Study Design

Percutaneous Coronary Interventional Strategies for the Treatment of Coronary In-Stent Restenosis: Systematic Review and Network Meta-analysis

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This is the protocol for a systematic review and there is no abstract. We aim to conduct a systematic review and network meta-analysis of randomized controlled trials (RCTs) that compare different percutaneous invasive strategies for the treatment of any type of coronary in-stent restenosis (ISR). To create this protocol we used the proposed template for network meta-analyses that is available on the following website mtm.uoi.gr.
Background

Description of the condition

Percutaneous coronary interventions (PCI) are routinely performed with the use of bare metal (BMS) or drug eluting stents (DES) in a broad spectrum of clinical and anatomic settings. Stent design has continuously improved through technological advances over the last two decades, with the aim to optimize clinical and angiographic outcomes. Introduced in 2002, DES represented a paradigm shift in PCI primarily by mitigating the risk of in-stent restenosis (ISR), defined as a recurrent diameter stenosis >50% within the stented segment or its edges (5-mm proximal or distal segments adjacent to the stent), which has been the major limitation of BMS.

Early-generation DES have been largely replaced by new-generation DES, which have further improved the safety and efficacy of PCI. However, ISR requiring repeat revascularization is still observed in 5-10% of patients undergoing PCI with DES and in 15-30% of patients undergoing PCI with BMS. Although ISR reaches a peak during the first year after stenting, late restenosis has been described for both DES and BMS. Accumulating evidence suggests important differences not only in ISR frequency but also pattern of ISR between BMS and DES. Of note, the risk of recurrent ISR remains high and various treatments options including balloon angioplasty (BA), BMS, vascular brachytherapy (VBT), DES, and drug-coated balloons (DCB) have been applied. However, to date the optimal treatment of ISR has not been determined and it remains unclear whether there are differences in terms of treatment choice between BMS- and DES-ISR.

Description of the interventions

Numerous treatment strategies have been investigated, including BA, rotablation, VBT, BMS, DES with different antiproliferative drugs, and DCB. All of these percutaneous catheter-based interventions aim to restore coronary blood flow by effectively treating in-stent neointimal hyperplasia and preventing and recurrent restenosis.

BA refers to the intracoronary dilatation with a balloon within the diseased coronary segment. Rotational atherectomy (rotablation) is a debulking technique whereby a diamond tipped device spins at high revolutions to remove atheroma or tissue. VBT consists of the local application of an intracoronary ionizing radiation source at the site of the diseased coronary
segment. BMS are metallic prostheses which are implanted within the diseased coronary segment. DES are metallic prostheses which – beyond providing scaffolding properties – locally release antiproliferative agents over time. Finally, with DCB interventions, a balloon coated with an antiproliferative agent dilates a coronary ISR lesion and the released drug is retained in the treated tissue.

How the interventions might work
The interventions work by initially restoring flow with mechanical means which can be followed by interventions to prevent recurrent neointimal hyperplasia and recurrent restenosis. This can be achieved with the use of antiproliferative drugs in stents or dilatation balloons, or local radiation therapy. Restoration of coronary flow and prevention of restenosis may reduce symptoms and incidence of adverse cardiovascular outcomes (such as myocardial infarction) and ultimately prolong survival.

Why it is important to do this review
Although the incidence of ISR has declined with the systematic use of DES, ISR still occurs in up to 10% of patients treated with new generation DES within 4 years of the intervention.(9) Moreover, patients with ISR have a high risk of recurrent restenosis after different interventions.(18,19) So far, randomized trials have directly compared several of the available percutaneous catheter-based interventions for the treatment of ISR. However, the absence of head-to-head trials for most of the treatments and the limited number of patients and trials leave considerable uncertainty for decision-making and the optimal percutaneous treatment strategy for patients presenting with ISR is still a matter of debate.(18)

OBJECTIVES
We aim to systematically review the literature and quantitatively synthesize currently available evidence in order to compare directly and indirectly clinical and angiographic outcomes of different percutaneous catheter-based coronary interventional strategies for the treatment of patients with any type of coronary ISR after BMS or DES implantation. We aim to create a clinically meaningful hierarchy of the effectiveness of available invasive strategies.
Methods

Criteria for considering studies for this review

Types of studies
Randomized controlled trials (RCTs) comparing different invasive strategies for the treatment of coronary ISR will be identified through a broad systematic literature search. We will include trials that investigated any type of PCI strategy under different clinical settings for the treatment of ISR. Trials with 2 or more arms of interventions irrespective of the type of ISR (BMS or DES related) will be eligible. Trials with 2 or more arms for which a subset of interventions satisfy the inclusion criteria will be kept in the analysis after having discarded those arms that do not satisfy inclusion criteria. No language or year restrictions will be applied. From our systematic review, we will exclude studies that allowed a mixture of interventions of interest in one study arm (i.e., balloon angioplasty, rotablation, or stenting); and studies that were not completed at the time of our search (October 2014).

