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Do bisphosphonates and RANKL inhibitors alter the progression of coronary artery calcification? A systematic review

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ABSTRACT

Objectives To determine whether bisphosphonates and NF-κB ligand (RANKL) inhibitors delay coronary artery calcification (CAC).

Design A systematic review was conducted.

Data sources MEDLINE, EMBASE and CENTRAL.

Eligibility criteria Longitudinal studies investigating CAC progression in adults (>18 years) taking either a bisphosphonate or denosumab compared with those who did not.

Data extraction and synthesis Study and participant characteristics, and primary outcome (ΔCAC from baseline to follow-up) were extracted. The Risk Of Bias In Non-Randomised Studies-of Interventions (ROBINS-I) and Risk-of-Bias Tool for Randomised Trials (RoB2) tools were used to assess the risk of bias for observational and randomised controlled trials (RCTs), respectively. Outcome measures were reported.

Results Four observational studies and one RCT (n=377) were included. Three studies solely reported the effect of bisphosphonates on ΔCAC; one study (n=56) demonstrated a statistically significant CAC reduction in the intervention group (−372 mm^3/year) compared with control (+159 mm^3/year) (p<0.01). One study (n=14) demonstrated a difference in ΔCAC between intervention (+880 mm^3/year) versus control (+2220 mm^3/year), however, no p value comparing groups was reported. One study (n=115) found no statistically significant difference between intervention and control.

One study (n=42) exclusively investigated the effect of RANKL on ΔCAC; there was a statistically significant reduction in CAC at 6-month follow-up between intervention (−133±124 modified Agatston unit (AU)) and control (+188±72 modified AU), p=0.03.

One study (n=150) compared both bisphosphonates and denosumab to control and found no statistically significant difference between either intervention group and control over 24 months. Meta-analysis was not performed due to limited, heterogeneous studies.

Conclusions There is insufficient evidence supporting the correlation between bisphosphonate or RANKL inhibitor use and CAC progression. Further research is warranted.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Studies included in the review were not limited to study design; this means that most potentially relevant studies were not missed in synthesising the literature on this topic.
⇒ Three large databases were systematically searched from inception to the time of the first submission of the review, and therefore, it is unlikely that relevant articles were missed for potential inclusion in the study.
⇒ Meta-analysis was unable to be performed in view of the small number of heterogeneous papers eligible for inclusion in the review.
⇒ The review is limited to studies which have been published.
⇒ The review is limited to studies published in the English language.

INTRODUCTION

Coronary artery disease (CAD) is the leading cause of morbidity and mortality worldwide, accounting for 17.9 million deaths, annually.[1] Coronary artery calcium (CAC) is a highly specific marker of established atherosclerotic plaques[2] and is attained from axial non-contrast computed tomography (CT) slices. It is reported as the modified Agatston score, which is expressed as Agatston units (AUs).[3] CAC scoring has been shown to predict the risk of future cardiovascular events in asymptomatic patients.[4]

Bisphosphonates and NF-κB ligand (RANKL) inhibitors are medications typically indicated for the management of osteoporosis. Evidence suggests that there may be a role for their use in reducing the progression of CAD, via their effects on plaque formation.[5 6] Bisphosphonates have been shown to inhibit the crucial regulatory enzyme, farnesyl pyrophosphate synthase in the mevalonic acid pathway, which is implicated in both bone and lipid metabolism, and thus

alter the progression of ectopic calcification.[5 6] RANKL inhibitors, including denosumab, interfere with the glycoprotein, osteoprotegerin and other signalling pathways, again involved in lipid metabolism. Furthermore, calcified plaques shown on unenhanced CT images are much alike to bone itself. Together, this information suggests that the fundamental underlying biochemical pathways involved in bone formation and vascular calcification are likely shared. The implication of such could mean an additional therapeutic target in managing CAD, which is relevant in those for whom traditional cardiovascular therapies are no longer sufficient to control disease progression.

