and meta-analyses.

1. All-cause mortality: relative risk reduction or increase of 10% (Holmes 2004; Kastrati 2007; Roukoz 2009; Stettler 2007).
2. Serious adverse events: relative risk reduction or increase of 10%.
3. Composite event outcome (cardiovascular mortality and acute myocardial infarction): relative risk reduction or increase of 10% (Holmes 2004; Kastrati 2007; Roukoz 2009; Stone 2004; Stettler 2007).
4. Quality of life: we will use the observed SD, a clinically relevant mean difference equal to SD/2.

Secondary outcomes

We will estimate the diversity-adjusted required information size based on the proportion of participants with an outcome in the control group (Wetterslev 2009). We will use an alpha of 2.5% (Jakobsen 2014), a beta of 20%, and the diversity suggested by the trials in the meta-analysis (Jakobsen 2014).

As anticipated intervention effects for the secondary outcomes in the trial sequential analysis, we will use the following relative risk reductions or increases because they seem to be realistic intervention effect estimates based on former studies, trials, and meta-analyses as cited below.

- Angina (continuous outcome): we will use the observed SD, a clinically relevant mean difference equal to SD/2.

Exploratory outcomes

- Stent thrombosis: relative risk reduction or increase of 10%.
- Target vessel revascularisation: relative risk reduction or increase of 40% (Roukoz 2009; Stettler 2007).

As a supplementary trial sequential analysis, we will use the limit of the confidence interval closest to zero effect as the anticipated intervention effect for all trial sequential analyses (Jakobsen 2014).

Assessment of significance

We will assess our intervention effects with both random-effects meta-analyses, DerSimonian 1986, and fixed-effect meta-analyses,

Demets 1987, and 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 equal, we will use the estimate with the widest confidence interval. We have four primary outcomes and will therefore consider a P value less than 2% as significant (Jakobsen 2014). We will use the eight-step procedure to assess if the thresholds for significance are crossed or not (Jakobsen 2014).

We will present a table describing the types of serious adverse events in each trial.

'Summary of findings' tables

We will use the GRADE system to assess the quality of the body of evidence associated with each of the primary and secondary outcomes in our review (Guyatt 2008), constructing 'Summary of findings' ('SoF') tables using the GRADEpro software (www.grade.pro). The GRADE approach appraises the quality of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. The quality measure of a body of evidence considers within-study risk of bias, the directness of the evidence, heterogeneity of the data, precision of effect estimates, and risk of publication bias. We will include all studies in our analyses and conduct a sensitivity analysis with studies at low risk of bias. If we include no studies at low risk of bias studies, we will conduct the sensitivity analysis with studies at low risk of bias in all other domains than 'blinding of participants and personnel'. If the results are similar, we will base our primary 'SoF' tables and primary conclusions on the overall analysis. If they differ, we will base our primary 'SoF' and primary conclusions on studies with low risk of bias or alternatively, studies with low risk of bias in all 'Risk of bias' domains except 'blinding of participants and personnel' (Gluud 2006; Kjaergard 2001; Lundh 2012; Moher 1998; Savović 2012; Schulz 1995; Wood 2008).

Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses.

A) Type of drug-eluting stents used:

- paclitaxel-eluting stents;
- sirolimus-eluting stents;
- zotarolimus-eluting stents;
- everolimus-eluting stents;
- bioresorbable stents;
- polymer-free drug-eluting stents; and
- mixed drug-eluting stents.

B) Length of maximum follow up:

- less or equal to six months;
- between six months and 12 months;
- between one year and three years; and
- more than or equal to three years.

C) Participants with diabetes compared with participants without diabetes.

D) Participants with high risk of bleeding (as defined by the trialists) compared with participants without high risk of bleeding.

E) Age of participants:

- age 0 to 18;
- age 19 to 75; and
- age 76 or above.

F) Comparison of the effect of beta-blockers versus placebo or no intervention between trials with different clinical trial registration status:

- preregistration;
- postregistration; and
- no registration.

We will use the primary outcomes in our subgroup analyses.

We will use the formal test for subgroup interactions in Review Manager 5 (RevMan 2014).

Sensitivity analysis

To assess the potential impact of bias, we will perform a sensitivity analysis where we exclude trials with an overall high risk of bias.