Types of patients included
Eligible studies will include patients with any type of coronary ISR (following BMS or DES implantation) that present with stable coronary artery disease (CAD) or an acute coronary syndrome (ACS) and receive a percutaneous invasive strategy as treatment.

Types of interventions
We will consider trials that compare two or more of the following percutaneous invasive strategies for the treatment of coronary ISR after BMS or DES implantation: BA, VBT, BMS, as well as DES and DCB with different antiproliferative drugs. We will not consider studies that examined cutting balloon or laser atherectomy as the only interventions in a study arm since these interventions are exceedingly rare as single therapies. All possible comparisons are illustrated in the network plots in Figure 1A and 1B. Nodes refer to interventions and edges between nodes refer to the fact that there are studies directly comparing the interventions defined by the nodes. We will include any type of ISR (BMS- and DES-ISR) in the same analysis, while analyses for BMS- and DES-ISR will be also performed separately. For the primary and any additional analyses we will consider DES separately according to the type of antiproliferative agent but we will also present analyses grouping the different DES types together. In case that other than the pre-specified percutaneous coronary interventions will be identified through our
search and deemed eligible, these will be also considered and included in our analysis. We are mainly interested in the following two interventions of different types of DES versus DCB for the treatment of ISR. We will also include supplementary interventions in the network (i.e. VBT, rotablation) to increase the amount of available (indirect) information in the analysis.(20)

**Types of outcome measures**

As most of the clinical trials have used primary angiographic endpoints for the assessment of the efficacy of ISR therapies, percent diameter stenosis was chosen as the primary endpoint in the present study to provide sufficient precision and to arrive at a conclusive answer. It is known that currently applied interventions for ISR have little effect on hard clinical outcomes, and most trials have been underpowered to detect a difference for such outcomes. Percent diameter stenosis is a most sensitive endpoint for the evaluation of angiographic effectiveness as compared to binary restenosis, which is included as a secondary endpoint in our analysis.

More specifically, we will estimate the relative ranking of the competing interventions according to the following outcomes:

**Primary outcome:**

- Percent diameter stenosis (% DS) at follow-up.

**Secondary outcomes:**

- Binary restenosis (diameter stenosis of 50% or greater at follow-up angiography on the basis of the “in-segment” analysis)
- Target lesion revascularization (TLR)
- All-cause mortality
- Myocardial infarction (MI)

Target-vessel MI and clinically-driven TLR will be extracted whenever available. Finally, when TLR is not reported, we will extract target vessel revascularization (TVR) and consider it equivalent to TLR.

**Search methods for identification of studies**

Trials comparing any eligible invasive strategy for the treatment of coronary ISR will be identified through a systematic literature search of the following databases: PubMed, EMBASE, and Cochrane Library Central Register of Controlled Trials (CENTRAL); while the
ClinicalTrials.gov and Current Controlled Trials (controlled-trials.com) registries will be additionally scrutinized to ensure identification of all published trials. A modified search algorithm will be developed and adapted for each database with a combination of relevant text terms and key words (as provided in Appendix). Potentially eligible trials that have been only presented at conferences and of which a full manuscript is not yet available at the time of our search, will be considered eligible and the principal investigators will be contacted to participate in this meta-analysis by providing the required data. We will scrutinize for additional eligible studies the reference lists of the retrieved publications, and relevant meta-analyses in the field. No language, year of publication, or sample size restrictions will be applied.

Data collection and analysis

Selection of studies

The aforementioned search strategy will be performed for each database separately and search results will be entered in EROS (Early Review Organizing Software) (www.eros-systematic-review.org), a web-based software designed specifically for the first stages of a systematic review. Using this software, 2 investigators will scrutinize all the entries for eligibility in title and abstract level.

