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## 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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1 **Percutaneous coronary intervention in calcified stenoses. A protocol for a systematic review with meta-**  
2 **analysis, Trial Sequential Analysis, and network meta-analysis**

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15 Word count: 3,710

## 16 **ABSTRACT**

### 17 **Introduction**

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

### 25 **Methods and analysis**

26 We will conduct a systematic review of randomized trials enrolling patients with calcified coronary artery  
27 disease undergoing percutaneous coronary intervention. We will investigate any percutaneous treatment  
28 option including any lesion preparation, stenting, or postdilatation technique. We will search The Cochrane  
29 Central Register of Controlled Trials, Medical Literature Analysis and Retrieval System Online, Latin  
30 American and Caribbean Health Sciences Literature, Science Citation Index Expanded, and Excerpta Medica  
31 database for studies from inception to June 1<sup>st</sup>, 2022. The co-primary outcome is all-cause mortality and  
32 serious adverse events. If appropriate, we will conduct meta-analysis, Trial Sequential Analysis, and  
33 network meta-analysis.

### 35 **Ethics and dissemination**

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

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7 39 **Systematic review registration**8  
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10 40 PROSPERO registration CRD42021226034  
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1516 42 **Keywords**17  
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19 43 Percutaneous coronary intervention, lesion preparation, vascular calcification, ischemic heart disease,  
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21 44 stenosis  
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2627 46 **Strengths and limitations**

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- Several percutaneous treatment options exist to treat calcified coronary lesions, but there is no  
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32 48 consensus regarding the optimal choice of treatment strategy. We aim to assess the beneficial and  
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34 49 harmful effects of all available treatment options.
  - This protocol is based on the PRISMA-P guidelines and the Cochrane Handbook for Systematic  
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36 50 Reviews of Interventions.
  - We plan to conduct meta-analysis, Trial Sequential Analysis, and network meta-analysis.  
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  - We will assess all available interventions which may require many analyses and cause problems  
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## 56 INTRODUCTION

### 57 Ischemic heart disease

58 Ischemic heart disease is the most common cause of death globally and accounts for 1.8 million European  
59 deaths annually.[1,2] Ischemic heart disease is characterized by build-up of lipid containing plaques, chronic  
60 inflammation, and hardening in the walls of coronary arteries.[3] This process, i.e. atherosclerosis, is  
61 associated with traditional cardiovascular risk factors such as diabetes mellitus, hypertension, and  
62 hypercholesterolemia, among others.[3] Atherosclerosis may lead to reduced coronary blood flow due to  
63 narrowed vessels (stenosis), inadequate oxygen supply to the myocardium (ischemia), and heart attack  
64 (infarction). Affected individuals risk of loss of cardiac function, decrease in quality of life, and ultimately  
65 death.[3]

### 67 Calcified ischemic heart disease

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

75 The presence and severity of coronary calcification can be identified non-invasively by cardiac computed  
76 tomography or invasively by coronary angiography, optical coherence tomography, or intravascular  
77 ultrasound.[4] The degree of coronary artery calcification correlates with the severity of obstructive  
78 coronary artery disease.[4] Moderately to severely calcified coronary stenoses are present in 17-34% of

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4 79 patients with ischemic heart disease undergoing percutaneous coronary intervention.[4–6] Patients with  
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6 80 severe calcifications often have multivessel disease, greater anatomical complexity (greater SYNTAX score  
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8 81 and number of ACC/AHA type C lesions), and a lower preprocedural TIMI grade of flow through the lesion  
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11 82 compared to patients with no or only mild calcifications.[7–9] The presence of moderate to severe  
12  
13 83 calcifications is a risk factor of future cardiovascular events and death.[10,11]  
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### 19 85 **Coronary angiography and percutaneous coronary intervention**

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21  
22 86 Coronary angiography is an invasive procedure that allows visualization and treatment of coronary  
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24 87 stenoses.[12] Following local anesthesia in the wrist or groin, a sheath is inserted into a peripheral  
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26 88 artery.[12] Through the sheath, a catheter is advanced to the coronary ostia. By injecting contrast medium  
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29 89 and using x-ray fluoroscopy, an angiogram is produced that visualizes the coronary arteries, stenoses, and  
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31 90 calcifications (dense radiopacities in the vessel wall).[4,12]  
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34 91 Ischemic heart disease can be treated medically primarily by reducing the myocardial demand of oxygen, or  
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36 92 invasively by either opening (percutaneous coronary intervention) or bypassing (coronary artery bypass  
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38 93 grafting) the affected vessels. Percutaneous coronary intervention with implantation of drug-eluting stents  
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40 94 is the most frequently used method of coronary revascularization.  
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43 95 Percutaneous coronary intervention is usually carried out in three steps. First, after passing a thin and  
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45 96 flexible wire through the catheter into the coronary artery, a balloon is inserted over the wire and inflated  
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48 97 in the lesion (the process of lesion preparation or predilatation).[12] The purpose of lesion preparation is to  
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50 98 prepare the lesion for placement and expansion of a sufficiently sized stent by causing controlled dissection  
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52 99 and disruption of the lesion. Second, a stent mounted on a balloon is inserted over the wire and expanded  
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54 100 in the lesion to prevent recoil, acute blockage, and future stenosis (stenting). Third, the stent may be  
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57 101 further expanded with additional inflations to ensure optimal stent expansion to reduce the risk of future  
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59 102 restenosis (postdilatation).[12]  
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## 104 **Percutaneous coronary intervention in calcified lesions**

105 Calcifications complicate all aspects of interventional treatment and constitute one of the most common  
106 types of complex lesions in patients undergoing percutaneous coronary intervention.[7] Percutaneous  
107 intervention of calcified lesions has a higher risk of short- and long-term complications (coronary  
108 perforation, in-stent thrombosis, restenosis, and death) and a lower procedural success rate (e.g.  
109 incomplete revascularization and suboptimal stent expansion) compared to percutaneous treatment of  
110 non-calcified lesions.[9]

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

119 In addition to conventional techniques, several specialized lesion preparation techniques are available to  
120 optimize lesion preparation and stent expansion in calcified stenoses. 1) Rotational atherectomy utilizes a  
121 catheter with a rotating diamond-burr, which is advanced through the calcified segment to pulverize the  
122 superficial calcification.[18] 2) Orbital atherectomy utilizes a catheter with an eccentrically mounted  
123 diamond-coated crown that rotates and pulverizes the superficial calcification.[18] Potential complications  
124 of rotational and orbital atherectomy include coronary perforation, dissection and embolization of debris  
125 with risks of myocardial infarction or slow-flow/no-reflow phenomenon).[18] Atherectomy is affected by  
126 guidewire bias, which limits optimal modification of the calcification.[19] 3) Cutting or scoring balloons



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4 127 (modified balloons) have superficially mounted blades or wires, respectively, that create indents and more  
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6 128 controlled dissections in the plaque and calcification during inflation.[18] By creating indents and  
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9 129 dissections in the calcified intimal layer, the balloons expand in a focused location at less inflation pressure  
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11 130 at a lower risk of asymmetric expansion.[20] A limitation of modified balloons is the restricted flexibility of  
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13 131 the balloons through calcified segments. 4) Non-compliant high pressure balloons are double layered and  
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15 132 may deliver the very high pressure required for dilatation of severely calcified lesions, but at a risk of  
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18 133 rupture due to mechanical trauma.[18] 5) Excimer laser is a technique that delivers gases and generate  
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20 134 pulses of ultraviolet light that leads to ablation of the calcification. In severely calcified lesions, this  
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22 135 technique has been shown effective in otherwise uncrossable lesions, but at a risk of perforation and slow-  
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24 136 flow/no-reflow phenomena.[21] 6) Balloon lithoplasty is a technique that delivers high-frequency pressure  
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27 137 waves from a balloon inflated in the lesion at low pressure.[19] The pressure waves propagate through the  
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29 138 vessel wall to fracture calcification. In severely calcified lesions, this technique has been shown effective  
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31 139 and safe.[19]  
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37 141 No stent has been specifically designed for placement in calcified lesions. However, preliminary studies  
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39 142 have indicated that second-generation drug-eluting stents are superior to first generation drug-eluting  
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41 143 stents in calcified lesions.[8]  
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#### 47 145 **Why is it important to do this review?**

