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## Protocol

# BMJ Open Do bisphosphonates and RANKL inhibitors alter the progression of coronary artery calcification? A systematic review and meta-analysis protocol

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## ABSTRACT

**Introduction** Whether bisphosphonates and RANKL inhibitors play a novel role in delaying cardiovascular calcification is unknown. Their action on regulatory enzymes in the mevalonic acid pathway, which is implicated in both bone and lipid metabolism, may be a novel therapeutic target to manage coronary artery disease (CAD). Such therapies may particularly be relevant in those for whom traditional cardiovascular therapies are no longer sufficient to control disease progression.

**Methods and analysis** We will perform a systematic review which aims to synthesise evidence regarding whether use of bisphosphonates or use of the RANKL inhibitor denosumab delays coronary artery calcium (CAC) progression. Eligible studies will include longitudinal studies investigating CAC progression in patients aged >18 years taking either a bisphosphonate or denosumab compared with those who do not. Embase, MEDLINE and Cochrane will be searched using prespecified search terms. Studies will be screened by title and abstract independently and then in full to determine suitability for inclusion in the review. Extracted data will include that relating to study and participant characteristics. The primary outcome will be the CAC score. Secondary outcomes will include aortic and carotid artery calcification. Meta-analysis will be performed if sufficient data are available.

**Ethics and dissemination** This study does not require ethics as it is a systematic review of the literature. The results of the review described within this protocol will be distributed via presentations at relevant conferences and publication within a peer-reviewed journal.

**PROSPERO registration number** The systematic review pertaining to this protocol is registered with PROSPERO (Registration ID: CRD42022312377).

## INTRODUCTION

Coronary artery disease (CAD) remains the leading cause of morbidity and mortality globally, accounting for approximately 18 million deaths, annually.<sup>1</sup> Coronary artery calcium (CAC) is a highly specific marker of established atherosclerotic plaques.<sup>2</sup> CAC scores are attained from axial non-contrast CT slices

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Studies included in the review will not be limited to study design; both randomised controlled trials and observational studies will be included if they otherwise meet the inclusion criteria. This means fewer potentially relevant studies will be missed in synthesising the literature on this topic.
- ⇒ The review will synthesise the evidence regarding the cardiovascular effects of both bisphosphonates and the RANKL inhibitor, denosumab, which has not been performed previously.
- ⇒ The review will be generalisable to the wider population as studies included will not be restricted to particular patient subgroups, such as those with chronic kidney disease, those undergoing haemodialysis, or postmenopausal women. This will allow for more thorough subgroup analyses if meta-analysis is conducted.
- ⇒ The review is limited to studies which have been published.
- ⇒ The review is limited to studies published in the English language.

and are calculated using a numerical value, known as the modified Agatston score.<sup>3</sup> This can further be classified as a percentile based on the patient's age, sex and ethnicity.<sup>4</sup> The CAC score is a useful tool in predicting an asymptomatic patient's risk of myocardial infarction and sudden cardiac death in the next 10 years.<sup>5</sup> Evidence has shown that those with a moderately elevated CAC score may benefit from escalation of pharmacotherapy including statin therapy to diminish cardiovascular risk.<sup>6 7</sup> Hence, the CAC score is highly useful in guiding pharmacotherapy in these intermediate-risk patients. The reverse is also advantageous in that CAC scores may help identify patients who would derive minimal benefit from medication, and thus, eliminate the risks of long-term side effects and ongoing costs from unwarranted therapy.

