


BMJ Open Percutaneous coronary intervention in calcified stenoses: a protocol for a systematic review with meta-analysis, trial sequential analysis and network meta-analysis

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ABSTRACT

Introduction Severely calcified coronary stenoses are difficult to treat with percutaneous coronary interventions. The presence of severe calcifications complicates lesion preparation, advancement of stents and achievement of full stent expansion. Intervention in these lesions is associated with an increased risk of complications and procedural failure compared with treatment of less calcified lesions. Due to the high burden of comorbidity, patients with severely calcified lesions are often excluded from interventional trials, and there is little evidence on how to treat these patients.

Methods and analysis We will conduct a systematic review of randomised trials enrolling patients with calcified coronary artery disease undergoing percutaneous coronary intervention. We will investigate any percutaneous treatment option including any lesion preparation, stenting or postdilatation technique. We will search The Cochrane Central Register of Controlled Trials, Medical Literature Analysis and Retrieval System Online, Latin American and Caribbean Health Sciences Literature, Science Citation Index Expanded, and Excerpta Medica database for studies from inception to 31 October 2022. The coprimary outcome is all-cause mortality and serious adverse events. If appropriate, we will conduct meta-analysis, trial sequential analysis and network meta-analysis.

Ethics and dissemination No ethics approval is required for this study. The results will be published in a peer-reviewed journal in this field.

PROSPERO registration number CRD42021226034.

INTRODUCTION

Ischaemic heart disease

Ischaemic heart disease is the most common cause of death globally and accounts for 1.8 million European deaths annually.^{1 2} Ischaemic heart disease is characterised by build-up of lipid-containing plaques, chronic inflammation and hardening in the walls of coronary arteries.³ This process, that is, atherosclerosis, is associated with traditional cardiovascular risk factors such as diabetes mellitus, hypertension and

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Several percutaneous treatment options exist to treat calcified coronary lesions. However, there is no consensus regarding the optimal choice of treatment strategy. We aim to assess the beneficial and harmful effects of all available treatment options.
- ⇒ This protocol is based on the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines and the Cochrane Handbook for Systematic Reviews of Interventions.
- ⇒ We plan to conduct meta-analysis, trial sequential analysis and network meta-analysis.
- ⇒ We will assess all available interventions which may require many analyses and cause problems with multiplicity.

hypercholesterolaemia. Atherosclerosis may lead to reduced coronary blood flow due to narrowed vessels (stenosis), inadequate oxygen supply to the myocardium (ischaemia) and heart attack (infarction). Affected individuals risk loss of cardiac function, reduction in quality of life and ultimately death.³

Calcified ischaemic heart disease

Coronary calcification is a feature of late-stage atherosclerosis. Atherosclerosis is a chronic and degenerative process that involves apoptosis of foam cells and smooth muscle cells in the arterial wall. Early deposition of hydroxyapatite crystals, primarily in the intimal layer (microcalcification), may lead to the formation of calcified sheets and nodules that complicate coronary interventions.⁴ Coronary calcification is associated with increasing age and presence and severity of diabetes mellitus and chronic kidney disease, among other conditions.⁴ As the number of elderly individuals is expected to increase, so will the number of elderly individuals living with calcified ischaemic heart disease. The presence of

moderate-to-severe calcifications is a risk factor for future cardiovascular events and death.^{5 6}

The presence and severity of coronary calcification can be identified non-invasively by cardiac CT or invasively by coronary angiography, optical coherence tomography or intravascular ultrasound.⁴ The degree of coronary artery calcification correlates with the severity of obstructive coronary artery disease.⁴ Moderately to severely calcified coronary stenoses are present in 17%–34% of patients with ischaemic heart disease undergoing percutaneous coronary intervention.^{4 7 8} Patients with severe calcifications often have multivessel disease, greater anatomical complexity (greater SYNTAX score and number of American College of Cardiology/American Heart Association type C lesions), and a lower preprocedural flow through the lesion compared with patients with no or only mild calcifications.^{9–11}

Coronary angiography and percutaneous coronary intervention

Coronary angiography is an invasive procedure that allows visualisation and treatment of coronary stenoses.¹² Following local anaesthesia in the wrist or groin, a sheath is inserted into a peripheral artery.¹² Through the sheath, a catheter is advanced to the coronary ostia. By injecting a contrast medium and using X-ray fluoroscopy, an angiogram is produced that visualises the coronary arteries, stenoses and calcifications (radiopacities in the vessel wall).^{4 12}

Ischaemic heart disease can be treated medically primarily by reducing the myocardial demand for oxygen or invasively by dilating (percutaneous coronary intervention) or bypassing (coronary artery bypass grafting) the affected vessels. Percutaneous coronary intervention with implantation of drug-eluting stents is the most frequently used method of coronary revascularisation.