Data extraction and management

Two investigators will perform study identification, data abstraction, and risk of bias assessment independently. Any discrepancies will be resolved by consensus and arbitration by a third investigator.

We will review the main report, subsequent publications of each trial and any supplementary material of the included trials and extract the following data:

- **study characteristics**: first author, study acronym, year of publication, interventions of interest, study arms, number of patients in each arm of randomisation, and the sponsor of the study.
- **patient data**: age, gender, comorbidities, and clinical indication for coronary intervention (stable angina or ACS).
- **lesion characteristics**: target vessel, bifurcations, ostial lesions, total occlusion, and index stent type of restenosis (BMS- or DES-ISR).
- **quantitative angiographic measurements** (in-segment and in-stent): before procedure [lesion length (mm), reference vessel diameter (RVD), minimal luminal diameter (MLD)],
and % of diameter stenosis (%DS); post-procedure [MLD and %DS]; and at available angiographic follow-up [late luminal loss (LLL), MLD, %DS, and binary restenosis]. The pre-specified time of angiographic and clinical follow-up will be recorded for each trial, while for the clinical endpoints of interest we will consider the longest available follow-up period.

- *clinical outcomes*: the clinical outcomes of interest will be extracted.

**Outcome data**

From each eligible trial we will extract the number of individuals randomized to each arm. We will also extract any summary metric (mean (standard deviation) or median (interquartile range)) that is reported for each arm of intervention for the main angiographic outcome of interest at follow-up (percent diameter stenosis). For the secondary outcomes of interest (overall mortality, myocardial infarction, target lesion revascularisation, binary restenosis), the respective number of participants in each arm of interventions and the number of participants with one of the events of interest, will be also recorded.

**Data on potential effect modifiers**

We will report separate effect estimates for the primary outcome of interest only and the main network (including any type of ISR and different types of DES separately (**Figure 1B**)) with respect to the following potential effect modifiers:

1. Year of study publication.
2. Sample size of the trial.
3. Clinical indication for coronary intervention (stable angina or ACS)
4. Index stent type of restenosis (BMS- or DES-ISR)

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

We will investigate study limitations using the Cochrane risk of bias tool to evaluate the internal validity and conduct of included studies. Two authors will independently assess risk of bias for each included study using the risk of bias assessment tool.(21) We will resolve any disagreements with discussion and involvement of a third author. Each item will be described as being at low, high or unclear risk of bias. The areas that will be evaluated are:

- *random sequence generation*: Was there adequate sequence generation (selection bias)?
- *allocation concealment*: Was allocation adequately concealed (selection bias)?
- **blinding**: Was knowledge of the allocated intervention adequately prevented during the study (detection bias)?
  - participants and personnel
  - outcome assessors
- **incomplete outcome data**: Were incomplete outcome data adequately addressed (attrition bias)?
- **selective outcome reporting**: Are reports of the study free of possible selective outcome reporting (reporting bias)?

We will evaluate the aforementioned items not only in each study but also in each pairwise comparison.(22) We will classify each piece of direct evidence in the network as low, moderate, or high risk of bias. We will illustrate these assessments in the network plot for the primary outcome with colored edges according to the risk of bias. We will also produce the contribution matrix which gives the percentage contribution of each direct estimate to the network meta-analysis estimates.(23) This will help to delineate the contribution of direct and indirect evidence to each network meta-analysis estimate.

**Measures of treatment effect**

**Relative treatment effects**

First, we will conduct a pair-wise meta-analysis by synthesizing at least two studies that compare the same interventions using a random-effects model (24) in STATA 12. A random-effects model assumes that different studies assessed different yet related treatment effects. We will estimate the pairwise relative treatment effects of the competing interventions using standardized mean differences for the primary outcome (percent diameter stenosis). We will estimate odds ratios (OR) for dichotomous outcomes. We will produce summary results for all outcomes and give 95% confidence intervals. We will use restricted maximum likelihood to estimate heterogeneity. If we have skewed data, we will use the methods presented in to pool results.(25)

**Relative treatment ranking**

We will estimate the ranking probabilities for all treatments of being at each possible rank for each intervention using the mvmeta command in STATA.(26) We will obtain a hierarchy of the competing interventions using rankograms.(27) We will obtain a treatment hierarchy using the
surface under the cumulative ranking curve (SUCRA) and mean ranks.(28) We will produce the relevant plots using the suite of STATA commands by Chaimani et al.(28)

**Unit of analysis issues**

We expect that some studies will not report mean values and standard deviations (SD) but would report certain quantiles instead. If a study reports the median, minimum, and maximum values, we will use the methodology from (29) to estimate the respective mean and SD of the study population. We will include also those studies that report the median and the interquartile range (IQR) assuming that data are normally distributed and the standard deviation would be $s=\text{IQR}/1.35$ while the mean would be equal to the median. However, use of median and IQR is usually an indicator that data are not normal (Cochrane handbook chapter 7, available from www.cochrane-handbook.org).(30) We will repeat the analysis excluding these studies as a sensitivity analysis for the main network.