Etidronate is one bisphosphonate whose effects upon CAD have been studied. Three studies have shown that etidronate may delay the progression of CAD, which has been measured through the surrogate endpoints of aortic calcification scores, CAC scores and carotid artery intima–media thickness, respectively.[7–9] The effects of nitrogen-containing bisphosphonates (NC-BPs), however, on vascular calcification are contradictory in the literature. Some randomised controlled trials (RCTs) have suggested that alendronate, the most studied of the NC-BPs, is protective against CAD progression, again through a reduction in carotid intima–media thickness,[10 11] and total volume of vascular calcification.[12 13] These trials all contained less than 75 patients, with effects on vascular calcification largely observed in patients with chronic kidney disease (CKD) or in those receiving haemodialysis, only. Meanwhile, one small pilot study by Hill *et al*, showed that there was no significant difference in CAC progression between those receiving alendronate and placebo.[14]

There is very limited evidence assessing the role of the RANKL inhibitor, denosumab, in the progression of vascular calcification. A recent RCT revealed that after 12-month follow-up there was no significant difference in CAC and carotid artery intima–media thickness between those on denosumab versus control.[15] Conversely, another study demonstrated that denosumab may indeed suppress the progression of CAC,[16] although this was restricted to patients with secondary hyperparathyroidism. These conflicting data highlight the need for consolidation of the literature by means of a systematic review.

Over the last decade, 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.[17] However, the review published 10 years ago included only two papers which investigated the effects of 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. Additionally, no systematic review to our knowledge has explored the impact of denosumab on vascular calcification.

The primary aim of the systematic review was to evaluate the relationship between the use of bisphosphonates and the RANKL inhibitor, denosumab, with CAC. We hypothesised that there would be an inverse relationship between bisphosphonate and denosumab use and CAC. Furthermore, this review aimed to assess the relationship between these medications and aortic and carotid calcification through its secondary outcomes. If a true association between bisphosphonate or RANKL inhibitor use and CAC can be established in a large, diverse cohort of patients, it may warrant their use in those with elevated CAC. This could prove vital in both the primary and secondary prevention of cardiovascular events in those who are at high risk of severe complications.

Table 1 PICO-D criteria for inclusion of studies in the review

Participants	Participants in the included studies were over the age of 18 and must have had a CAC score documented. Participants were not limited according to sex or presence of comorbidities.
Intervention	The intervention group must have had a CAC score measured at baseline, prior to receiving bisphosphonate or denosumab therapy for a period of at least 6 months. CAC scoring must have been repeated at least 6 months following the commencement of therapy.
Comparator	Patients who were not receiving or did not receive the aforementioned medications. CAC must have been measured at baseline and repeated at a second time point, which was 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 were included if they measured the CAC at least twice (minimum before and at least 6 months after initiation of treatment) to monitor progression.

CAC, coronary artery calcification; PICO-D, Patient-Intervention-Comparator-Outcome-Duration.

METHODS

The methods of this review have been published as a protocol[18] and are outlined in brief (please see online supplemental file 1).

Eligibility criteria

Definitions as per Patient-Intervention-Comparator-Outcome-Duration (PICO-D) were adapted for the purpose of this review. An article was included in the study if it met the PICO-D criteria as outlined in table 1.

Search strategy

A structured search of MEDLINE (inception – present), Embase (inception – present) and the Cochrane Central Register of Controlled Trials (CENTRAL) was performed. Citation lists of any relevant papers found were handsearched to identify further pertinent articles. 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. Search keywords included CAC, bisphosphonates, RANKL inhibitors and denosumab.

Study selection

The articles yielded by the search were screened by title and abstract against our inclusion and exclusion criteria. Following initial title/abstract screening, the full text of potentially eligible papers was then appraised for final inclusion in the systematic review. A third reviewer adjudicated if there was a discrepancy in the inclusion status of any study. This process was documented in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Data collection

Two independent reviewers (NSM and KG) extracted data items from included reviews as per a standardised data extraction form (online supplemental file 3). Extracted data included study design, country and setting, aims and objectives, study population, intervention, control, outcomes, risk of bias and demographical data.