Percutaneous coronary intervention is usually carried out in three steps. First, after passing a thin and flexible wire through the catheter into the coronary artery, a balloon is inserted over the wire and inflated in the lesion (the process of lesion preparation or predilatation).¹² The purpose of lesion preparation is to prepare the lesion for placement and expansion of a sufficiently sized stent by causing controlled dissection and disruption of the lesion. Second, a stent mounted on a balloon is inserted over the wire and expanded in the lesion to prevent recoil, acute blockage and future stenosis (stenting). Third, the stent may be further expanded with additional inflations to ensure optimal stent expansion to reduce the risk of restenosis (postdilatation).¹²

Percutaneous coronary intervention in calcified lesions

Calcifications complicate all aspects of interventional treatment and constitute one of the most common types of complex lesions in patients undergoing percutaneous coronary intervention.⁹ Percutaneous intervention in calcified lesions has a higher risk of short-term and long-term complications (coronary perforation, in-stent

thrombosis, restenosis and death) and a lower procedural success rate (eg, incomplete revascularisation and suboptimal stent expansion) compared with treatment of non-calcified lesions.¹¹

Lesion preparation in severely calcified lesions with conventional techniques is often ineffective. It can be difficult to advance catheters, balloons or stents through segments of rigid calcifications with irregular geometry.¹³ Expansion of a balloon will often be directed towards the most compliant part of the vessel wall which may be non-calcified. Furthermore, advancing a stent through a calcified segment may cause damage to the stent surface and reduce the drug-eluting capability.¹⁴ Consequently, suboptimal lesion preparation and underexpansion of stents are predictors of stent thrombosis and long-term restenosis.^{15 16} Lastly, the use of high inflation pressures sometimes necessary for calcified lesions may cause vessel rupture.¹⁷

In addition to conventional techniques, several specialised techniques are available to optimise lesion preparation and stent expansion in calcified stenoses. (1) Rotational atherectomy uses a catheter with a rotating diamond-burr, which is advanced through the calcified segment to pulverise the superficial calcification.¹⁸ (2) Orbital atherectomy uses a catheter with an eccentrically mounted diamond-coated crown that rotates and pulverises the superficial calcification.¹⁸ Potential complications of rotational and orbital atherectomy include coronary perforation, dissection and embolisation of debris with risks of myocardial infarction or slow-flow/no-reflow phenomena.¹⁸ Atherectomy is affected by guidewire bias, which limits optimal preparation of the calcification.¹⁹ (3) Cutting or scoring balloons (modified balloons) have superficially mounted blades or wires, respectively, that create indents and more controlled dissections in the plaque and calcification during inflation.¹⁸ By creating indents and dissections, the balloons expand in a focused location at less inflation pressure at a lower risk of asymmetric expansion.²⁰ A limitation of modified balloons is the restricted flexibility of the balloons through calcified segments. (4) Non-compliant high-pressure balloons are double layered and may deliver the very high pressure required for dilatation of severely calcified lesions, but at a risk of rupture due to mechanical trauma.¹⁸ (5) Excimer laser is a technique that delivers gases and generates pulses of ultraviolet light that lead to ablation of the calcification. In severely calcified lesions, this technique has been shown effective in otherwise uncrossable lesions, but at a risk of perforation and slow-flow/no-reflow phenomena.²¹ (6) Balloon lithoplasty is a technique that delivers high-frequency pressure waves from a balloon inflated in the lesion at low pressure.¹⁹ The pressure waves propagate through the vessel wall to fracture the calcification. In severely calcified lesions, this technique has been shown effective and safe.¹⁹

No stent has been specifically designed for placement in calcified lesions. However, preliminary studies have indicated that second-generation drug-eluting stents are

superior to first-generation drug-eluting stents in calcified lesions.¹⁰

Why is it important to do this review?