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Bisphosphonates and NF- $\kappa$ B ligand (RANKL) inhibitors are medications typically indicated for the management of osteoporosis. Their introduction to the pharmacological sphere has considerably reduced the incidence of pathological fractures and consequent rates of disability in patients with osteoporosis. Novel evidence suggests that there may be a role for their use in reducing the progression of CAD via their effects on atheroma formation.<sup>8-9</sup> Bisphosphonates have been shown to inhibit the progression of ectopic calcification through inhibitory action on the crucial regulatory enzyme, farnesyl pyrophosphate synthase, in the mevalonic acid pathway, which is implicated in both bone and lipid metabolism.<sup>8-9</sup> RANKL inhibitors interfere with the glycoprotein, osteoprotegerin (OPG) and other signalling pathways, again involved in lipid metabolism. Furthermore, the pathophysiological processes underpinning both osteoporosis and atherosclerosis are hypothesised to overlap.<sup>10</sup> While the exact mechanisms remain unclear, one key hypothesis has been proposed involving OPG, which prevents the development and survival of osteoclasts, which function to resorb bone.<sup>11</sup> Therefore, in those with malfunctioning or deficient OPG, osteoclast-induced bone resorption is dysregulated, and inappropriate loss of the trabecular meshwork occurs, clinically resulting in osteopaenia or osteoporosis. Similarly, OPG is released from vascular smooth muscle cells in the tunica media of arteries and function in a parallel way.<sup>12</sup> In clinical studies, deficient OPG serum levels have been shown to be associated with increased incidence of pathological fractures and cardiovascular mortality.<sup>13-14</sup> This suggests that the fundamental biochemical mechanisms of the two pathologies are likely shared. Moreover, calcified plaques shown on unenhanced CT images are almost indistinguishable from bone itself, further suggesting that the underlying biochemical pathways involved in bone formation may be alike those in vascular calcification. The implication of such could mean an additional therapeutic target in managing CAD, which is especially noteworthy in those for whom traditional cardiovascular therapies are no longer sufficient to control disease progression.

There are two generations of bisphosphonates: the 'simple' bisphosphonates (S-BPs) and the more recently developed nitrogen-containing bisphosphonates (NC-BPs). These categories are established based on the molecular structure of the drug, as well as the mechanism by which the drug inhibits osteoclastic activity.<sup>15</sup> Etidronate is one such S-BP whose effects on CAD and vascular calcification have been well documented. Three studies have shown that etidronate may delay CAD progression, which has been measured through the surrogate endpoints of aortic calcification scores, CAC scores and carotid artery intima-media thickness, respectively.<sup>16-18</sup> Two other papers further support the notion that etidronate may delay or halt vascular calcification, specifically in the abdominal aorta.<sup>19-20</sup> NC-BPs include alendronate, pamidronate, zoledronate and risedronate, of which

alendronate is the most studied. The effects of N-BPs on vascular calcification are somewhat varying in the literature. Several randomised controlled trials (RCTs) have demonstrated that alendronate is protective against CAD progression, again through reduction in carotid intima-media thickness<sup>21-22</sup> and total volume of vascular calcification.<sup>23-24</sup> These trials all contained fewer than 75 patients, with effects on vascular calcification largely observed in patients with chronic kidney disease or in those receiving haemodialysis only. Meanwhile, one small pilot study by Hill *et al* showed that there was no significant difference in progression in CAC between those receiving alendronate and the control group.<sup>25</sup>

There is very limited evidence assessing the role of the RANKL inhibitor, denosumab, in progression of vascular calcification. A recent RCT revealed that there was no significant difference in CAC and carotid artery intima-media thickness between those on denosumab versus control after 12-month follow-up.<sup>26</sup> Conversely, another study revealed that denosumab may indeed suppress the progression of CAC,<sup>27</sup> although this was specific to patients with secondary hyperparathyroidism. These conflicting data highlight the need for amalgamation of the literature by means of a systematic review.

Over the last 10 years, two systematic reviews have been performed on similar topics. The first investigated the effects of bisphosphonates on multiple vessels, including the carotids, coronaries, and aorta in patients undergoing haemodialysis.<sup>28</sup> However, the review published a decade ago included only two papers which investigated the effects of the S-BP, etidronate, on CAC specifically, in a highly selected population group, limiting the generalisability of the findings. The second, more recent study was also limited by the inclusion of small sample size studies and a short duration of follow-up. Consequently, the effect size of bisphosphonate use could not be accurately quantified. Furthermore, the authors recognised that some of the articles included in their study were of suboptimal quality, as the risk of bias was high in the categories of allocation concealment and blinding.<sup>29</sup> This may have inadvertently led to an overestimation of the cardiovascular benefit of bisphosphonate use. Additionally, no systematic review has explored the impact of denosumab on vascular calcification.