Outcomes

The primary outcome extracted was the difference in CAC from baseline to follow-up in patients who used either a bisphosphonate or denosumab compared with those who did not. The secondary outcomes of the review were 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 was assessed using the ROBINS-I tool[19] for non-randomised studies and the RoB2 tool[20] for RCTs. The studies were graded as low, moderate or high for risk of bias per criterion and for overall bias.

Data synthesis and analysis

Studies were included if they fulfilled the eligibility criteria. Data were presented narratively and complemented with tables and figures as appropriate. The outcomes of each study were extracted, with their effect size measured by OR or relative risk and their corresponding 95% CIs, where available. The statistical significance reported by their p values was also collected where available, as stated by the study authors. Lastly, the main conclusions drawn by the authors were extracted. Meta-analysis was not performed due to the heterogeneity of included studies, which was assessed per the definition reported in the Cochrane Handbook for Systematic Reviews of Interventions.[21] Heterogeneity in the included studies was demonstrated in their clinical variation that is, diverse populations studied with variations in treatment type and dose, and methodological variation as evidenced by study design (prospective observational vs RCT) and variance in reporting of the outcome measure (CAC reported in cubic millimetres vs AU), the latter of which most markedly precluded meta-analysis.

Patient and public involvement

None.

RESULTS

Study inclusion

112 potentially relevant articles were identified from a systematic search of the literature, of which five met the review inclusion criteria (see figure 1); four observational studies and one RCT were included with a total of 377 patients.[7 8 14 16 22] Individual study characteristics are documented in table 2. Three studies reported outcomes pertaining to bisphosphonate use, one on denosumab use and one study investigated the use of both.

Risk of bias in included studies

A summary of the risk of bias in each study can be found in tables 3 and 4 for observational studies and RCTs, respectively. Low overall risk inferred a low risk in each criterion. Moderate overall risk was determined by moderate risk in at least one criterion, without high risk in any criterion. High overall risk was determined by high risk in at least one criterion.

Demographical data and population

Demographical outcomes included age, sex, presence of hypertension, diabetes, dyslipidaemia, CKD and smoking status (see table 5). There was a large proportion of patients who had end-stage renal disease on dialysis (three studies, n=112) and osteoporosis (one study, n=115). One study did not report any demographical baseline characteristics of participants except for age. One study reported only on age and sex. The remaining studies reported on each of the aforementioned characteristics. No studies reported on family history of CAD, and consequently, these data are not included in table 5.

Primary outcomes

Bisphosphonate use

Nitta *et al* (n=56) reported the action of the bisphosphonate, etidronate on CAC progression and demonstrated a statistically significant reduction in CAC (−372 mm^3 over 12 months) compared with patients not taking etidronate (+159 mm^3 over 12 months) (p<0.01). Ariyoshi *et al* (n=14) who also reported the effect of etidronate use on CAC progression demonstrated a difference between intervention (+880 mm^3 over 12 months) vs control (+2220 mm^3 over 12 months), however, no p value directly comparing the two groups was reported.

A third study by Hill *et al* (n=115) found no statistically significant difference between intervention with the bisphosphonate, alendronate (+2.4 modified AU per month) and control (+3.1 modified AU per month), p=0.46. Pawade *et al* (alendronate use, n=51; control n=50) similarly found no statistically significant difference between alendronate use (+326 (138–813) modified