As a secondary sensitivity analysis, we will only include trials with low risk of bias in all domains except 'blinding of participants and personnel', as we do not expect to find any trials at low risk of bias in this domain.

To assess the potential impact of the missing data for dichotomous outcomes, we will perform the two following analyses.

1. 'Best-worst-case' scenario: we will assume that all participants lost to follow up in the experimental group survived, had no serious adverse event, had no major cardiovascular event, had no stent thrombosis, and had no target vessel revascularisation. We will assume that they also had a beneficial event with regard to quality of life and angina, defined as the group mean plus both one and two standard deviations of the group mean (Jakobsen 2014). We will assume that all of those with missing outcomes in the control group died, had a serious adverse event/s, had a major cardiovascular event, had stent thrombosis, and had target vessel revascularisation. We will assume that they also had a harmful event with regard to quality of life and angina, defined as the group mean plus both one and two standard deviations of the group mean (Jakobsen 2014).

2. 'Worst-best-case' scenario: we will assume that all participants lost to follow up in the experimental group died, had a serious adverse event, had a major cardiovascular event, had stent thrombosis, and had target vessel revascularisation. We will assume that they also had a harmful event with regard to quality of life and angina, defined as the group mean plus both one and two standard deviations of the group mean (Jakobsen 2014). We will assume that all of those with missing outcomes in the control group control group survived, had no serious adverse

event, had no major cardiovascular event, had no stent thrombosis, and had no target vessel revascularisation. We will assume that they also had a beneficial event with regard to quality of life and angina, defined as the group mean plus both one and two standard deviations of the group mean (Jakobsen 2014).

We will present results from both scenarios.

To assess the potential impact of missing SDs for continuous outcomes, we will perform the following sensitivity analyses.

- Where SDs are missing and not possible to calculate, 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.

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- * Indicates the major publication for the study

APPENDICES

Appendix I. Preliminary MEDLINE Ovid search strategy

1. Stents/
2. stent*.tw.
3. 1 or 2
4. drug elut*.tw.
5. Sirolimus/
6. sirolimus.tw.
7. rapamycin.tw.
8. paclitaxel.tw.
9. taxol.tw.
10. exp Immunosuppressive Agents/
11. coat* stent*.tw.
12. exp Taxoids/
13. taxane*.tw.
14. qp2.tw.
15. hexanoyltaxol.tw.
16. everolimus.tw.
17. abt-578.tw.
18. Tacrolimus/
19. Dactinomycin/
20. actinomycin.tw.
21. batimastat.tw.
22. exp Dexamethasone/
23. dexamethasone.tw.
24. exp Estradiol/
25. estradiol.tw.
26. praxel.tw.
27. paxene.tw.
28. onxol.tw.
29. anzatax.tw.
30. immunosuppress*.tw.
31. prograf*.tw.
32. meractinomycin.tw.
33. cosmegen.tw.
34. dactinomycin.tw.
35. millicorten.tw.
36. maxidex.tw.
37. decaspray.tw.
38. dexpak.tw.
39. dexasone.tw.
40. oradexon.tw.
41. hexadecadrol.tw.
42. decaject.tw.
43. hexadrol.tw.
44. decameth.tw.
45. methylfluorprednisolone.tw.
46. vivelle.tw.
47. oestradiol.tw.
48. estrace.tw.