Our review will not only further evaluate the effect of bisphosphonate use on cardiovascular disease, but it will also appraise the role of denosumab in CAC progression. If a true association between bisphosphonate or RANKL inhibitor use and CAC can be established by this review in a large cohort of individuals from a diverse range of ages, both sexes, and comorbidities, it may warrant their use in those with elevated CAC. This could prove vital in both the primary and the secondary prevention of cardiovascular events in those who are at high risk of severe complications.

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<b>Table 1</b> PICO-D criteria for inclusion of studies in the review	
Participants	Participants in the included studies must be over the age of 18 and have a CAC score documented. Participants will not be limited according to sex or presence of comorbidities.
Intervention	The intervention group must have a CAC score measured at baseline, prior to receiving bisphosphonate or denosumab therapy . CAC scoring must be repeated at least 6 months following the commencement of therapy.
Comparator	Patients who are not receiving or have not received the aforementioned medications. CAC must be measured at baseline and repeated at a second time point, which is at least 6 months following the initial CAC score.
Outcomes	Coronary artery calcification as quantified by the CAC score (modified Agatston score) or other appropriate method of measuring CAC. Studies will be included if they measure the CAC at least twice to monitor progression.
CAC, coronary artery calcium.	

AIMS AND OBJECTIVES

The primary aim of the systematic review is to evaluate the relationship between the use of bisphosphonates and the RANKL inhibitor, denosumab, with CAC. A systematic review correlating the use of these medications with coronary artery calcification specifically has not yet been performed. We hypothesise that there will be an inverse relationship between bisphosphonate and denosumab use and CAC. Furthermore, this review aims to assess the relationship between these medications and the degree of aortic and carotid calcification.

METHODS  
Registration

The methods of the systematic review are described as per the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines. A checklist is included as online supplemental file 1. The final reporting of this study will be compliant with the main PRISMA statement. The systematic review pertaining to this protocol is registered with PROSPERO (Registration ID: CRD42022312377).

Eligibility criteria

Definitions as per PICO-D have been adapted for the purpose of this review. An article will be included in the study if it meets the PICO-D criteria as outlined in table 1. There are multiple controls which may be presented in studies suitable for inclusion, including patients receiving placebo, and patients receiving standard therapy. However, as different controls result in differing reported outcome measures, we will only include studies which use placebo as the control.

Timing

Studies from all countries published from inception of database and the time of performing the review.

Design

This systematic review focuses on observational studies and RCTs. Studies will be excluded if they are performed on animals, are cases reports, case series, conference abstracts, letters to the editor, or review articles. Studies

will also be excluded if they are published in a language other than English.

Information sources

A structured search of MEDLINE (inception–present), Embase (inception–present) and the Cochrane Central Register of Controlled Trials (CENTRAL) will be performed. Citation lists of any relevant papers found will be hand searched to identify any further pertinent articles.

Search strategy

The search strategy was developed by a medical librarian (online supplemental file 2), with search syntax altered as appropriate according to each database’s subject headings and thesaurus. Keywords included coronary artery calcium, bisphosphonates, RANKL inhibitors, and denosumab.

Data management and software

EndNote V.20.2.1 and Microsoft Excel V.2019 16.0.6742.2048 will be used for study selection and data extraction, respectively. The data in both files will be stored on a shared, password protected drive, accessible by other reviewers granted access by the principal investigator only. Versioned files will be created at key stages of the review, with older versions of the file kept for record-keeping purposes. Review Manager (RevMan V.5.4) will be used for meta-analysis if deemed appropriate.