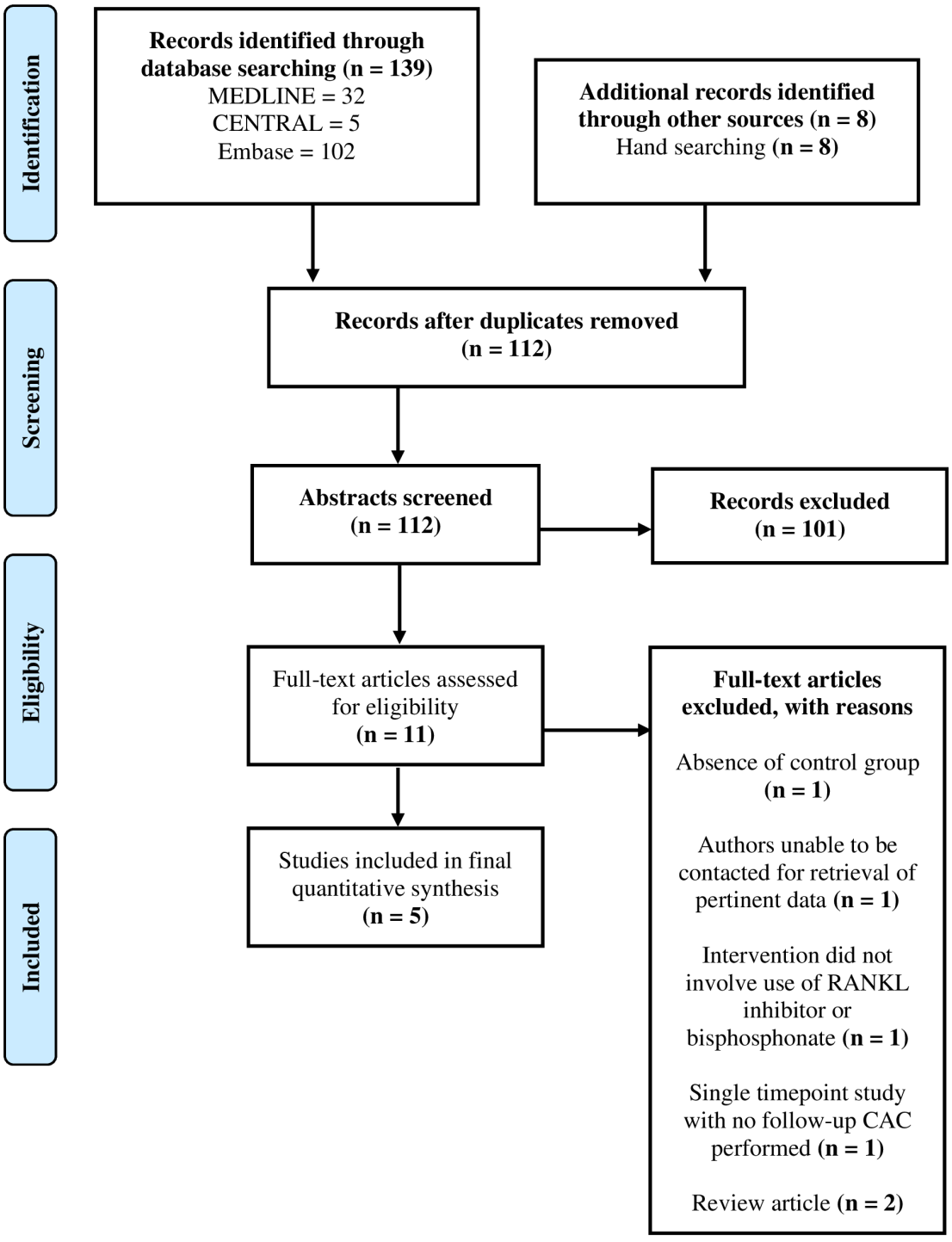

Figure 1 PRISMA diagram demonstrating how studies were included in the review. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta- Analyses; RANKL, NF-κB ligand.

AU over 24 months) and control (+354 (76–675) modified AU over 24 months), p=0.49.

Denosumab use

Chen *et al* (n=42) investigated denosumab use on CAC progression and found a statistically significant reduction at 6-month follow-up between intervention (−133±124 modified AU) and control (+188±72 modified AU), p=0.03. Pawade *et al* (denosumab use, n=49; control, n=50) found no statistically significant difference between denosumab use (+343 (198–804) modified AU) vs control (+354 (76–675)) over a 24-month period, p=0.41. Primary outcome data can be seen in table 6. Meta-analysis was not performed due to limited, heterogeneous studies as previously discussed.