A wide range of treatment techniques are available to treat severely calcified lesions, but there is no consensus regarding the optimal choice in terms of efficacy or safety. Patients with calcified lesions compared with patients without calcifications are more often elderly or have complex lesions, diabetes mellitus or chronic kidney disease.⁴ For these reasons, patients with calcified lesions are often excluded from controlled studies and there is little evidence on how to treat these patients. Treatment algorithms have been proposed, but they have not been validated nor implemented internationally.^{18 22 23}

Several reviews on percutaneous coronary intervention techniques on calcified lesions have been published. These reviews are limited due to their use of non-systematic searches, inclusion of non-randomised studies, non-adherence to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines or focus on only a few selected treatment options (table 1). A preliminary search identified four randomised trials on calcified lesions that compare the use of atherectomy versus no atherectomy,²⁴ atherectomy versus cutting or scoring balloons,²⁵ non-compliant high-pressure balloons versus scoring balloons²⁶ and paclitaxel-eluting stent versus bare-metal stent.⁷

Effective lesion preparation and stenting are considered vital predictors of short-term and long-term outcomes following percutaneous coronary intervention. So far, no systematic review has comprehensively examined all available percutaneous treatment options in patients with calcified coronary stenoses.

Objective

The objective of this review is to assess the beneficial and harmful effects of all percutaneous treatment options to treat calcified coronary lesions.

METHODS AND ANALYSES

The protocol is registered at PROSPERO (registration CRD42021226034) and the methodology is based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis-Protocols statement²⁷ and the Cochrane Handbook of Systematic Review of Interventions.²⁸ We plan to conduct the searches and analyses and to write the manuscript from November 2022 to February 2022.

Eligibility criteria

Study designs

Only randomised clinical trials will be included. Quasi-randomised trials and cluster randomised trials will not be included.

Participants

We will include trials involving participants undergoing percutaneous coronary intervention on any native

coronary artery de-novo stenosis due to ST-segment elevation myocardial infarction (STEMI), non-STEMI, unstable angina or chronic coronary artery disease. Participants must be enrolled in the trial based on grading of the severity of coronary calcification or the trial must report prespecified subgroup analyses based on the severity of lesion calcification. Any definition of the severity of calcification is accepted, but severity must correspond to moderate or severe to be eligible.

Interventions

Any method of performing percutaneous coronary intervention on a calcified coronary lesion including any specific predilatation, stenting or postdilatation technique will be included. For the control group, any relevant comparison (any head-to-head comparison with another method, usual care or no intervention) will be eligible. Any cointervention is accepted if it is planned to be applied similarly across intervention groups.

Outcomes

Primary outcomes

1. All-cause mortality.
2. Proportion of participants with one or more serious adverse events. We will use the 'International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use — Good Clinical Practice' (ICH-GCP) definition of a serious adverse event, which is any untoward medical occurrence that resulted in death, was life-threatening, required hospitalisation or prolonging of existing hospitalisation and resulted in persistent or significant disability or jeopardised the participant.²⁹ If the trialists do not use this definition, we will include the data if the trialists use the term 'serious adverse event'. If the trialists do not use the ICH-GCP definition nor the term serious adverse event, then we will also include the data if the event clearly fulfils the ICH-GCP definition. We will second assess each type of serious adverse event separately.

Secondary outcomes

Patient oriented

1. Myocardial infarction (as defined by trialists).
2. Stroke (as defined by trialists).
3. Health-related quality of life (any validated continuous scale).
4. Proportion of participants with one or more non-serious adverse events (any adverse event not classified as serious). We will exploratorily assess each adverse event separately.
5. Coronary angiography.

Device oriented

1. Target vessel myocardial infarction.
2. Target vessel revascularisation.

Exploratory outcomes

1. Any coronary revascularisation.

Table 1 Published reviews of percutaneous coronary interventions techniques in patients with calcified coronary lesions