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50 146 A wide range of treatment techniques are available to treat severely calcified lesions, but there is no  
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52 147 consensus regarding the optimal choice in terms of efficacy or safety. Patients with calcified lesions  
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54 148 compared to patients without calcifications are more often elderly or have complex lesions, diabetes, or  
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57 149 chronic kidney disease.[4] For these reasons, patients with calcified lesions are often excluded from  
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4 150 controlled studies and there is little evidence on how to treat these patients. Treatment algorithms have  
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6 151 been proposed, but they have not been validated nor implemented internationally.[18,22,23]  
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9 152 Several reviews on percutaneous coronary intervention techniques on calcified lesions have been  
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11 153 published. These reviews are limited due to their use of non-systematic searches, inclusion of non-  
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14 154 randomized studies, non-adherence to PRISMA guidelines, and focus on only few selected treatment  
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16 155 options (**Table 1**). A preliminary search identified four randomized trials on calcified lesions that compare  
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18 156 atherectomy versus no atherectomy,[24] atherectomy versus cutting or scoring balloons,[25] non-  
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21 157 compliant high pressure balloons versus scoring balloons,[26] and paclitaxel-eluting stent versus bare-metal  
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23 158 stent.[5]

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26 159 Effective lesion preparation and stenting is considered a vital predictor of short- and long-term outcomes  
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28 160 following percutaneous coronary intervention. So far, no systematic review has comprehensively examined  
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30 161 all available percutaneous treatment options in patients with calcified coronary stenoses.  
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162 **Table 1** Previous 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			
Galougahi[22]	2021	Non-systematic and narrative	X	X	X	X	X	X	X	X		Overview of evaluation and treatment	Intravascular imaging can guide percutaneous coronary intervention. More studies are required.
De Maria[23]	2019	Non-systematic and narrative	X	X	X	X	X	X	X			Overview with focus on technologies and the role of intravascular imaging	Recommend the use of an algorithm to guide management according to balloon crossability and findings on intravascular imaging. Lithoplasty seem promising.
Barbato[13]	2017	Non-systematic and narrative	X	X	X	X		X				Summary of principles, technique, and evidence	Not stated.
Allen[44]	2019	Non-systematic and narrative	X	X	X	X						Summary of principles, technique, and evidence	Not stated.
Chambers[45]	2016	Non-systematic and narrative	X	X					X			Review of atherectomy devices.	Atherectomy may improve procedural outcomes.
Goel[46]	2019	Systematic with meta-analysis	X	X								Rotational versus orbital atherectomy	Except for fluoroscopy time, there are no differences between OA or RA in outcomes.
Baber[47]	2010	Non-systematic and narrative	X		X							Outline difficulties and interventional techniques for complex lesions	Unclear.
Shlofmitz[48]	2019	Non-systematic and narrative		X								Review of orbital atherectomy	Orbital atherectomy plays an important role in lesion preparation to ensure optimal results.
Chambers[49]	2014	Non-systematic and narrative		X						X		Review of orbital atherectomy	Orbital atherectomy may improve outcomes.
Khan[50]	2019	Systematic and narrative								X		Summarize outcomes of lithoplasty in peripheral and coronary artery disease.	Lithoplasty decreases vessel stenosis.
Kassimis[51]	2020	Non-systematic and narrative								X		Describe evidence and highlight best clinical applications.	Lithoplasty is easy to use and has predictable results.
Zhang[52]	2014	Systematic with meta-analysis									X	Drug-eluting versus bare-metal stents	Drug-eluting stents is superior to bare-metal stents in terms of target lesion revascularization

163 RA = rotational atherectomy, OA = orbital atherectomy, CU = cutting balloon, SC = scoring balloon, HP = high pressure non-compliant

164 balloon, EX = excimer laser, LI = lithoplasty, ST = stent

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7 166 **Objective**8  
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10 167 The objective of this review is to assess the beneficial and harmful effects of all percutaneous treatment  
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12 168 options to treat calcified coronary lesions.  
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18 170 **METHODS AND ANALYSES**19  
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21 171 The protocol is registered at PROSPERO (registration CRD42021226034) and the methodology is based on  
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23 172 the Preferred Reporting Items for Systematic Reviews and Meta-Analysis - Protocols (PRISMA-P)  
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25 173 statement[27] and the Cochrane Handbook of Systematic Review of Interventions.[28]  
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31 175 **Eligibility criteria**32  
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34 176 Study designs35  
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37 177 Only randomized clinical trials will be included. Quasi-randomized trials and cluster randomized trials will  
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39 178 not be included.  
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45 180 Participants and coronary lesions46  
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48 181 We will include trials involving participants undergoing percutaneous coronary intervention on any native  
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50 182 coronary artery de-novo stenosis due to ST-segment elevation myocardial infarction (STEMI), non-STEMI,  
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52 183 unstable angina, or chronic coronary artery disease. Participants must be enrolled in the trial based on  
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54 184 grading of the severity of coronary calcification or the trial must report prespecified subgroup analyses  
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185 based on the severity of lesion calcification. Any definition of the severity of calcification is accepted, but  
186 severity must correspond to moderate or severe to be eligible.

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## 188 Interventions

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

194

## 195 Outcomes

### 196 Primary outcome

- 197 1. All-cause mortality.
- 198 2. Proportion of participants with one or more serious adverse events. We will use the 'International  
199 Conference on Harmonization of technical requirements for registration of pharmaceuticals for  
200 human use - Good Clinical Practice' (ICH-GCP) definition of a serious adverse event, which is any  
201 untoward medical occurrence that resulted in death, was life-threatening, required hospitalization  
202 or prolonging of existing hospitalization, and resulted in persistent or significant disability or  
203 jeopardized the participant.[29] If the trialists do not use this definition, we will include the data if  
204 the trialists use the term "serious adverse event." If the trialists do not use the ICH-GCP definition  
205 nor the term serious adverse event, then we will also include the data if the event clearly fulfills the  
206 ICH-GCP definition. We will secondly assess each type of serious adverse event separately.

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4 208 Secondary outcomes

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7 209 *Patient-oriented:*

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10 210 1. Myocardial infarction (as defined by trialists).  
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12 211 2. Stroke (as defined by trialists).  
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15 212 3. Health-related quality of life (any validated continuous scale).  
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17 213 4. Proportion of participants with one or more non-serious adverse events (any adverse event not  
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19 214 classified as serious). We will exploratorily assess each adverse event separately.  
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21 215 5. Coronary angiography.

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25 216 *Device-oriented:*

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28 217 1. Target vessel myocardial infarction.  
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30 218 2. Target vessel revascularization.

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33 219 Exploratory outcomes

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36 220 1. Any coronary revascularization.  
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38 221 2. In-stent restenosis (as defined by trialists).  
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40 222 3. Cardiovascular mortality (as defined by trialists).  
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42 223 4. Any physiological or imaging-derived measurement of improved myocardial perfusion after  
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44 224 intervention.  
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46 225 5. Proportion of participants with failed or no stenting.  
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48 226 6. Use of bailout atherectomy, stent delivery, successful device crossing, study group cross over,  
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50 227 study-defined procedural success.  
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52 228 7. Procedure duration, fluoroscopy time, contrast dose.  
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4 230 Assessment time points

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7 231 We will assess outcomes at maximum follow-up.