49. aerodiol.tw.
50. estraderm.tw.
51. ovocyclin.tw.
52. estramustin*.tw.
53. estracyt.tw.
54. emcyt.tw.
55. tacrolimus.tw.
56. taxoids.tw.
57. zotarolimus.tw.
58. umirolimus.tw.
59. biolimus.tw.
60. pimecrolimus.tw.
61. elidel.tw.
62. or/4-61
63. 3 and 62
64. eluting stent*.tw.
65. 63 or 64
66. exp Angioplasty, Balloon, Coronary/ or exp Percutaneous Coronary Intervention/
67. balloon angioplast*.tw.
68. (percutaneous adj6 coronary intervention*).tw.
69. PCI.tw.
70. (intervention* adj6 percutaneous coronary).tw.
71. (revascularization* adj6 percutaneous coronary).tw.
72. (angioplast* adj6 coronary).tw.
73. percutaneous coronary.tw.
74. ((transluminal or trans-luminal) adj6 coronary).tw.
75. or/66-74
76. exp Myocardial Ischemia/
77. ((myocardial or myocardium or subendocardial or transmural or cardiac or cardial or coronary or heart) adj2 (infarct* or postinfarct* or hypoxi* or anoxi* or failure* or decompensation or insufficien*)).tw.
78. (heart disease* or coronary disease* or IHD or CIHD or CHD).tw.
79. (myocardial dysfunction or angina or stenocardia).tw.
80. ((ischemi* or ischaemi*) adj2 (myocardium or myocardial or heart or coronary or cardiac or cardial or subendocardial or cardiomyopath*)).tw.
81. ((artery occlusion* or artery disease* or arterioscleros* or atheroscleros*) adj2 coronary).tw.
82. or/76-81
83. Acute Coronary Syndrome/
84. exp Myocardial Infarction/
85. exp Coronary Thrombosis/
86. coronary thrombosis.tw.
87. acute coronary.tw.
88. exp Angina, Unstable/
89. myocardial infarct*. tw.
90. heart infarct*.tw.
91. acs.tw.
92. ami.tw.
93. (coronary adj3 syndrome*).tw.
94. acute angina.tw.
95. (unstable adj3 angina).tw.
96. unstable coronary.tw.
97. or/83-96
98. randomized controlled trial.pt.
99. controlled clinical trial.pt.

100. randomized.ab.
101. placebo.ab.
102. drug therapy.fs.
103. randomly.ab.
104. trial.ab.
105. groups.ab.
106. or/98-105
107. exp animals/ not humans.sh.
108. 106 not 107
109. 65 or 75
110. 82 or 97
111. 108 and 109 and 110

Appendix 2. Details on assessment of risk of bias

We will classify each trial according to the domains below for each outcome result.

Random sequence generation

- Low risk: if sequence generation is achieved using a computer random number generator or a random numbers table. We will also consider drawing lots, tossing a coin, shuffling cards, and throwing dice as adequate if an independent adjudicator performs these methods.
- Unclear risk: if there is insufficient information to permit judgement of 'low risk' or 'high risk'.
- High risk: if the allocation sequence is not randomised or only quasi-randomised.

Allocation sequence concealment

- Low risk: if the allocation of participants results from a central independent unit, on-site locked computer, identical-looking numbered sealed opaque envelopes, drug bottles, or containers prepared by an independent investigator. There must be no risk of the investigator knowing the sequence.
- Unclear risk: if there is insufficient information to permit judgement of 'low risk' or 'high risk'.
- High risk: if the allocation sequence is known to the investigators who assigned participants.

Blinding of participants and personnel

- Low risk: if the participants and the personnel are blinded to treatment allocation and this is described.
- Unclear risk: if there is insufficient information to permit judgement of 'low risk' or 'high risk'.
- High risk: if blinding of participants and personnel is not performed.

Blinding of outcome assessment

- Low risk: if the trial investigators performing the outcome assessments, analyses, and calculations are blinded to the intervention.
- Unclear risk: if there is insufficient information to permit judgement of 'low risk' or 'high risk'.
- High risk: if blinding of outcome assessment is not performed.

Incomplete outcome data

- Low risk: (1) there are no dropouts or withdrawals for all outcomes, or (2) the numbers and reasons for the withdrawals and dropouts for all outcomes are clearly stated, can be described as being similar in both groups, and the trial handles missing data appropriately in intention-to-treat analysis using proper methodology, e.g. multiple imputations. As a general rule, we will judge the trial as at low risk of bias due to incomplete outcome data if the number of dropouts is less than five per cent. However, the five per cent cut off is not definitive.
- Unclear risk: if there is insufficient information to permit judgement of 'low risk' or 'high risk'.

- High risk: the pattern of dropouts can be described as being different in the two intervention groups or the trial uses improper methodology in dealing with the missing data, e.g. last observation carried forward.

Selective outcome reporting

- Low risk: a protocol is published before or at the time the trial begins and the outcomes called for in the protocol are reported on. If there is no protocol or the protocol is published after the trial begins, reporting of the primary outcomes will grant the trial a grade of low risk of bias.
- Unclear risk: if there is no protocol and the primary outcomes are not reported on.
- High risk: if the outcomes that are called on in a protocol are not reported on.