Author	Year	Review type	Techniques assessed							Stated purpose	Recommendation, result or conclusion
			RA	OA	CU	SC	HP	EX	LI	ST	
Karimi Galougahi <i>et al</i> ²²	2021	Non-systematic and narrative	X	X	X	X	X	X	X	X	Intravascular imaging can guide percutaneous coronary intervention. More studies are required.
De Maria <i>et al</i> ²³	2019	Non-systematic and narrative	X	X	X	X	X	X	X	X	Recommend the use of an algorithm to guide management according to balloon crossability and findings on intravascular imaging. Lithoplasty seems promising.
Barbato <i>et al</i> ¹³	2017	Non-systematic and narrative	X	X	X	X	X	X			Not stated.
Allen and Kaul ⁴⁴	2019	Non-systematic and narrative	X	X	X	X	X				Not stated.
Chambers <i>et al</i> ⁴⁵	2016	Non-systematic and narrative	X	X				X			Atherectomy may improve procedural outcomes.
Goel <i>et al</i> ⁴⁶	2019	Systematic with meta-analysis	X	X							Except for fluoroscopy time, there are no differences between OA or RA in outcomes.
Baber <i>et al</i> ⁴⁷	2010	Non-systematic and narrative	X	X	X						Unclear.
Shlofmitz <i>et al</i> ⁴⁸	2019	Non-systematic and narrative		X							Orbital atherectomy plays an important role in lesion preparation to ensure optimal results.
Chambers and Diage ⁴⁹	2014	Non-systematic and narrative	X	X					X		Orbital atherectomy may improve outcomes.
Khan <i>et al</i> ⁵⁰	2019	Systematic and narrative							X		Lithoplasty decreases vessel stenosis.
Kassimis <i>et al</i> ⁵¹	2020	Non-systematic and narrative							X		Lithoplasty is easy to use and has predictable results.
Zhang <i>et al</i> ⁵²	2014	Systematic with meta-analysis							X		Drug-eluting stents are superior to bare-metal stents in terms of target lesion revascularisation
CU, cutting balloon; EX, excimer laser; HP, high pressure non-compliant balloon; LI, lithoplasty; OA, orbital atherectomy; RA, rotational atherectomy; SC, scoring balloon; ST, stent.											

2. In-stent restenosis (as defined by trialists).
3. Cardiovascular mortality (as defined by trialists).
4. Any physiological or imaging-derived measurement of improved myocardial perfusion after intervention.
5. Proportion of participants with failed or no stenting.
6. Use of bailout atherectomy, stent delivery, successful device crossing, study group crossover, study-defined procedural success.
7. Procedure duration, fluoroscopy time, contrast dose.

Assessment time points

We will assess outcomes at maximum follow-up.

Search strategy

One review author (ATK) will search Cochrane Central Register of Controlled Trials, Medical Literature Analysis and Retrieval System Online, Latin American and Caribbean Health Sciences Literature, Science Citation Index Expanded and Excerpta Medica database from inception to 31 October 2022. No restrictions based on language or year of publication will be applied. The search will be supplemented by manually screening the reference lists of included trials. The search strategy can be found in online supplemental file 1.

Data collection

The review will be reported as recommended by the PRISMA statement.³⁰

Selection of studies

Two review authors (ATK and NTO) will independently screen search results based initially on title and abstract, then based on full-text review and provide reasons for exclusion of ineligible studies. Disagreements will be resolved through discussion, or by consulting a third person (JCJ).

Data extraction

Two review authors (ATK and NTO) will independently extract data from included trials. The reviewers will assess duplicate publications and companion papers of a trial together to evaluate all available data simultaneously.

From each trial, the following will be extracted: type of intervention, severity of calcification, trial design (parallel, factorial or crossover), number of experimental groups, length of follow-up, number of randomised participants, number of participants (analysed, lost to follow-up, withdrawn or crossover), outcome data (only data from last follow-up time), types of comorbidities, age range, sex ratio and risk of bias domains (see below).

Assessment of risk of bias

Risk of bias will be evaluated by the Cochrane Risk of Bias tool (V.2) using five bias domains, each classified as either low risk of bias, some concerns or high risk of bias.³¹ Bias assessment will be conducted on an outcome level.

Bias arising from the randomisation process

Low risk of bias: adequately concealed allocation and absence of baseline imbalances between groups, and random or unpredictable method to generate the allocation sequence. Some concerns: (1) adequately concealed allocation and a problem with the method of sequence generation or baseline imbalances that suggest a problematic randomisation process, or (2) if no information is provided about concealment of allocation and baseline imbalances appear to be compatible with chance or (3) if no information to answer any of the signalling questions. High risk of bias: (1) allocation sequence not adequately concealed or (2) there is no information about concealment of the allocation sequence and baseline imbalances that suggest a problem with the randomisation process.