Study selection

The articles yielded by the search will be screened by title and abstract against our inclusion and exclusion criteria. Following initial title/abstract screening, the full text of potentially eligible papers will then be appraised for final inclusion in the systematic review. They will be categorised into three groups: ‘appropriate’, ‘inappropriate’ and ‘unsure’, by two independent reviewers. Cross-referencing of this categorisation will then be performed. Articles that are classified as ‘appropriate’ by both reviewers will be reviewed in full text. Those classified as ‘inappropriate’ by both reviewers will be excluded. Articles that are categorised as ‘unsure’ by either reviewer will be further discussed with a third reviewer for classification.



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Where there is a discrepancy in the inclusion status of any study, a third reviewer will act as the adjudicator. This process will be documented in a PRISMA flow diagram.

### Data collection

Two independent reviewers (SLS, NM) will extract data items from included reviews as per a standardised data extraction form (online supplemental file 3). Authors of the included studies will be contacted if required to clarify information from the paper in question, or to gather missing data. The form will be piloted to be optimised by the two reviewers using a subset of randomly selected studies that satisfy the eligibility criteria. Reviewers will independently extract data from the rest of the included list of articles.

### Data items

General information pertaining to each study will be extracted, including the title of the paper and its citation, author, and year of publication. Study characteristics will also be extracted, including country of origin, study design, aims and objectives of the study, number of participants in the control and intervention groups, respectively, medication dose, route, and frequency, and follow-up timeframe. Participant characteristics to be extracted will include the number of participants in the study, in total, and in each of the control and intervention groups. Demographic data will include age, sex, smoking status, body mass index, the presence of diagnosed pathologies including hypertension, diabetes, dyslipidaemia and chronic kidney disease, and a positive family history of CAD.

### Outcomes and prioritisation

The primary outcome is difference in CAC from timepoint zero to follow-up in patients using either a bisphosphonate or denosumab compared with those who have not. As CAC is a virtually continuous variable, the mean difference (or standardised mean difference if more appropriate) will be reported on. The secondary outcomes of the review are carotid artery intima-media thickness and aortic calcification, both measured in cubic millimetres, in those using either a bisphosphonate or denosumab compared with placebo.

### Risk of bias

Risk of bias will be assessed using the ROBINS-I tool<sup>30</sup> for non-randomised studies and the RoB2 tool<sup>31</sup> for RCTs. This will be completed as per the following categories for observational studies: bias due to confounding, bias in the selection of participants into the study, bias in classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in the measurement of outcomes, and bias in the selection of the reported result. RCTs will be evaluated as per the following domains: bias arising from the randomisation process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in the measurement of outcome, and bias in selection of the

reported results. The studies will then be graded as low, moderate or high for risk of bias per criterion, and for overall bias.

### Data synthesis and analysis

Studies will be included if they fulfil the eligibility criteria. Data will be presented narratively and complemented with tables and figures as appropriate. The outcomes of each study will be extracted, as well as any statistical significance. Raw data will be collected. P values will be reported where available, as stated by the study authors. Lastly, the main conclusions drawn by the authors will be extracted. Meta-analysis will be performed on the data using RevMan V.5.4. To account for heterogeneity, subgroup analysis will be performed to further explore any differences in CAC scores and medication use. The likely subgroups investigated will be women with osteoporosis and patients undergoing dialysis, as these groups have been studied more frequently, as identified in preliminary studies. Meta-regression will only be performed if more than 10 studies are included in the review, as per Cochrane recommendations. If suitable, a pooled analysis of the effect of bisphosphonate versus RANKL inhibitors on CAC will be performed.

### ETHICS AND DISSEMINATION

This study is a systematic review; therefore, it does not require ethics approval. The results of the review described within this protocol will be distributed via presentations at relevant conferences and publication within a peer-reviewed journal.

**Contributors** NM conducted scoping searches and piloted the data extraction form. SLS drafted the manuscript, designed the data extraction template and manages the overall review. KC, NSM and SRG reviewed and edited the manuscript. SLS, NSM and KC were involved in study selection, data extraction and data analysis. SLS and GS were involved in conceptualisation of the question. All authors read and approved the final manuscript before submission.