Other bias risk

- Low risk of bias: the trial appears to be free of other components (for example, academic bias or for-profit bias) that could put it at risk of bias.
- Unclear risk of bias: the trial may or may not be free of other components that could put it at risk of bias.
- High risk of bias: there are other factors in the trial that could put it at risk of bias (for example, authors have conducted trials on the same topic, for-profit bias, etc).

Overall risk of bias

- Low risk of bias: we will classify the outcome as overall 'low' risk of bias only if we classify all of the bias domains described in the aforementioned text as low risk of bias.
- High risk of bias: we will classify the outcome result as 'high' risk of bias if we classify any of the bias risk domains described in the aforementioned text as 'unclear' or 'high' risk of bias.

We will grade each potential source of bias as high, low, or unclear and provide a quote from the study report together with a justification for our judgment in the 'Risk of bias' table. We will summarise the 'Risk of bias' judgements across different studies for each of the domains listed. Where information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the 'Risk of bias' table.

When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

Appendix 3. Glossary

Ischaemic: reduced blood supply to an organ.

Angina pectoris: medical term for chest pain or discomfort due to ischaemic heart disease.

ST: ST is short for the ST-segment, which is a specific segment of the printout when recording an electrocardiogram. It is used to differentiate between ST and non-ST myocardial infarction.

Non-ST-elevation myocardial infarction: a kind of heart attack which does not show ST-segment elevation on an electrocardiogram.

ST-elevation myocardial infarction: a kind of heart attack which shows ST-segment elevation on an electrocardiogram.

Atherosclerosis: arterial wall-thickening due to build up of plaque.

Stent thrombosis: blockage of the stent by a blood clot.

Angiography: visualisation of the blood vessels typically by injection of contrast and using x-ray.

Myocardium: the muscle tissue of the heart.

Myocardial necrosis: death of the muscle tissue of the heart.

Restenosis: narrowing of a previously narrowed blood vessel due to a blood clot.

Biolimus: the trade name of the drug Umirolimus. The mechanism of action is believed to be anti proliferation of smooth muscle cells.

Myocardial ischaemia: reduced blood supply to the heart.

Cardiomyocyte necrosis: undesirable death of the cells of the heart.

Atheroembolism: embolism originating from an atherosclerotic plaque.

Retroperitoneal bleeding: bleeding behind the peritoneum, a membrane lining the abdominal cavity.

Luminal stenosis: narrowing of the lumen of the vessel.

Neointimal: scar tissue formed in a vessel after an injury.

Revascularisation: removing the cause of the stenosed blood vessel, allowing blood flow to resume.
Sirolimus stent: a stent using the sirolimus drug, a drug used in stents with the aim of reducing restenosis.
Paclitaxel stent: a stent using the paclitaxel drug, a drug used in stents with the aim of reducing restenosis.
Bifurcation: when a blood vessel splits into two different blood vessels.
Saphenous vein grafts: when performing bypass surgery, one may use the saphenous vein (located in the leg) to bypass the occluded vessel, ultimately reestablishing heart flow.
Bioresorbable stents: stents that are absorbed after initial placement with the intent of reducing restenosis.
Everolimus: a drug used in stents with the aim of reducing restenosis.
Zotarolimus: a drug used in stents with the aim of reducing restenosis.
Paclitaxel: a drug used in stents with the aim of reducing restenosis.
Polymer-free drug-eluting stents: a stent coated with a drug with the aim of reducing restenosis, but without the polymer coating that normally binds the drug to the stent.
Ischaemic cardiomyopathy: a disease of the heart caused by the narrowing of the coronary arteries which supply blood to the heart.
Balloon angioplasty: using a balloon to open a narrowed vessel.
Re-endothelialisation: regrowth of endothelium after injury.

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Emil E Nielsen (EEN) conceived and revised the protocol.
Joshua Feinberg (JF) conceived and revised the protocol.
Janette Greenhalgh (JG) commented on the protocol.
Juliet Hounscome (JH) commented on the protocol.
Naqash J. Sethi (NJS) commented on the protocol.
Sanam Safi (SS) commented on the protocol.
Christian Gluud (CG) provided advice and revised the protocol.
Janus C Jakobsen (JCJ) conceived, designed and drafted the protocol.
All authors agreed on the final protocol version.

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, on any subsidy derived from any source that may have or be perceived to have an interest in the outcomes of the review.

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