Bias due to deviation from intended interventions

Low risk of bias: (1) if participants, carers and people delivering the interventions were unaware of randomisation groups during the trial or (2) aware of intervention groups during the trial but deviations from the intended were usual practice, or unlikely to impact the outcome and no participants were analysed in a group that the participant was not assigned to. Some concerns: participants, carers and people were aware of intervention groups and (1) there was no information on whether there were deviations from the intended interventions or (2) there were deviations from the interventions but the deviations were not likely to have affected outcome, or were balanced between the groups. High risk of bias: participants, carers or people were aware of the intervention groups during the trial and there were deviations from the intended interventions that were unbalanced between the groups and likely to have affected the outcome, or some participants were analysed in the wrong intervention group, and there was potential for substantial impact on the estimated effect size.

Bias due to missing outcome data

Low risk of bias: data were available for all, or nearly all randomised participants or there is evidence that the result was not biased by missing data or that missingness in the outcome could not depend on its true value. Some concerns: an unclear degree of missing data and there is no evidence that the effect estimate is robust to missing data. High risk of bias: high degree of missing data, differential missing data and no evidence that the effect estimate is robust to missing data.

Bias in measurement of outcomes

Low risk of bias: outcome assessors were unaware of the intervention received by study participants, or aware but were unlikely to be influenced by this knowledge. Some concerns: no information available to determine if the outcome is likely influenced by knowledge of the intervention received. High risk of bias: the outcome assessment was likely to be influenced by knowledge of the intervention received.

Bias arising from selective reporting of results

Low risk of bias: reported outcome data was unlikely to have been selected on the basis of the results from multiple outcome measurements. Some concern: insufficient information available to rule out the possibility of selective outcome reporting on the basis of the results from multiple outcome measurements. High risk of bias: reported data are likely to have been selected on the basis of the results from multiple outcome measurements or analyses.

Overall assessment of risk of bias

Low risk of bias: if the study is judged as low risk across all domains. High risk of bias: if the study is judged as some concerns or high risk of bias in at least one domain. If a trial is sponsored by the industry and or if just one author has affiliation to the industry, the publication will be judged as having some concern or high risk of for-profit bias. The domains 3, 4 and 5 will be assessed for each outcome result.

Differences between the protocol and review

The review will be conducted according to this published protocol and any deviations from the protocol and their reasons will be stated in the review.

Measurement of treatment effect

Continuous outcomes

Mean differences with 95% CI and trial sequential analysis adjusted 95% CI will be calculated.

Dichotomous outcomes

Risk ratios (RRs) with 95% CI and trial sequential analysis adjusted 95% CI will be calculated.

Dealing with missing data

Trialists will be contacted to obtain relevant missing data.

Assessment of heterogeneity

Signs of heterogeneity will primarily be assessed by forest plots, and second by the I^2 statistic^{31–33} and the restricted maximum likelihood method.^{34 35} It may be decided that meta-analysis is inappropriate if heterogeneity is high.

Data synthesis

Results of each type of intervention will be analysed separately based on intention-to-treat data. Rstudio and Stata V.16 (StataCorp LLC) will be used for analyses.

Meta-analysis

Meta-analysis will be conducted according to the Cochrane Handbook of Systematic Reviews of Interventions,³¹ Keus *et al.*,³⁶ and Jakobsen *et al.*³⁷ and supplemented by trial sequential analysis. Intervention effects will be analysed with both a random-effects and fixed-effect meta-analysis for each comparison. The estimate with the highest p value will be primarily used. Because we assess two primary outcomes, we will consider a p value of 0.03 or less as statistically significant.³⁷

Trial sequential analysis

Trial sequential analysis is a test of the statistical reliability of data in meta-analyses. Trial sequential analysis adjusts significance levels for sparse data and controls the risk of both type I and type II errors due to accumulating data.³⁸ Trial sequential analysis will be performed on all outcomes to calculate the required information size (number of participants required in the meta-analysis to confirm or reject a given intervention effect) and the cumulative Z-curve's breach of relevant trial sequential monitoring boundaries.^{38 39} For dichotomous outcomes, the required information size will be calculated based on the observed proportion of patients with an outcome in the control group, a relative risk reduction or increase of 25%, an alpha of 3.3% for all outcomes, a beta of 10%, and the observed diversity as suggested by the trials in the meta-analysis. For continuous outcomes, the information size will be calculated based on the observed SD, a mean difference equal to the observed SD/2, an alpha of 3.3% for all outcomes, a beta of 10%, and the observed diversity as suggested by the trials in the meta-analysis.