**Studies with multiple treatment groups**

We will take into account the correlations between effect sizes measured within a single trial.

**Assessment of reporting biases**

For each pairwise comparison that includes at least 10 trials we will draw funnel plots and compute Egger’s test to test visually and statistically for small-study effects. For these comparisons we will draw contour-enhanced funnel plots to disentangle small study effects from publication bias.(31) We will also draw a comparison-adjusted funnel plot to explore for small study effects assuming that small study effects favour the novel treatment.(28,32) In case publication bias is suspected (by funnel plot asymmetry) and enough studies are included in the synthesis, we will also apply a selection model to explore if probability of publication is associated with magnitude of effect.(33)

**Dealing with missing data**

Missing data and dropouts will be assessed in all included studies. Details and characteristics of dropouts will be investigated and reported. We will explore if reasons for missing data are related to the actual outcome and if missing data are balanced in the intervention arms. We will extract if authors accounted for missing data and which method they used to do so. If the authors have used naïve imputation methods (best/worst case scenarios, mean imputation), we will
consider the study to be at high risk of bias whereas if they have used methods that take into account the fact that data have been imputed using statistical methods that take uncertainty in the imputed values into account (e.g. multiple imputation) we will consider the study to be at low risk of bias.

Assessment of clinical and methodological heterogeneity within treatment comparisons

There are three different types of heterogeneity, namely clinical, methodological and statistical heterogeneity (Cochrane handbook chapter 9).(34) To evaluate the presence of clinical heterogeneity we will generate descriptive statistics for trial and study population characteristics across all eligible trials that compare each pair of interventions. We will assess the presence of clinical heterogeneity within each pairwise comparison by comparing these characteristics. We will assess methodological heterogeneity by evaluating the design of the studies. Statistical heterogeneity refers to differences in true effect sizes.

Assessment of transitivity across treatment comparisons

Although participants are randomized within a study, treatment strategy comparisons are not randomized across studies. We assume that an intervention is missing from a trial for reasons not associated with its relative effectiveness and any patient that meets the inclusion criteria is, in principle, equally likely to be randomized to any of the eligible interventions.(35,36) This is a key assumption in network meta-analysis called transitivity. It states that we can genuinely learn about the relative effectiveness between two treatments via an indirect route. If for example the treatments “rotablation” and “BMS” are both directly compared to “BA”, then we can assess “rotablation” vs. “BMS” indirectly through “BA”. This assumption entails that “BA” is similar when it appears in “BA” vs. “rotablation” and “BA” vs. “BMS” trials and also that the distribution of effect modifiers is similar in “BA” vs. “rotablation” and “BA” vs. “BMS” trials. This will be extended in all treatment comparisons. We will assess the assumption of transitivity by comparing the distribution of the potential effect modifiers across the different pairwise comparisons. We suspect that year of study publication, sample size of the trial, clinical indication for coronary intervention (stable angina or ACS), and index stent type of restenosis (BMS- or DES-ISR) can be effect modifiers and we will explore if the distribution of these differs across treatment comparisons. We assume that the most common treatment (BA) that would be probably used for indirect comparisons is similar when it appears in different trials.
The assessment of statistical heterogeneity in the entire network will be based on the magnitude of the heterogeneity variance parameter ($\tau^2$) estimated from the network meta-analysis models. We will also estimate a total I-squared value for heterogeneity in the network as described elsewhere.(37)

**Data synthesis**

**Methods for direct treatment comparisons**

We will conduct pairwise meta-analyses in Stata by assuming a random effects model (DerSimonian1986) for every treatment comparison with at least two studies.