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13 233 **Search strategy**

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16 234 One review author (ATK) will search Cochrane Central Register of Controlled Trials (CENTRAL), Medical

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18 235 Literature Analysis and Retrieval System Online (MEDLINE), Latin American and Caribbean Health Sciences

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20 236 Literature (LILACS), Science Citation Index Expanded (SCI-EXPANDED), and Excerpta Medica database

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22 237 (EMBASE) from inception to present. No restrictions based on language or year of publication will be

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24 238 applied. The search will be supplemented by manually screening the reference lists of included trials. The

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26 239 search strategy can be found in **supplemental file 1**.

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33 241 **Data collection**

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36 242 The review will be reported as recommended by the Preferred Reporting Items for Systematic Reviews and

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38 243 Meta-Analysis (PRISMA) statement.[30]

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44 245 **Selection of studies**

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47 246 Two review authors (ATK and NTO) will independently screen search results based initially on title and

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49 247 abstract, then based on full-text review and provide reasons for exclusion of ineligible studies.

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51 248 Disagreements will be resolved through discussion, or by consulting a third person (JCJ).

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57 250 **Data extraction**

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4 251 Two review authors (ATK and NTO) will independently extract data from included trials. The reviewers will  
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6 252 assess duplicate publications and companion papers of a trial together to evaluate all available data  
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9 253 simultaneously.

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14 255 From each trial, the following will be extracted: type of intervention, severity of calcification, trial design  
15  
16 (parallel, factorial, or crossover), number of experimental groups, length of follow-up, number of  
17 256 randomized participants, number of participants (analyzed, lost to follow-up, withdrawn, or crossover),  
18  
19 257 outcome data (only data from last follow-up time), types of comorbidities, age range, sex ratio, and risk of  
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21 258 bias domains (see below).  
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#### 25 260 26 27 261 **Assessment of risk of bias**

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29 262 Risk of bias will be evaluated by the Cochrane Risk of Bias tool (version 2) using five bias domains, each  
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32 263 classified as either low risk of bias, some concerns, or high risk of bias.[31] Bias assessment will be  
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35 264 conducted on an outcome level.  
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#### 41 42 266 1: Bias arising from the randomization process

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45 267 Low risk of bias: Adequately concealed allocation and absence of baseline imbalances between groups, and  
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47 268 random or unpredictable method to generate the allocation sequence. Some concerns: 1) Adequately  
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49 269 concealed allocation and a problem with the method of sequence generation or baseline imbalances that  
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51 270 suggest a problematic randomization process, or 2) if no information is provided about concealment of  
52  
53 271 allocation and baseline imbalances appear to be compatible with chance, or 3) if no information to answer  
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55 272 any of the signaling questions. High risk of bias: 1) Allocation sequence not adequately concealed, or 2)  
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273 there is no information about concealment of the allocation sequence and baseline imbalances that  
274 suggest a problem with the randomization process.

## 276 2: Bias due to deviation from intended interventions

277 Low risk of bias: 1) If participants, carers, and people delivering the interventions were unaware of  
278 randomization groups during the trial, or 2) aware of intervention groups during the trial but deviations  
279 from the intended was usual practice, or unlikely to impact the outcome and no participants were analyzed  
280 in a group that the participant was not assigned to. Some concerns: Participants, carers, and people were  
281 aware of intervention groups and 1) there was no information on whether there were deviations from the  
282 intended interventions, or 2) there were deviations from the interventions but the deviations were not  
283 likely to have affected outcome, or were balanced between the groups. High risk of bias: Participants,  
284 carers or people were aware of the intervention groups during the trial and there were deviations from the  
285 intended interventions that were unbalanced between the groups and likely to have affected the outcome,  
286 or some participants were analyzed in the wrong intervention group, and there was potential for  
287 substantial impact on the estimated effect size.

## 289 3: Bias due to missing outcome data

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

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#### 296 4: Bias in measurement of outcomes

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

#### 302 5: Bias arising from selective reporting of results

303 Low risk of bias: Reported outcome data was unlikely to have been selected on the basis on the results  
304 from multiple outcome measurements. Some concern: Insufficient information available to rule out the  
305 possibility of selective outcome reporting on the basis of the results from multiple outcome measurements.  
306 High risk of bias: Reported data is likely to have been selected on the basis of the results from multiple  
307 outcome measurements or analyses.

#### 309 Overall assessment of risk of bias

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

#### 315 **Differences between the protocol and review**

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

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## 319 **Measurement of treatment effect**

320 Continuous outcomes

321 Mean differences with 95% confidence intervals (CI) and Trial Sequential Analysis adjusted 95% CI will be  
322 calculated.

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324 Dichotomous outcomes

325 Risk ratios (RRs) with 95% CI and Trial Sequential Analysis adjusted 95% CI will be calculated.

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## 327 **Dealing with missing data**

328 Trialists will be contacted to obtain relevant missing data.

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## 330 **Assessment of heterogeneity**

331 Signs of heterogeneity will primarily be assessed by forest plots, and secondly by the  $I^2$  statistic[31–33] and  
332 the restricted maximum likelihood method.[34,35] It may be decided that meta-analysis is inappropriate if  
333 heterogeneity is high.

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## 335 **Data synthesis**

336 Results of each type of intervention will be analyzed separately based on intention-to-treat data. Rstudio  
337 and Stata version 16 (StataCorp LLC, College Station, TX, USA) will be used for analyses.

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7 339 Meta-analysis

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10 340 Meta-analysis will be conducted according to the Cochrane Handbook of Systematic Reviews of  
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12 341 Interventions,[31] Keus et al.,[36] and Jakobsen et al.[37] and supplemented by Trial Sequential Analysis.  
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14 342 Intervention effects will be analyzed with both a random-effects and fixed-effect meta-analysis for each  
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16 343 comparison. The estimate with the highest  $p$  value will be primarily used. Because we assess two primary  
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18 344 outcomes, we will consider a  $p$  value of 0.03 or less as statistically significant.[37]  
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25 346 Trial Sequential Analysis

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28 347 Trial Sequential Analysis is a test of the statistical reliability of data in meta-analyses. Trial Sequential  
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30 348 Analysis adjusts significance levels for sparse data and controls the risk of both type I and type II errors due  
31  
32 349 to accumulating data.[38] Trial Sequential Analysis will be performed on all outcomes to calculate the  
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34 350 required information size (number of participants required in the meta-analysis to confirm or reject a given  
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36 351 intervention effect) and the cumulative Z-curve's breach of relevant trial sequential monitoring  
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38 352 boundaries.[38,39] For dichotomous outcomes, the required information size will be calculated based on  
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40 353 the observed proportion of patients with an outcome in the control group, a relative risk reduction or  
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42 354 increase of 20% or 10%, an alpha of 2% for all outcomes, a beta of 10%, and the observed diversity as  
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44 355 suggested by the trials in the meta-analysis. For continuous outcomes, the information size will be  
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46 356 calculated based on the observed standard deviation (SD), a mean difference equal to the observed SD/2,  
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48 357 an alpha of 2% for all outcomes, a beta of 10%, and the observed diversity as suggested by the trials in the  
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50 358 meta-analysis.  
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361 The synthesis comparator consists of all the interventions listed in Eligibility Criteria section, as well as  
362 placebo, standard care, no intervention, or “active placebo” trials. Interventions will be analyzed separately  
363 and not grouped. The characteristics of the trials and their populations will be described by frequencies and  
364 percentages for dichotomous data and means with SD for continuous data. Descriptive statistics for each  
365 treatment comparison will be generated describing important clinical and methodological characteristics.  
366 Each outcome dataset will be presented in a separate network diagram, where the size of the nodes is  
367 proportional to the total number of participants, and the width of each line corresponds to the number of  
368 studies comparing the connected treatments. Furthermore, the connecting lines will be marked according  
369 to the average risk of bias per treatment comparison, using green for low, yellow for moderate, and red for  
370 high risk of bias. It is assumed that any participant who meets inclusion criteria is equally likely to be  
371 randomized to each intervention in the comparator set. The analyses will be conducted using with Stata  
372 under frequentist framework (command: mvmeta).[40]