Network meta-analysis

The synthesis comparator consists of all the interventions listed in the Eligibility criteria section, as well as placebo, standard care, no intervention, or 'active placebo' trials. Interventions will be analysed separately and not grouped. The characteristics of the trials and their populations will be described by frequencies and percentages for dichotomous data and means with SD for continuous data. Descriptive statistics for each treatment comparison will be generated describing important clinical and methodological characteristics. Each outcome dataset will be presented in a separate network diagram, where the size of the nodes is proportional to the total number of participants, and the width of each line corresponds to the number of studies comparing the connected treatments. Furthermore, the connecting lines will be marked according to the average risk of bias per treatment comparison, using green for low, yellow for moderate and red for high risk of bias. It is assumed that any participant who meets inclusion criteria is equally likely to be randomised to each intervention in the comparator set. The analyses will be conducted using Stata under frequentist framework (command: mvmeta).⁴⁰

Network meta-analysis will only be conducted if a connected network of trials can be constructed. If conducted, the assumptions of transitivity and consistency will be assessed prior to analysis. The assumptions will be assessed in five steps. First, a network geometry will be drawn to review the network relationship. Second, the transitivity assumption across treatment comparisons will be assessed using boxplots. The assumption of consistency will be evaluated using the design-by-treatment interaction model as a global test.^{41 42} Third, a network forest or interval plot is made to illustrate the summary effect size of the comparative effectiveness of the interventions. Fourth, is to calculate the cumulative rankings

to identify a superiority among interventions. Fifth, is to evaluate publication bias or effect modifiers for a valid inference from results. Effects estimates will be reported using relevant effect size (RR, mean difference, or standardized mean difference), a 95% CI, and a 95% prediction interval.

Planned subgroup analyses

For trials comparing stent types, the following categories will be applied: (1) bare-metal stents, (2) first-generation drug-eluting stents and (3) later-generation drug-eluting stents.

Summary of findings table

For each prespecified outcome, a summary of findings table will be created. The five Grading of Recommendations, Assessment, Development and Evaluations (GRADE) considerations (bias risk, consistency of the effect, imprecision, indirectness and publication bias) will be used to assess the certainty of the evidence.⁴³ Imprecision will be assessed using trial sequential analysis. All downgrading of the certainty of the evidence will be justified in writing.

Patient and public involvement statement

Patients were not directly involved in the planning of this study.

DISCUSSION

Coronary calcifications complicate all aspects of percutaneous coronary intervention and are a risk factor for short-term and long-term complications.^{9 11} Several treatment options exist, but there is no consensus regarding the optimal choice of treatment strategy. This systematic review with meta-analysis, trial sequential analysis and network meta-analysis aims to assess the beneficial and harmful effects of all percutaneous treatment options in the treatment of calcified coronary lesions.

This protocol has several methodological strengths. First, the methodology is predefined and based on the PRISMA guidelines²⁷ and the Cochrane Handbook for Systematic Reviews of Interventions.³¹ Second, risk of bias will be assessed, and significance thresholds will be adjusted to control for random and systematic errors. The primary limitation of the review is the combined assessment of all available interventions, which may require many analyses and cause problems with multiplicity. The results of the review will be interpreted considering this increased risk of type 1 errors.

ETHICS AND DISSEMINATION

No ethics approval is required for this study. The results of this study will be published in peer-reviewed academic journals in this field.

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**Search strategies for
Percutaneous coronary intervention in calcified stenoses
(Andreas Torp Kristensen)
Preliminary searches prepared 8 April 2022**

Cochrane Central Register of Controlled Trials (latest issue) in the Cochrane Library