Secondary outcomes

Aortic calcification

Ariyoshi *et al* (n=14) reported the progression of aortic calcification in those receiving etidronic acid versus those

Table 2 Study characteristics

Paper	Country/ setting	Design	Aims and objectives	Participants	Intervention group	Control group	Outcomes investigated	Major conclusions
Ariyoshi *et al*, 2006[7]	A hospital in Nagasaki, Japan.	Single-centre prospective study, 6-month follow-up period.	To characterise the effect of etidronic acid on arterial calcification in patients undergoing chronic haemodialysis.	Patients with ESRD undergoing chronic haemodialysis who had been treated for ischaemic heart disease at the hospital between 2002 and 2003.	Etidronic acid 400 mg/ day for 24 weeks, n=8.	No etidronic acid therapy, n=6.	The primary outcomes were changes in CAC over a 6-month period and aortic calcification over a 12-month period.	Etidronic acid reduced aortic calcification but not CAC in patients with ESRD undergoing chronic haemodialysis.
Chen *et al*, 2020[16]	Kaohsiung Veterans General Hospital, a tertiary medical centre in southern Taiwan.	Single-centre case series, 6-month follow-up period.	To determine the short-term changes in coronary artery calcification following denosumab treatment in patients with SHPT and low bone mass.	Patients with ESRD and severe SHPT who were undergoing dialysis between October 2014 and 2016.	A subcutaneous dose of denosumab 60 mg was given on day 1, n=21.	Placebo injection, n=21.	The primary outcomes were changes in CAC, calcium, phosphate and alkaline phosphatase levels. The secondary outcomes included factors affecting changes in CAC scores.	The progression of CAC in patients with severe SHPT may be suppressed by denosumab. This may also lead to regression of osseous calcification in patients with extremely high bone turnover.
Hill *et al*, 2002[14]	USA	Pilot comparative analysis, 54- month follow-up period.	To determine whether alendronate accelerates the rate of coronary artery calcification.	Patients with osteoporosis warranting treatment with alendronate and consented to participate in a study of changes in CAC and dual-energy X-ray absorptiometry scores at yearly intervals after initiation of treatment.	Alendronate 10 mg orally each morning, n=59 (56 were matched in a pair).	Subjects with osteoporosis who were asymptomatic for ischaemic heart disease and not taking any bone-active agent were eligible for matching. Matching was performed on the basis of age, sex, baseline CAC score (within 20%) and cardiac risk factors, n=56.	Primary outcome was change in CAC, calculated on the basis of the absolute change in the CAC score per month.	Oral alendronate administration does not accelerate the rate of CAC, but a larger cohort should be studied to confirm these findings.
Nitta *et al*, 2004[8]	Takeda General Hospital, Fukushima, Japan.	Comparative analysis, 7- month follow-up period.	To assess the effects of etidronate on the progression of CAC by using multidetector spiral CT in haemodialysis patients.	Patients undergoing haemodialysis without obvious acute inflammation and who complied with their drug therapy.	Intermittent cyclical etidronate 200 mg/day for 14 days. The cycle was repeated three times, every 90 days, n=35.	Patients on long-term haemodialysis therapy without etidronate therapy, n=21 (retrospectively analysed).	Primary outcome was change in CAC from baseline to follow-up.	CAC may be suppressed by etidronate in association with a reduction in chronic inflammatory response.

Continued

Table 2 Continued

Paper	Country/ setting	Design	Aims and objectives	Participants	Intervention group	Control group	Outcomes investigated	Major conclusions
Pawade *et al*, 2021[22]	Cardiology outpatient clinics across Scotland: Edinburgh Heart Centre, Borders General Hospital, Victoria Hospital, Ninewells Hospital and Forth Valley Royal Hospital.	Single-centre, parallel-group, double-blind randomised control trial, 24-month follow-up period.	To determine whether the RANKL inhibitor denosumab or the bisphosphonate alendronic acid could reduce disease progression in patients with calcific aortic stenosis, as evaluated using the aortic valve calcium score.	Patients >50 years with a peak aortic jet velocity >2.5 m/s on Doppler echocardiography and grades 2–4 aortic valve calcification on semiquantitative echocardiographic assessment were included.	There were two intervention groups in the study: Denosumab 60 mg every 6 months, n=49 Alendronate=70 mg once weekly, n=51.	Placebo injection (if paired intervention group was receiving denosumab) or placebo capsule (if paired intervention group was receiving alendronic acid), n=50.	The primary end point was the valve calcium score at 24 months. Key secondary end points included change in peak aortic jet velocity at 24 months and change in aortic valve uptake at 12 months.	Neither denosumab nor alendronate cause major amelioration or acceleration of aortic valve calcification or disease progression.