**Methods for indirect and mixed comparisons**

We will use network meta-analysis to compare different percutaneous coronary interventions for coronary in-stent restenosis. Network meta-analysis synthesizes both direct and indirect evidence, estimates the relative effectiveness between pair of interventions even if these interventions have never been compared directly in RCTs and provides a ranking of interventions.(38-41) For a comparison, for example BA vs. rotablation, direct evidence is provided by trials directly comparing these two interventions whereas indirect evidence is provided if there is an indirect path linking these two treatments (e.g., if both BA and rotablation are compared to BMS).(42) By combining direct and indirect evidence we obtain estimates with increased precision. We will perform network meta-analysis in Stata using the mvmeta command (37,43) and self-programmed Stata routines available at http://www.mtm.uoi.gr/index.php/stata-routines-for-network-meta-analysis.(28) We will use the restricted maximum likelihood method to estimate heterogeneity assuming a common estimate for the heterogeneity variance across the different comparisons.

**Assessment of statistical heterogeneity**

**Assumptions when estimating heterogeneity**

In standard pairwise meta-analyses, we assume different heterogeneity estimates for different comparisons. In network meta-analysis we assume that heterogeneity is the same for all treatment comparisons. We estimate heterogeneity using restricted maximum likelihood both in pairwise and network meta-analysis.

**Measures and tests for heterogeneity**
We will assess statistical heterogeneity visually by inspecting the forest plot for each pairwise comparison. We will also compute the $I^2$ and its 95% confidence interval that shows the percentage of variation that is not attributed to random error.

The assessment of statistical heterogeneity in the entire network will be based on the magnitude of the heterogeneity variance parameter ($\tau^2$) estimated from the network meta-analysis models. For dichotomous outcomes magnitude of heterogeneity variance will be compared with the empirical distribution as derived by Turner. We will also estimate a total $I^2$ value for heterogeneity as described elsewhere.

**Assessment of statistical inconsistency**

**Local approaches for evaluating inconsistency**

To evaluate the presence of inconsistency locally we will use the loop-specific approach.(42) This method evaluates the consistency assumption in each closed loop of the network separately as the difference between direct and indirect estimates for a specific comparison in the loop (inconsistency factor). Then, the magnitude of the inconsistency factors and their 95% CIs can be used to infer about the presence of inconsistency in each loop. We will assume a common heterogeneity estimate within each loop.(44) We will present the results of this approach graphically in a forest plot using the *iplot* command in Stata.(28) Dias et al. suggested a method which separates evidence on a particular comparison into ‘direct’ and ‘indirect’. (45) This ‘node-splitting’ method excludes one direct comparison at a time and estimates the indirect treatment effect for the excluded comparison. The direct and indirect evidence is subsequently compared to see if direct and indirect evidence is in agreement.

**Global approaches for evaluating inconsistency**

To check the assumption of consistency in the entire network we will use the ‘design-by-treatment’ model as described by Higgins and colleagues.(46) This method accounts for different source of inconsistency that can occur when studies with different designs (two-arm trials vs. three-arm trials) give different results as well as disagreement between direct and indirect evidence. Using this approach we will infer about the presence of inconsistency from any source in the entire network based on a chi-square test. The design-by-treatment model will be performed in Stata using the mvmeta command.

Inconsistency and heterogeneity are interweaved; to distinguish between these two sources of variability we will employ the I-squared for inconsistency (47) that measures the percentage
of variability that cannot be attributed to random error or heterogeneity (within comparison variability).

**Investigation of heterogeneity and inconsistency**
If we find important heterogeneity or/and inconsistency, we will explore the possible sources. If sufficient studies are available, we will perform meta-regression or subgroup analyses for the primary outcome by using the following effect modifiers as possible sources of inconsistency and or heterogeneity: (i) year of study publication; (ii) sample size of the trial; (iii) clinical indication for coronary intervention (stable angina or ACS); (iv) index stent type of restenosis (BMS- or DES-ISR).

**Sensitivity analyses**
For the primary angiographic outcome, we will repeat the analysis including those studies that report only the median and the IQR assuming that data are normally distributed. For the primary outcome and the main network we will repeat the analysis excluding those studies that are at high or unclear risk of bias.
**Figures**

**Figure 1:** Network plots illustrating all possible comparisons of the available interventions for the treatment of any type of ISR. In panel A, any type of DES has been included in the same group, while in panel B different types of DES have been included separately.
### Appendices

**Appendix 1: Search algorithms.**

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<th>Search algorithm</th>
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References