373 Network meta-analysis will only be conducted if a connected network of trials can be constructed. If  
374 conducted, the assumptions of transitivity and consistency will be assessed prior to analysis. The  
375 assumptions will be assessed in five steps. First, a network geometry will be drawn to review the network  
376 relationship. Second, the transitivity assumption across treatment comparisons will be assessed using  
377 boxplots. The assumption of consistency will be evaluated using the design-by-treatment interaction model  
378 as a global test.[41,42] Third, a network forest or interval plot is made to illustrate the summary effect size  
379 of the comparative effectiveness of the interventions. Fourth, is to calculate the cumulative rankings to  
380 identify a superiority among interventions. Fifth, is to evaluate publication bias or effect modifiers for a  
381 valid inference from results. Effects estimates will be reported using relevant effect size (RR, MD, or SMD),  
382 a 95% CI, and a 95% prediction interval.

384 Planned subgroup analyses

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4 385 For trials comparing stent types, the following categories will be applied: a) Bare metal stents, b) first  
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6 386 generation drug-eluting stents, and c) later-generation drug-eluting stents.  
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### 11 12 388 **Summary of findings table** 13 14

15 389 For each prespecified outcome a summary of findings table will be created. The five GRADE considerations  
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17 390 (bias risk, consistency of the effect, imprecision, indirectness, and publication bias) will be used to assess  
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19 the certainty of the evidence.[43] Imprecision will be assessed using Trial Sequential Analysis. All  
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22 392 downgrading of the certainty of the evidence will be justified in writing.  
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### 28 394 **Patient and Public Involvement statement** 29

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31 395 Patients were not directly involved in the planning of this study.  
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## 36 397 **DISCUSSION** 37 38

39 398 Coronary calcifications complicate all aspects of percutaneous coronary intervention and is a risk factor of  
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41 399 short- and long-term complications.[7,9] Several treatment options exist, but there is no consensus  
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43 regarding the optimal choice of treatment strategy. This systematic review with meta-analysis, Trial  
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45 Sequential Analysis, and network meta-analysis aims to assess the beneficial and harmful effects of all  
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47 percutaneous treatment options in the treatment of calcified coronary lesions.  
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51 403 This protocol has several methodological strengths. First, the methodology is predefined and based on the  
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53 404 PRISMA guidelines[27] and the Cochrane Handbook for Systematic Reviews of Interventions.[31] Second,  
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55 risk of bias will be assessed, and significance thresholds will be adjusted to control for random and  
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57 systematic errors. The primary limitation of the review is the combined assessment of all available  
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407 interventions, which may require many analyses and cause problems with multiplicity. The results of the  
408 review will be interpreted considering this increased risk of type 1 errors.

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410 **ETHICS AND DISSEMINATION**

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

For peer review only

For peer review only

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419 All authors declare that they have no competing interests.

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#### 425 **Contributors:**

426 ATK, JCJ, and NTO drafted the manuscript. NTO had the original idea for the study. All authors read and  
427 approved the final manuscript. ATK is the guarantor of the protocol.

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566 **Supplemental Material**

567 Supplemental file 1: Search strategies.

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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 myocardialinfarct\* 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 myocardialinfarct\* 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 atherectom\* 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 atherectom\$ 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 atherectom\* 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\*)



## PRISMA-P 2015 Checklist

This checklist has been adapted for use with systematic review protocol submissions to BioMed Central journals from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement *Systematic Reviews* 2015 4:1

An Editorial from the Editors-in-Chief of *Systematic Reviews* details why this checklist was adapted – Moher D, Stewart L & Shekelle P: Implementing PRISMA-P: recommendations for prospective authors. *Systematic Reviews* 2016 5:15

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
<b>ADMINISTRATIVE INFORMATION</b>					
<b>Title</b>					
Identification	1a	Identify the report as a protocol of a systematic review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	<input checked="" type="checkbox"/>	<input type="checkbox"/>	1
<b>Registration</b>	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	<input checked="" type="checkbox"/>	<input type="checkbox"/>	39
<b>Authors</b>					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	<input checked="" type="checkbox"/>	<input type="checkbox"/>	3-10
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	426-428
<b>Amendments</b>	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	<input checked="" type="checkbox"/>	<input type="checkbox"/>	314-316
<b>Support</b>					
Sources	5a	Indicate sources of financial or other support for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	422-424
Sponsor	5b	Provide name for the review funder and/or sponsor	<input checked="" type="checkbox"/>	<input type="checkbox"/>	422-424
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	<input checked="" type="checkbox"/>	<input type="checkbox"/>	422-424
<b>INTRODUCTION</b>					
<b>Rationale</b>	6	Describe the rationale for the review in the context of what is already known	<input checked="" type="checkbox"/>	<input type="checkbox"/>	56-166

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
<b>Objectives</b>	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	170-172
<b>METHODS</b>					
<b>Eligibility criteria</b>	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	179-196
<b>Information sources</b>	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	<input checked="" type="checkbox"/>	<input type="checkbox"/>	224-229
<b>Search strategy</b>	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Supplemental file 1
<b>STUDY RECORDS</b>					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	233-259
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	245-248
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	<input checked="" type="checkbox"/>	<input type="checkbox"/>	255-259
<b>Data items</b>	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	<input checked="" type="checkbox"/>	<input type="checkbox"/>	198-231
<b>Outcomes and prioritization</b>	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	<input checked="" type="checkbox"/>	<input type="checkbox"/>	198-231
<b>Risk of bias in individual studies</b>	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	<input checked="" type="checkbox"/>	<input type="checkbox"/>	261-313
<b>DATA</b>					
<b>Synthesis</b>	15a	Describe criteria under which study data will be quantitatively synthesized	<input checked="" type="checkbox"/>	<input type="checkbox"/>	336-382
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., $I^2$ , Kendall's tau)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	366-382
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	384-386
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	<input checked="" type="checkbox"/>	<input type="checkbox"/>	388-392

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
<b>Meta-bias(es)</b>	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	261-313
<b>Confidence in cumulative evidence</b>	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	388-392

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# 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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<b>Primary Subject Heading</b>:	Cardiovascular medicine
Secondary Subject Heading:	Evidence based practice
Keywords:	Coronary intervention < CARDIOLOGY, Ischaemic heart disease < CARDIOLOGY, Myocardial infarction < CARDIOLOGY

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1 **Percutaneous coronary intervention in calcified stenoses. A protocol for a systematic review with meta-**  
2 **analysis, Trial Sequential Analysis, and network meta-analysis**

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15 Word count: 3,715

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4 16 **ABSTRACT**

7 17 **Introduction**

10 18 Severely calcified coronary stenoses are difficult to treat with percutaneous coronary interventions. The  
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12 19 presence of severe calcifications complicates lesion preparation, advancement of stents, and achievement  
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14 20 of full stent expansion. Intervention in these lesions is associated with an increased risk of complications  
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17 21 and procedural failure compared with treatment of less calcified lesions. Due to the high burden of  
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19 22 comorbidity, patients with severely calcified lesions are often excluded from interventional trials, and there  
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21 23 is little evidence on how to treat these patients.  
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27 25 **Methods and analysis**