CAC, coronary artery calcification; ESRD, end stage renal disease; RANKL, NF-κB ligand; SHPT, secondary hyperparathyroidism.

Table 3 Risk of bias in included studies for observational studies and randomised controlled trials

	Bias due to confounding	Bias due to selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended intervention	Missing data bias	Outcome measure bias	Selective reporting bias	Overall bias
Ariyoshi *et al*, 2006[7]	Moderate	Low	Low	Moderate	Low	Low	Low	Moderate
Chen *et al*, 2020[16]	Low	Low	Low	Low	Unclear	Low	Low	Low
Hill *et al*, 2002[14]	Low	Moderate	Low	Low	Unclear	Low	Low	Moderate
Nitta *et al*, 2004[8]	High	Moderate	Moderate	Low	Low	Low	Low	High

Table 4 Risk of bias in included studies for randomised controlled trials

	Bias arising from the randomisation process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of reported result	Overall bias
Pawade *et al*, 2021[22]	Low	Low	Moderate	Low	Low	Moderate

who were not.[7] Aortic calcification was found to improve in the intervention group (–64.1% (–6.5 to –50.1)) versus in the control group (+130% (2.1–414%)) over a 12-month period (p=0.006).

Carotid artery calcification

None of the included studies reported on carotid artery intima–media thickness in those using either a bisphosphonate or denosumab compared with a placebo.

DISCUSSION

Optimisation of risk factors remains challenging for many patients with moderate to severe CAD, and subsequently, the search for additional therapeutic targets is needed. Our review collected data from observational studies and a single RCT and is the first to summarise the evidence exploring the role of bisphosphonates and RANKL inhibitors, respectively, in the progression of CAD as objectively measured via CAC.

Bisphosphonates and CAC

Four studies investigated the action of bisphosphonates on CAC progression. Nitta *et al*'s study was the only study to report a statistically significant reduction in CAC progression in patients receiving the first-generation bisphosphonate, etidronic acid, which was given in doses of 200 mg/day for 14 days, every 90 days for a total of three cycles, compared with control in patients with end-stage CKD.[8] Furthermore, the findings reported by Ariyoshi *et al*,[7] also in a cohort of haemodialysis patients receiving etidronate but at a higher dose of 400 mg/day for 24 weeks, are worth noting; while the authors did not report any statistical hypothesis result, a large difference in CAC of 1340 mm^3 between the groups was observed at 1-year follow-up. This would support the notion that etidronic acid is capable of reducing CAC in patients with CKD. The remaining studies in this category investigated the NC-BP, alendronate, in a broader range of individuals which could explain the differences in outcomes seen. This also correlates to the difference in molecular structure between first-generation bisphosphonates and NC-BPs, with etidronate theorised to have a greater capacity for inhibition of crystallisation and thus calcification of soft tissues.[23] Furthermore, a literature review showed that inhibition of soft tissue calcification by bisphosphonates is likely restricted to etidronate.[24] However, the review warns that etidronate poses a risk of causing osteomalacia in patients taking it at the high doses recommended to suppress vascular calcification. Conversely, other reviews[25 26] suggest that etidronate is safe if given cyclically (as was performed in the Nitta *et al*, protocol) up to a dose of 400 mg daily. Osteomalacia was not reported in the 2–3 years follow-up period.[26] Continuous therapy at these doses, however, is not recommended due to intolerable gastrointestinal side effects and subsequent poor adherence. Given that etidronate displayed benefit at 200 mg daily in the Nitta *et al*, paper, we posit that this could be an optimal starting dose that also allows for up-titration in the management of vascular calcification to balance the risks and benefits of treatment. This could be an area of future research.