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**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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## Correction

## Correction: 'Do bisphosphonates and RANKL inhibitors alter the progression of coronary artery calcification? A systematic review and meta-analysis protocol'

Saunders SL, McOrist NS, Chaudhri K, *et al.* Do bisphosphonates and RANKL inhibitors alter the progression of coronary artery calcification? A systematic review and metaanalysis protocol. *BMJ Open* 2022;12:e066255. doi:10.1136/bmjopen-2022-066255

This article has been corrected since it was published online. The order of authors has been changed from “Samantha Louise Saunders, Nathan Scott McOrist, Kanika Chaudhri, Sonali R Gnanenthiran, Grant Shalaby” to “Saunders SL, Chaudhri K, McOrist NS, Gnanenthiran SR, Shalaby G”.

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# Reporting checklist for protocol of a systematic review and meta analysis.

Based on the PRISMA-P guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

Reporting Item			Page Number
Title			
Identification	<a href="#">#1a</a>	Identify the report as a protocol of a systematic review	1
Update	<a href="#">#1b</a>	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration			
	<a href="#">#2</a>	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors			
Contact	<a href="#">#3a</a>	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Title Page

Contribution	<a href="#">#3b</a>	Describe contributions of protocol authors and identify the guarantor of the review	Title Page
Amendments			
	<a href="#">#4</a>	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	N/A
Support			
Sources	<a href="#">#5a</a>	Indicate sources of financial or other support for the review	11
Sponsor	<a href="#">#5b</a>	Provide name for the review funder and / or sponsor	11
Role of sponsor or funder	<a href="#">#5c</a>	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	N/A
Introduction			
Rationale	<a href="#">#6</a>	Describe the rationale for the review in the context of what is already known	6
Objectives	<a href="#">#7</a>	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	7
Methods			
Eligibility criteria	<a href="#">#8</a>	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	7
Information sources	<a href="#">#9</a>	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	8
Search strategy	<a href="#">#10</a>	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	8



Supplemental material	BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)			BMJ Open
Study records - data management	<a href="#">#11a</a>	Describe the mechanism(s) that will be used to manage records and data throughout the review	8	
Study records - selection process	<a href="#">#11b</a>	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	9	
Study records - data collection process	<a href="#">#11c</a>	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	9	
Data items	<a href="#">#12</a>	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	9	
Outcomes and prioritization	<a href="#">#13</a>	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	10	
Risk of bias in individual studies	<a href="#">#14</a>	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	10	
Data synthesis	<a href="#">#15a</a>	Describe criteria under which study data will be quantitatively synthesised	10-11	
Data synthesis	<a href="#">#15b</a>	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 (such as I <sup>2</sup> , Kendall's $\tau$ )	10-11	
Data synthesis	<a href="#">#15c</a>	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	10-11	
Data synthesis	<a href="#">#15d</a>	If quantitative synthesis is not appropriate, describe the type of summary planned	N/A	
Meta-bias(es)	<a href="#">#16</a>	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	10	

Confidence in cumulative evidence	<a href="#">#17</a>	Describe how the strength of the body of evidence will be assessed (such as GRADE)	11
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## Supplementary File 2 – Search Strategy

The following were searched using the parameter Title/Abstract

1. coronary artery calcium OR CAC OR coronary artery calcification
2. coronary artery plaque OR coronary plaque
3. coronary atherosclerosis
4. coronary artery calcium score OR calcium score OR coronary calcium score OR CAC score
5. 1 + 2 + 3 + 4
6. bisphosphonate OR bisphosphonates
7. alendronate OR alendronic acid
8. etidronate OR etidronic acid
9. pamidronate OR pamidronic acid
10. zoledronate OR zoledronic acid
11. risedronate OR risedronic acid
12. ibandronate OR ibandronic acid
13. minodronate OR minodronic acid
14. neridronate OR neridronic acid
15. RANKL OR RANKL inhibitor OR RANK-L or RANK-L inhibitor
16. denosumab
17. 6 + 7 + 8 + 9 + 10 + 11 + 12 + 13 + 14 + 15 +16
18. 5 AND 17
19. Limited to studies published in English, only