30 26 We will conduct a systematic review of randomized trials enrolling patients with calcified coronary artery  
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32 27 disease undergoing percutaneous coronary intervention. We will investigate any percutaneous treatment  
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34 28 option including any lesion preparation, stenting, or postdilatation technique. We will search The Cochrane  
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36 29 Central Register of Controlled Trials, Medical Literature Analysis and Retrieval System Online, Latin  
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38 30 American and Caribbean Health Sciences Literature, Science Citation Index Expanded, and Excerpta Medica  
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40 31 database for studies from inception to September 31<sup>st</sup>, 2022. The co-primary outcome is all-cause mortality  
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42 32 and serious adverse events. If appropriate, we will conduct meta-analysis, Trial Sequential Analysis, and  
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44 33 network meta-analysis.  
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51 35 **Ethics and dissemination**

54 36 No ethics approval is required for this study. The results will be published in a peer-reviewed journal in this  
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7 39 **Systematic review registration**8  
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1516 42 **Keywords**17  
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19 43 Percutaneous coronary intervention, lesion preparation, vascular calcification, ischemic heart disease,  
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21 44 stenosis  
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27 46 **Strengths and limitations**  
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- Several percutaneous treatment options exist to treat calcified coronary lesions. However, there is  
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32 48 no consensus regarding the optimal choice of treatment strategy. We aim to assess the beneficial  
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34 49 and harmful effects of all available treatment options.
  - This protocol is based on the PRISMA-P guidelines and the Cochrane Handbook for Systematic  
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36 50 Reviews of Interventions.
  - We plan to conduct meta-analysis, Trial Sequential Analysis, and network meta-analysis.  
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  - We will assess all available interventions which may require many analyses and cause problems  
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## 56 INTRODUCTION

### 57 Ischemic heart disease

58 Ischemic heart disease is the most common cause of death globally and accounts for 1.8 million European  
59 deaths annually.[1,2] Ischemic heart disease is characterized by build-up of lipid-containing plaques,  
60 chronic inflammation, and hardening in the walls of coronary arteries.[3] This process, i.e. atherosclerosis,  
61 is associated with traditional cardiovascular risk factors such as diabetes mellitus, hypertension, and  
62 hypercholesterolemia. Atherosclerosis may lead to reduced coronary blood flow due to narrowed vessels  
63 (stenosis), inadequate oxygen supply to the myocardium (ischemia), and heart attack (infarction). Affected  
64 individuals risk of loss of cardiac function, reduction in quality of life, and ultimately death.[3]

### 66 Calcified ischemic heart disease

67 Coronary calcification is a feature of late-stage atherosclerosis. Atherosclerosis is a chronic and  
68 degenerative process that involves apoptosis of foam cells and smooth muscle cells in the arterial wall.  
69 Early deposition of hydroxyapatite crystals, primarily in the intimal layer (microcalcification), may lead to  
70 the formation of calcified sheets and nodules that complicate coronary interventions.[4] Coronary  
71 calcification is associated with increasing age and presence and severity of diabetes mellitus and chronic  
72 kidney disease, among other conditions.[4] As the number of elderly individuals is expected to increase, so  
73 will the number of elderly individuals living with calcified ischemic heart disease. The presence of moderate  
74 to severe calcifications is a risk factor for future cardiovascular events and death.[5,6]

75 The presence and severity of coronary calcification can be identified non-invasively by cardiac computed  
76 tomography or invasively by coronary angiography, optical coherence tomography, or intravascular  
77 ultrasound.[4] The degree of coronary artery calcification correlates with the severity of obstructive  
78 coronary artery disease.[4] Moderately to severely calcified coronary stenoses are present in 17-34% of



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4 79 patients with ischemic heart disease undergoing percutaneous coronary intervention.[4,7,8] Patients with  
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6 80 severe calcifications often have multivessel disease, greater anatomical complexity (greater SYNTAX score  
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8 81 and number of ACC/AHA type C lesions), and a lower preprocedural flow through the lesion compared to  
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11 82 patients with no or only mild calcifications.[9–11]  
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#### 17 84 **Coronary angiography and percutaneous coronary intervention**

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19  
20 85 Coronary angiography is an invasive procedure that allows visualization and treatment of coronary  
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22 86 stenoses.[12] Following local anesthesia in the wrist or groin, a sheath is inserted into a peripheral  
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24 87 artery.[12] Through the sheath, a catheter is advanced to the coronary ostia. By injecting a contrast  
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26 88 medium and using x-ray fluoroscopy, an angiogram is produced that visualizes the coronary arteries,  
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28 89 stenoses, and calcifications (radiopacities in the vessel wall).[4,12]  
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31 90 Ischemic heart disease can be treated medically primarily by reducing the myocardial demand for oxygen or  
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33 91 invasively by dilating (percutaneous coronary intervention) or bypassing (coronary artery bypass grafting)  
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35 92 the affected vessels. Percutaneous coronary intervention with implantation of drug-eluting stents is the  
36  
37 93 most frequently used method of coronary revascularization.  
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41 94 Percutaneous coronary intervention is usually carried out in three steps. First, after passing a thin and  
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43 95 flexible wire through the catheter into the coronary artery, a balloon is inserted over the wire and inflated  
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45 96 in the lesion (the process of lesion preparation or predilatation).[12] The purpose of lesion preparation is to  
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47 97 prepare the lesion for placement and expansion of a sufficiently sized stent by causing controlled dissection  
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49 98 and disruption of the lesion. Second, a stent mounted on a balloon is inserted over the wire and expanded  
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51 99 in the lesion to prevent recoil, acute blockage, and future stenosis (stenting). Third, the stent may be  
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53 100 further expanded with additional inflations to ensure optimal stent expansion to reduce the risk of  
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55 101 restenosis (postdilatation).[12]  
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### 103 **Percutaneous coronary intervention in calcified lesions**

104 Calcifications complicate all aspects of interventional treatment and constitute one of the most common  
105 types of complex lesions in patients undergoing percutaneous coronary intervention.[9] Percutaneous  
106 intervention of calcified lesions has a higher risk of short- and long-term complications (coronary  
107 perforation, in-stent thrombosis, restenosis, and death) and a lower procedural success rate (e.g.  
108 incomplete revascularization and suboptimal stent expansion) compared to treatment of non-calcified  
109 lesions.[11]

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

118 In addition to conventional techniques, several specialized techniques are available to optimize lesion  
119 preparation and stent expansion in calcified stenoses. 1) Rotational atherectomy utilizes a catheter with a  
120 rotating diamond-burr, which is advanced through the calcified segment to pulverize the superficial  
121 calcification.[18] 2) Orbital atherectomy utilizes a catheter with an eccentrically mounted diamond-coated  
122 crown that rotates and pulverizes the superficial calcification.[18] Potential complications of rotational and  
123 orbital atherectomy include coronary perforation, dissection, and embolization of debris with risks of  
124 myocardial infarction or slow-flow/no-reflow phenomena.[18] Atherectomy is affected by guidewire bias,  
125 which limits optimal modification of the calcification.[19] 3) Cutting or scoring balloons (modified balloons)

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4 126 have superficially mounted blades or wires, respectively, that create indents and more controlled  
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6 127 dissections in the plaque and calcification during inflation.[18] By creating indents and dissections, the  
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8  
9 128 balloons expand in a focused location at less inflation pressure at a lower risk of asymmetric expansion.[20]  
10  
11 129 A limitation of modified balloons is the restricted flexibility of the balloons through calcified segments. 4)  
12  
13 130 Non-compliant high-pressure balloons are double layered and may deliver the very high pressure required  
14  
15 131 for dilatation of severely calcified lesions, but at a risk of rupture due to mechanical trauma.[18] 5) Excimer  
16  
17 132 laser is a technique that delivers gases and generates pulses of ultraviolet light that lead to ablation of the  
18  
19  
20 133 calcification. In severely calcified lesions, this technique has been shown effective in otherwise uncrossable  
21  
22 134 lesions, but at a risk of perforation and slow-flow/no-reflow phenomena.[21] 6) Balloon lithoplasty is a  
23  
24 135 technique that delivers high-frequency pressure waves from a balloon inflated in the lesion at low  
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26 136 pressure.[19] The pressure waves propagate through the vessel wall to fracture the calcification. In  
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29 137 severely calcified lesions, this technique has been shown effective and safe.[19]  
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35 139 No stent has been specifically designed for placement in calcified lesions. However, preliminary studies  
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37 140 have indicated that second-generation drug-eluting stents are superior to first-generation drug-eluting  
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39 141 stents in calcified lesions.[10]  
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#### 45 143 **Why is it important to do this review?**