RANKL inhibitors and CAC

Evidence regarding the action of denosumab on CAC progression also remains conflicting, with one study reporting a statistically significant hypothesis result between intervention and control, and one study demonstrating no statistically significant difference in this review. RANKL inhibitors are comparably novel to bisphosphonates, and subsequently, research into their use is not as ubiquitous. Denosumab's ability to inhibit vascular calcification has been proven both in vitro[27] and in vivo in mice models.[28] In the latter study, osteoporosis was induced by prednisone in human RANKL knock-in mice, who became responsive to denosumab, unlike their wild-type counterparts. Subsequent denosumab therapy resulted in attenuation of aortic calcium deposition up to 50% compared with the control group. In humans the data remains conflicting. An RCT conducted in haemodialysis patients by Iseri *et al*, did not demonstrate a statistically significant difference in CAC progression from baseline to follow-up at 12 months. Notably, only 18 patients reached follow-up time. Additionally, this study did not include a control group and hence did not meet the eligibility criteria for inclusion in the present review. In contrast, a larger, more recent study published by Suzuki *et al*[29] conducted over a 30-month period demonstrated the capabilities of denosumab in reducing aortic arch calcification in haemodialysis patients. Given the narrow patient selection criteria, the results may not be generalisable to a wider cohort. However, these findings corroborate those published by Chen *et al*,[16] suggesting that denosumab may have selective utility to improve vascular calcification in those with end-stage CKD.

CAC progression versus prevalence

Notably, the review included only papers which investigated the impact of antiosteoporotic medications on CAC progression over time. Hence, studies evaluating the point prevalence of CAC in bisphosphonate or

Table 5 Baseline characteristics

	Intervention						Control						
	Age (years)	Sex (% male)	HTN (%)	Diabetes (%)	Dyslipidaemia (%)	CKD (%)	Smoking (%)	Age (years)	Sex (% male)	HTN (%)	Diabetes (%)	Dyslipidaemia (%)	CKD (%)	Smoking (%)
Studies investigating bisphosphonates on CAC progression														
Ariyoshi *et al*, 2006[7]	63.5±8.3	83.3	–	–	–	100	–	66.3±5.1	83.3	–	–	–	100	–
Hill *et al*, 2002[14]	60±10	–	–	–	–	–	–	62±10	–	–	–	–	–	–
Nitta *et al*, 2004[8]	63.2±8.2	82.9	100	23	–	100	20	–	–	–	–	–	–	–
Pawade *et al*, 2021[22]	73±8	80	75	22	43	7.8	Current: 16 Former: 47	72±7	80	82	24	70	4	Current: 6 Former: 54
Studies investigating denosumab use on CAC progression														
Chen *et al*, 2020[16]	62.1±2.5	14.3	90.5	14.3	0	100	Current: 0 Former: 9.5	54.8±2.0	42.9	95.2	9.5	9.5	100	Current: 0 Former: 14.3
Pawade *et al*, 2021[22]	72±8	78	71	24	69	12	Current: 4.1 Former: 53	72±7	80	82	24	70	4	Current: 6 Former: 54

CAC, coronary artery calcification; CKD, chronic kidney disease; HTN, hypertension.

Table 6 Primary Outcomes

	Bisphosphonate use						Denosumab use					
	Intervention baseline CAC (modified AU)	ΔCAC from baseline (modified AU)	Control baseline CAC (modified AU)	ΔCAC from baseline (modified AU)	P value	Effect size	Intervention baseline CAC (modified AU)	ΔCAC from baseline (modified AU)	Control baseline CAC (modified AU)	ΔCAC from baseline (Modified AU)	P value	Effect size
Ariyoshi *et al*, 2006[7]†	4100±2440	+880/12 months	8990±15180	+2220/12 months	–	Not reported						
Chen *et al*, 2020[16]							2271±511	−133±124/6 months	2034±653	+188±72/6 months	0.03	Not reported
Hill *et al*, 2002[14]	108±290 (0–1650)	+2.4/month	102±264 (0–1467)	+3.1 /month	0.46	Not reported						
Nitta *et al*, 2004[8]†	1489 (168–8768)	−372/12 months	1303 (231–3133)	+159/12 months	0.01	Not reported						
Pawade *et al*, 2021[22]*	1268 (672–2065)	+326 (138–813)/24 months	1127 (617–2059)	+354 (76–675)/24 months	0.49	Difference in means: 196 AU (95% CI −286 to 679 AU), p=0.42 Effect size powered at 40%	1163 (598–2151)	+343 (198–804)/24 months	1127 (617 to 2059)	+354 (76–675)/24 months	0.41	Difference in means: 169 AU (95% CI −304 to 643 AU), p=0.48 Effect size powered at 40%