- #1 MeSH descriptor: [Coronary Artery Disease] explode all trees
- #2 MeSH descriptor: [Myocardial Infarction] explode all trees
- #3 MeSH descriptor: [Coronary Stenosis] explode all trees
- #4 (coronar* or myocardial infarct* or angina or arteriosclero* or STEMI or (left next ma in) or stenosis* or ischemic heart disease*)
- #5 #1 or #2 or #3 or #4
- #6 MeSH descriptor: [Calcinosis] this term only
- #7 MeSH descriptor: [Vascular Calcification] explode all trees
- #8 (calcif* or calcinos*)
- #9 #6 or #7 or #8
- #10 MeSH descriptor: [Coronary Angiography] explode all trees
- #11 MeSH descriptor: [Percutaneous Coronary Intervention] explode all trees
- #12 MeSH descriptor: [Angioplasty, Balloon, Coronary] explode all trees
- #13 MeSH descriptor: [Atherectomy, Coronary] explode all trees
- #14 (angiogra* or arterygra* or coronarygra* or percutaneous coronary intervention or lesion preparation or predilat* or postdilat* or stent* or angioplast* or atherectom* or balloon*)
- #15 #10 or #11 or #12 or #13 or #14
- #16 #5 and #9 and #14

MEDLINE Ovid (1946 to the date of the search)

- 1. exp Coronary Artery Disease/
- 2. exp Myocardial Infarction/
- 3. exp Coronary Stenosis/
- 4. (coronar* or myocardial infarct* or angina or arteriosclero* or STEMI or (left adj main) or stenosis* or ischemic heart disease*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
- 5. 1 or 2 or 3 or 4
- 6. Calcinosis/
- 7. exp Vascular Calcification/
- 8. (calcif* or calcinos*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
- 9. 6 or 7 or 8
- 10. exp Coronary Angiography/
- 11. exp Percutaneous Coronary Intervention/
- 12. exp Angioplasty, Balloon, Coronary/
- 13. exp Atherectomy, Coronary/
- 14. (angiogra* or arterygra* or coronarygra* or percutaneous coronary intervention or lesion preparation or predilat* or postdilat* or stent* or angioplast* or atherectom* or balloon*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
- 15. 10 or 11 or 12 or 13 or 14
- 16. 5 and 9 and 14
- 17. (randomized controlled trial or controlled clinical trial or retracted publication or retraction of publication).pt. or clinical trials as topic.sh. or trial.ti.
- 18. (random* or blind* or placebo*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
- 19. 16 and (17 or 18)

Embase Ovid (1974 to the date of the search)

- 1. exp coronary artery disease/

2. exp heart infarction/
3. (coronar* or myocardical infarct* or angina or arteriosclero* or STEMI or (left adj main) or stenosis* or ischemic heart disease*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]
4. 1 or 2 or 3
5. exp calcification/
6. exp cardiovascular calcification/
7. (calcif* or calcinos*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]
8. 5 or 6 or 7
9. exp coronary angiography/
10. exp percutaneous coronary intervention/
11. exp percutaneous transluminal angioplasty/
12. exp coronary atherectomy/
13. exp coronary artery surgery/
14. (angiogra* or arterygra* or coronarygra* or percutaneous coronary intervention or lesion preparation or predilat* or postdilat* or stent* or angioplast* or atherectomy* or balloon*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]
15. 9 or 10 or 11 or 12 or 13 or 14
16. 4 and 8 and 15
17. Randomized controlled trial/ or Controlled clinical trial/ or retracted article/ or (erratum or tombstone).pt. or trial.ti. or yes.nr.
18. (random* or blind* or placebo*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]
19. 16 and (17 or 18)

LILACS (Bireme; 1982 to the date of the search)

(coronar\$ or myocardical infarct\$ or angina or arteriosclero\$ or STEMI or left main or stenosis\$ or ischemic heart disease\$) [Words] and (calcif\$ or calcinos\$) [Words] and (angiogra\$ or arterygra\$ or coronarygra\$ or percutaneous coronary intervention or lesion preparation or predilat\$ or postdilat\$ or stent\$ or angioplast\$ or atherectomy\$ or balloon\$) [Words]

Science Citation Index Expanded (1900 to the date of the search) and Conference Proceedings Citation Index – Science (1990 to the date of the search) (Web of Science)

#6 #4 AND #5

#5 TI=(random* or blind* or placebo* or trial*) OR TS=(random* or blind* or placebo*)

#4 #3 AND #2 AND #1

#3 TS=(angiogra* or arterygra* or coronarygra* or percutaneous coronary intervention or lesion preparation or predilat* or postdilat* or stent* or angioplast* or atherectomy* or balloon*)

#2 TS=(calcif* or calcinos*)

#1 TS=(coronar* or myocardical infarct* or angina or arteriosclero* or STEMI or left NEXT main or stenosis* or ischemic heart disease*)