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48 144 A wide range of treatment techniques are available to treat severely calcified lesions, but there is no  
49  
50 145 consensus regarding the optimal choice in terms of efficacy or safety. Patients with calcified lesions  
51  
52 146 compared to patients without calcifications are more often elderly or have complex lesions, diabetes  
53  
54 147 mellitus, or chronic kidney disease.[4] For these reasons, patients with calcified lesions are often excluded  
55  
56  
57 148 from controlled studies and there is little evidence on how to treat these patients. Treatment algorithms  
58  
59 149 have been proposed, but they have not been validated nor implemented internationally.[18,22,23]  
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4 150 Several reviews on percutaneous coronary intervention techniques on calcified lesions have been  
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6 151 published. These reviews are limited due to their use of non-systematic searches, inclusion of non-  
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9 152 randomized studies, non-adherence to PRISMA guidelines, or focus on only a few selected treatment  
10  
11 153 options (**Table 1**). A preliminary search identified four randomized trials on calcified lesions that compare  
12  
13 154 atherectomy versus no atherectomy,[24] atherectomy versus cutting or scoring balloons,[25] non-  
14  
15 155 compliant high-pressure balloons versus scoring balloons,[26] and paclitaxel-eluting stent versus bare-  
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18 156 metal stent.[7]  
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20  
21 157 Effective lesion preparation and stenting are considered vital predictors of short- and long-term outcomes  
22  
23 158 following percutaneous coronary intervention. So far, no systematic review has comprehensively examined  
24  
25 159 all available percutaneous treatment options in patients with calcified coronary stenoses.  
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160 **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			
Galougahi[22]	2021	Non-systematic and narrative	X	X	X	X	X	X	X			Overview of evaluation and treatment	Intravascular imaging can guide percutaneous coronary intervention. More studies are required.
De Maria[23]	2019	Non-systematic and narrative	X	X	X	X	X	X	X			Overview with focus on technologies and the role of intravascular imaging	Recommend the use of an algorithm to guide management according to balloon crossability and findings on intravascular imaging. Lithoplasty seems promising.
Barbato[13]	2017	Non-systematic and narrative	X	X	X	X		X				Summary of principles, technique, and evidence	Not stated.
Allen[27]	2019	Non-systematic and narrative	X	X	X	X						Summary of principles, technique, and evidence	Not stated.
Chambers[28]	2016	Non-systematic and narrative	X	X					X			Review of atherectomy devices.	Atherectomy may improve procedural outcomes.
Goel[29]	2019	Systematic with meta-analysis	X	X								Rotational versus orbital atherectomy	Except for fluoroscopy time, there are no differences between OA or RA in outcomes.
Baber[30]	2010	Non-systematic and narrative	X		X							Outline difficulties and interventional techniques for complex lesions	Unclear.
Shlofmitz[31]	2019	Non-systematic and narrative		X								Review of orbital atherectomy	Orbital atherectomy plays an important role in lesion preparation to ensure optimal results.
Chambers[32]	2014	Non-systematic and narrative		X						X		Review of orbital atherectomy	Orbital atherectomy may improve outcomes.
Khan[33]	2019	Systematic and narrative								X		Summarize outcomes of lithoplasty in peripheral and coronary artery disease.	Lithoplasty decreases vessel stenosis.
Kassimis[34]	2020	Non-systematic and narrative								X		Describe evidence and highlights the best clinical applications.	Lithoplasty is easy to use and has predictable results.
Zhang[35]	2014	Systematic with meta-analysis									X	Drug-eluting versus bare-metal stents	Drug-eluting stents are superior to bare-metal stents in terms of target lesion revascularization

161 RA = rotational atherectomy, OA = orbital atherectomy, CU = cutting balloon, SC = scoring balloon, HP = high pressure non-compliant

162 balloon, EX = excimer laser, LI = lithoplasty, ST = stent

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4 1635  
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7 164 **Objective**8  
9  
10 165 The objective of this review is to assess the beneficial and harmful effects of all percutaneous treatment  
11  
12 166 options to treat calcified coronary lesions.  
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15 167

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18 168 **METHODS AND ANALYSES**19  
20  
21 169 The protocol is registered at PROSPERO (registration CRD42021226034) and the methodology is based on  
22  
23 170 the Preferred Reporting Items for Systematic Reviews and Meta-Analysis - Protocols (PRISMA-P)  
24  
25 171 statement[36] and the Cochrane Handbook of Systematic Review of Interventions.[37] We plan to conduct  
26  
27  
28 172 the searches and analyses and to write the manuscript from September 2022 to November 2022.  
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31 173

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34 174 **Eligibility criteria**35  
36 175 Study designs37  
38  
39 176 Only randomized clinical trials will be included. Quasi-randomized trials and cluster randomized trials will  
40  
41  
42 177 not be included.  
43  
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47 179 Participants and coronary lesions48  
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50 180 We will include trials involving participants undergoing percutaneous coronary intervention on any native  
51  
52 181 coronary artery de-novo stenosis due to ST-segment elevation myocardial infarction (STEMI), non-STEMI,  
53  
54  
55 182 unstable angina, or chronic coronary artery disease. Participants must be enrolled in the trial based on  
56  
57 183 grading of the severity of coronary calcification or the trial must report prespecified subgroup analyses  
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184 based on the severity of lesion calcification. Any definition of the severity of calcification is accepted, but  
185 severity must correspond to moderate or severe to be eligible.

186

## 187 Interventions

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

193

## 194 Outcomes

### 195 Primary outcome

- 196 1. All-cause mortality.
- 197 2. Proportion of participants with one or more serious adverse events. We will use the 'International  
198 Conference on Harmonization of technical requirements for registration of pharmaceuticals for  
199 human use - Good Clinical Practice' (ICH-GCP) definition of a serious adverse event, which is any  
200 untoward medical occurrence that resulted in death, was life-threatening, required hospitalization  
201 or prolonging of existing hospitalization, and resulted in persistent or significant disability or  
202 jeopardized the participant.[38] If the trialists do not use this definition, we will include the data if  
203 the trialists use the term "serious adverse event." If the trialists do not use the ICH-GCP definition  
204 nor the term serious adverse event, then we will also include the data if the event clearly fulfills the  
205 ICH-GCP definition. We will secondly assess each type of serious adverse event separately.