Data are either given as means±SD, with ranges in parentheses, or as means with ranges in parentheses.
*The study conducted by Pawade *et al*[22] reported specifically on the aortic valve calcium score (modified AU).
†The studies conducted by Ariyoshi *et al*[7] and Nitta *et al*[8] reported CAC in mm^3 rather than modified AU.
AU, Agatston unit; CAC, coronary artery calcification.

denosumab users were excluded. The largest study to date investigating bisphosphonate use on the prevalence of atherosclerosis is the Multi-Ethnic Study of Atherosclerosis study.[30] The study included over 3000 women from diverse ethnic backgrounds and found that bisphosphonate use was associated with a reduced prevalence of overall cardiovascular calcification in women over the age of 65. However, this was not statistically significant for CAC, which is supported by our review. While men made up the bulk of participants in our review, the mean age of participants was alike, which may explain the similarity to the review's findings.

Antiosteoporotics and calcification in other vasculature

To the authors' knowledge, the RCT conducted by Pawade *et al* is the first of its kind to apply CAC scoring to measure aortic valve stenosis (AS) in the context of bisphosphonate and denosumab use.[22] The study did not find a statistically significant result between intervention and control in either case. Other papers have reported the effect of bisphosphonates on the progression of AS but measured via aortic valve area and mean and peak gradients. Using these parameters, the literature remains conflicting, with some evidence to suggest the slowing of AS by bisphosphonates,[31 32] and other evidence contradicting such an effect.[33]

One study reported on the review's secondary outcome of aortic calcification.[7] A statistically significant reduction in aortic calcification in the etidronic acid group compared with control was demonstrated; whilst not statistically significant in the coronary arteries, a reduction was still noted. Whilst the underlying mechanism of calcification remains analogous between the two arteries, the differences in intimal and medial histological elastic and smooth muscle fibre composition[34] as well as differences in shearing forces between the vessels could theoretically result in delayed improvement in calcification measurements over the given timeframe.[35]

Strengths and limitations

This review is likely to have captured most, if not all papers reporting on the topic of CAC progression in antiresorptive medication use, through its use of (1) inclusion of multiple study designs, (2) inclusion of wide study populations, that is, no limitation according to sex or presence of comorbidities and (3) a methodical search of three large databases and citation lists of relevant papers.

Meta-analysis was unable to be performed in view of the small number of heterogeneous papers eligible for inclusion in the review. Furthermore, three of the four studies were shown to have a moderate risk of bias which may limit the interpretation of the data. Two studies were undertaken in patients with end-stage renal failure on dialysis, specifically, and one in patients with concomitant secondary hyperparathyroidism with normocalcaemia. Therefore, these studies may not be generalisable to the broader population, particularly in those with alternate pathological mechanisms to cause their osteoporotic bony disease and simultaneous vascular calcification.

Future directions

Further research on etidronate in renal failure patients appears warranted, given previous promising results in this demographic. Larger scale studies which aim to balance therapeutic dosing with adverse events appear worthwhile. Additionally, data pertaining to the long-term use of both first generation and nitrogen-containing bisphosphonates, and RANKL inhibitors in patients with and without renal disease would be useful to establish the temporal relationship between antiosteoporotic medications and CAC. Large-scale RCTs would be most beneficial to draw valid conclusions.

CONCLUSIONS

Given the limited number of heterogeneous studies, the present review demonstrates that there is insufficient evidence currently available to support a correlation between bisphosphonate or RANKL inhibitor use and CAC progression. Further research is warranted.

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