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4 207 Secondary outcomes

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7 208 *Patient-oriented:*

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9  
10 209 1. Myocardial infarction (as defined by trialists).  
11  
12 210 2. Stroke (as defined by trialists).  
13  
14 211 3. Health-related quality of life (any validated continuous scale).  
15  
16 212 4. Proportion of participants with one or more non-serious adverse events (any adverse event not  
17  
18 213 classified as serious). We will exploratorily assess each adverse event separately.  
19  
20 214 5. Coronary angiography.  
21  
22

23  
24  
25 215 *Device-oriented:*

- 26  
27  
28 216 1. Target vessel myocardial infarction.  
29  
30 217 2. Target vessel revascularization.  
31

32  
33 218 Exploratory outcomes

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36 219 1. Any coronary revascularization.  
37  
38 220 2. In-stent restenosis (as defined by trialists).  
39  
40 221 3. Cardiovascular mortality (as defined by trialists).  
41  
42 222 4. Any physiological or imaging-derived measurement of improved myocardial perfusion after  
43  
44 223 intervention.  
45  
46 224 5. Proportion of participants with failed or no stenting.  
47  
48 225 6. Use of bailout atherectomy, stent delivery, successful device crossing, study group cross-over,  
49  
50 226 study-defined procedural success.  
51  
52 227 7. Procedure duration, fluoroscopy time, contrast dose.  
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4 229 Assessment time points  
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7 230 We will assess outcomes at maximum follow-up.  
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13 232 **Search strategy**  
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15  
16 233 One review author (ATK) will search Cochrane Central Register of Controlled Trials (CENTRAL), Medical  
17

18 234 Literature Analysis and Retrieval System Online (MEDLINE), Latin American and Caribbean Health Sciences  
19

20 235 Literature (LILACS), Science Citation Index Expanded (SCI-EXPANDED), and Excerpta Medica database  
21

22 236 (EMBASE) from inception to September 31<sup>st</sup>, 2022. No restrictions based on language or year of publication  
23

24  
25 237 will be applied. The search will be supplemented by manually screening the reference lists of included  
26

27 238 trials. The search strategy can be found in **supplemental file 1**.  
28  
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30 239  
31  
32

33 240 **Data collection**  
34

35  
36 241 The review will be reported as recommended by the Preferred Reporting Items for Systematic Reviews and  
37

38 242 Meta-Analysis (PRISMA) statement.[39]  
39  
40

41 243  
42  
43

44 244 **Selection of studies**  
45

46  
47 245 Two review authors (ATK and NTO) will independently screen search results based initially on title and  
48

49 246 abstract, then based on full-text review and provide reasons for exclusion of ineligible studies.  
50

51 247 Disagreements will be resolved through discussion, or by consulting a third person (JCJ).  
52  
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57 249 **Data extraction**  
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4 250 Two review authors (ATK and NTO) will independently extract data from included trials. The reviewers will  
5  
6 251 assess duplicate publications and companion papers of a trial together to evaluate all available data  
7  
8  
9 252 simultaneously.

10  
11 253  
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13  
14 254 From each trial, the following will be extracted: type of intervention, severity of calcification, trial design  
15  
16  
17 255 (parallel, factorial, or crossover), number of experimental groups, length of follow-up, number of  
18  
19 256 randomized participants, number of participants (analyzed, lost to follow-up, withdrawn, or crossover),  
20  
21 257 outcome data (only data from last follow-up time), types of comorbidities, age range, sex ratio, and risk of  
22  
23  
24 258 bias domains (see below).

#### 25 26 26 259 27 28 29 260 **Assessment of risk of bias**

30  
31  
32 261 Risk of bias will be evaluated by the Cochrane Risk of Bias tool (version 2) using five bias domains, each  
33  
34 262 classified as either low risk of bias, some concerns, or high risk of bias.[40] Bias assessment will be  
35  
36  
37 263 conducted on an outcome level.

#### 38 39 40 264 41 42 265 1: Bias arising from the randomization process

43  
44  
45 266 Low risk of bias: Adequately concealed allocation and absence of baseline imbalances between groups, and  
46  
47 267 random or unpredictable method to generate the allocation sequence. Some concerns: 1) Adequately  
48  
49  
50 268 concealed allocation and a problem with the method of sequence generation or baseline imbalances that  
51  
52 269 suggest a problematic randomization process, or 2) if no information is provided about concealment of  
53  
54 270 allocation and baseline imbalances appear to be compatible with chance, or 3) if no information to answer  
55  
56 271 any of the signaling questions. High risk of bias: 1) Allocation sequence not adequately concealed, or 2)

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272 there is no information about concealment of the allocation sequence and baseline imbalances that  
273 suggest a problem with the randomization process.

274

275 2: Bias due to deviation from intended interventions

276 Low risk of bias: 1) If participants, carers, and people delivering the interventions were unaware of  
277 randomization groups during the trial, or 2) aware of intervention groups during the trial but deviations  
278 from the intended were usual practice, or unlikely to impact the outcome and no participants were  
279 analyzed in a group that the participant was not assigned to. Some concerns: Participants, carers, and  
280 people were aware of intervention groups and 1) there was no information on whether there were  
281 deviations from the intended interventions, or 2) there were deviations from the interventions but the  
282 deviations were not likely to have affected outcome, or were balanced between the groups. High risk of  
283 bias: Participants, carers or people were aware of the intervention groups during the trial and there were  
284 deviations from the intended interventions that were unbalanced between the groups and likely to have  
285 affected the outcome, or some participants were analyzed in the wrong intervention group, and there was  
286 potential for substantial impact on the estimated effect size.

287

288 3: Bias due to missing outcome data

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

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#### 295 4: Bias in measurement of outcomes

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

300

#### 301 5: Bias arising from selective reporting of results

302 Low risk of bias: Reported outcome data was unlikely to have been selected on the basis on the results  
303 from multiple outcome measurements. Some concern: Insufficient information available to rule out the  
304 possibility of selective outcome reporting on the basis of the results from multiple outcome measurements.  
305 High risk of bias: Reported data is likely to have been selected on the basis of the results from multiple  
306 outcome measurements or analyses.

307

#### 308 Overall assessment of risk of bias

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

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#### 314 **Differences between the protocol and review**

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

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## 318 **Measurement of treatment effect**

319 Continuous outcomes

320 Mean differences with 95% confidence intervals (CI) and Trial Sequential Analysis adjusted 95% CI will be  
321 calculated.

322

323 Dichotomous outcomes

324 Risk ratios (RRs) with 95% CI and Trial Sequential Analysis adjusted 95% CI will be calculated.

325

## 326 **Dealing with missing data**

327 Trialists will be contacted to obtain relevant missing data.

328

## 329 **Assessment of heterogeneity**

330 Signs of heterogeneity will primarily be assessed by forest plots, and secondly by the  $I^2$  statistic[40–42] and  
331 the restricted maximum likelihood method.[43,44] It may be decided that meta-analysis is inappropriate if  
332 heterogeneity is high.

333

## 334 **Data synthesis**

335 Results of each type of intervention will be analyzed separately based on intention-to-treat data. Rstudio  
336 and Stata version 16 (StataCorp LLC, College Station, TX, USA) will be used for analyses.

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7 338 Meta-analysis

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10 339 Meta-analysis will be conducted according to the Cochrane Handbook of Systematic Reviews of  
11  
12 340 Interventions,[40] Keus et al.,[45] and Jakobsen et al.[46] and supplemented by Trial Sequential Analysis.  
13  
14 341 Intervention effects will be analyzed with both a random-effects and fixed-effect meta-analysis for each  
15  
16 342 comparison. The estimate with the highest  $p$  value will be primarily used. Because we assess two primary  
17  
18 343 outcomes, we will consider a  $p$  value of 0.03 or less as statistically significant.[46]  
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25 345 Trial Sequential Analysis

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28 346 Trial Sequential Analysis is a test of the statistical reliability of data in meta-analyses. Trial Sequential  
29  
30 347 Analysis adjusts significance levels for sparse data and controls the risk of both type I and type II errors due  
31  
32 348 to accumulating data.[47] Trial Sequential Analysis will be performed on all outcomes to calculate the  
33  
34 349 required information size (number of participants required in the meta-analysis to confirm or reject a given  
35  
36 350 intervention effect) and the cumulative Z-curve's breach of relevant trial sequential monitoring  
37  
38 351 boundaries.[47,48] For dichotomous outcomes, the required information size will be calculated based on  
39  
40 352 the observed proportion of patients with an outcome in the control group, a relative risk reduction or  
41  
42 353 increase of 25%, an alpha of 3.3% for all outcomes, a beta of 10%, and the observed diversity as suggested  
43  
44 354 by the trials in the meta-analysis. For continuous outcomes, the information size will be calculated based  
45  
46 355 on the observed standard deviation (SD), a mean difference equal to the observed SD/2, an alpha of 3.3%  
47  
48 356 for all outcomes, a beta of 10%, and the observed diversity as suggested by the trials in the meta-analysis.  
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56 358 Network meta-analysis

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4 359 The synthesis comparator consists of all the interventions listed in the Eligibility Criteria section, as well as  
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6 360 placebo, standard care, no intervention, or “active placebo” trials. Interventions will be analyzed separately  
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8  
9 361 and not grouped. The characteristics of the trials and their populations will be described by frequencies and  
10  
11 362 percentages for dichotomous data and means with SD for continuous data. Descriptive statistics for each  
12  
13 363 treatment comparison will be generated describing important clinical and methodological characteristics.  
14  
15 364 Each outcome dataset will be presented in a separate network diagram, where the size of the nodes is  
16  
17  
18 365 proportional to the total number of participants, and the width of each line corresponds to the number of  
19  
20 366 studies comparing the connected treatments. Furthermore, the connecting lines will be marked according  
21  
22 367 to the average risk of bias per treatment comparison, using green for low, yellow for moderate, and red for  
23  
24 368 high risk of bias. It is assumed that any participant who meets inclusion criteria is equally likely to be  
25  
26  
27 369 randomized to each intervention in the comparator set. The analyses will be conducted using Stata under  
28  
29 370 frequentist framework (command: mvmeta).[49]  
30  
31  
32 371 Network meta-analysis will only be conducted if a connected network of trials can be constructed. If  
33  
34 372 conducted, the assumptions of transitivity and consistency will be assessed prior to analysis. The  
35  
36 373 assumptions will be assessed in five steps. First, a network geometry will be drawn to review the network  
37  
38  
39 374 relationship. Second, the transitivity assumption across treatment comparisons will be assessed using  
40  
41 375 boxplots. The assumption of consistency will be evaluated using the design-by-treatment interaction model  
42  
43 376 as a global test.[50,51] Third, a network forest or interval plot is made to illustrate the summary effect size  
44  
45 377 of the comparative effectiveness of the interventions. Fourth, is to calculate the cumulative rankings to  
46  
47  
48 378 identify a superiority among interventions. Fifth, is to evaluate publication bias or effect modifiers for a  
49  
50 379 valid inference from results. Effects estimates will be reported using relevant effect size (RR, MD, or SMD),  
51  
52 380 a 95% CI, and a 95% prediction interval.  
53  
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55 381  
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58 382 Planned subgroup analyses  
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4 383 For trials comparing stent types, the following categories will be applied: a) Bare metal stents, b) first-  
5  
6 384 generation drug-eluting stents, and c) later-generation drug-eluting stents.  
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### 11 12 386 **Summary of findings table** 13

14  
15 387 For each prespecified outcome, a summary of findings table will be created. The five GRADE considerations  
16  
17 388 (bias risk, consistency of the effect, imprecision, indirectness, and publication bias) will be used to assess  
18  
19  
20 389 the certainty of the evidence.[52] Imprecision will be assessed using Trial Sequential Analysis. All  
21  
22 390 downgrading of the certainty of the evidence will be justified in writing.  
23  
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### 27 28 392 **Patient and Public Involvement statement** 29

30  
31 393 Patients were not directly involved in the planning of this study.  
32  
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## 36 395 **DISCUSSION** 37

38  
39 396 Coronary calcifications complicate all aspects of percutaneous coronary intervention and are a risk factor  
40  
41  
42 397 for short- and long-term complications.[9,11] Several treatment options exist, but there is no consensus  
43  
44 398 regarding the optimal choice of treatment strategy. This systematic review with meta-analysis, Trial  
45  
46 399 Sequential Analysis, and network meta-analysis aims to assess the beneficial and harmful effects of all  
47  
48 400 percutaneous treatment options in the treatment of calcified coronary lesions.  
49

50  
51 401 This protocol has several methodological strengths. First, the methodology is predefined and based on the  
52  
53 402 PRISMA guidelines[36] and the Cochrane Handbook for Systematic Reviews of Interventions.[40] Second,  
54  
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56 403 risk of bias will be assessed, and significance thresholds will be adjusted to control for random and  
57  
58 404 systematic errors. The primary limitation of the review is the combined assessment of all available  
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405 interventions, which may require many analyses and cause problems with multiplicity. The results of the  
406 review will be interpreted considering this increased risk of type 1 errors.

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## 408 **ETHICS AND DISSEMINATION**

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

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414

### 415 **Competing interests statement**

416 All authors declare that they have no competing interests.

417

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421

### 422 **Contributors:**

423 ATK, JCJ, and NTO drafted the manuscript. NTO had the original idea for the study. All authors read and  
424 approved the final manuscript. ATK is the guarantor of the protocol.

425

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563 **Supplemental Material**

564 Supplemental File 1: Search strategies.

For peer review only

**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 myocardialinfarct\* 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 myocardialinfarct\* 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 atherectom\* 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 atherectom\$ 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 atherectom\* or balloon\*)

#2 TS=(calcif\* or calcinos\*)

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



## PRISMA-P 2015 Checklist

This checklist has been adapted for use with systematic review protocol submissions to BioMed Central journals from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement *Systematic Reviews* 2015 4:1

An Editorial from the Editors-in-Chief of *Systematic Reviews* details why this checklist was adapted – Moher D, Stewart L & Shekelle P: Implementing PRISMA-P: recommendations for prospective authors. *Systematic Reviews* 2016 5:15

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
<b>ADMINISTRATIVE INFORMATION</b>					
<b>Title</b>					
Identification	1a	Identify the report as a protocol of a systematic review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	<input checked="" type="checkbox"/>	<input type="checkbox"/>	1
<b>Registration</b>	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	<input checked="" type="checkbox"/>	<input type="checkbox"/>	39
<b>Authors</b>					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	<input checked="" type="checkbox"/>	<input type="checkbox"/>	3-10
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	423-424
<b>Amendments</b>	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	<input checked="" type="checkbox"/>	<input type="checkbox"/>	314-316
<b>Support</b>					
Sources	5a	Indicate sources of financial or other support for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	419-420
Sponsor	5b	Provide name for the review funder and/or sponsor	<input checked="" type="checkbox"/>	<input type="checkbox"/>	419-420
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	<input checked="" type="checkbox"/>	<input type="checkbox"/>	419-420
<b>INTRODUCTION</b>					
<b>Rationale</b>	6	Describe the rationale for the review in the context of what is already known	<input checked="" type="checkbox"/>	<input type="checkbox"/>	56-159

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
<b>Objectives</b>	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	180-185
<b>METHODS</b>					
<b>Eligibility criteria</b>	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	180-192
<b>Information sources</b>	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	<input checked="" type="checkbox"/>	<input type="checkbox"/>	233-238
<b>Search strategy</b>	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Supplemental File 1
<b>STUDY RECORDS</b>					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	241-258
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	241-258
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	<input checked="" type="checkbox"/>	<input type="checkbox"/>	241-258
<b>Data items</b>	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	<input checked="" type="checkbox"/>	<input type="checkbox"/>	241-258
<b>Outcomes and prioritization</b>	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	<input checked="" type="checkbox"/>	<input type="checkbox"/>	195-227
<b>Risk of bias in individual studies</b>	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	<input checked="" type="checkbox"/>	<input type="checkbox"/>	261-312
<b>DATA</b>					
<b>Synthesis</b>	15a	Describe criteria under which study data will be quantitatively synthesized	<input checked="" type="checkbox"/>	<input type="checkbox"/>	335-380
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., $I^2$ , Kendall's tau)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	387-390
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	383-384
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	<input checked="" type="checkbox"/>	<input type="checkbox"/>	387-390

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
<b>Meta-bias(es)</b>	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	335-380
<b>Confidence in cumulative evidence</b>	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	387-390

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