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REVIEW

Effect of osteoporosis medications on vascular and valvular calcification: a systematic review and meta-analysis

Hui Zhen Lo[1] · Kevin Leow[2] · Rachael Hii[3] · Nitesh Nerlekar[3,4,5] · Peter R. Ebeling[4] · Alexander J. Rodríguez[6]

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Abstract

Objective Vascular calcification shares many features with skeletal mineralisation and shares an inverse relationship with osteoporosis (skeletal de-mineralisation). However, medications that reduce bone loss (anti-resorptives) have had inconsistent effects on extra-skeletal mineralisation (i.e. vascular and valvular calcification). As such, this paper aims to synthesise existing literature examining the effect of anti-resorptive treatments on extra-skeletal (vascular and valvular) calcification across populations.

Methods Medline and Embase were searched (inception to October 2024) for studies that assessed the association between anti-resorptive medication use and vascular/valvular calcification. Pooled standardised mean differences (SMDs) with 95% confidence intervals (CI) were calculated for all outcomes, using random-effects model. Leave-one-out sensitivity analyses were performed for internal validity.

Results Of 4071 articles screened, 33 were included in the review, and 15 (2344 participants) had data available for meta-analysis. Anti-resorptive use was associated with non-significant, small magnitude improvements in abdominal aortic calcification (decreased value), coronary artery calcification (decreased value) and ejection fraction (increased value) but significant small reduction in aortic valve area (representing less calcification on the valve) with standardised mean difference of − 0.45 (95% confidence interval (CI) − 0.99; 0.08, $I^2 = 84\%$), − 1.19 (95% CI − 2.92; 0.55, $I^2 = 91\%$), − 0.67 (95% CI − 1.72; 0.38, $I^2 = 94\%$), 0.26 (95% CI − 0.14; 0.66, $I^2 = 62\%$) and 0.56 (95% CI 0.07; 1.06, $I^2 = 76\%$), respectively.

Conclusion The significance of small positive effect of anti-resorptives on aortic stenosis is clinically uncertain. Despite strong biological links between vascular calcification and skeletal mineralisation, anti-resorptives do not appear to have a strong favourable influence on extra-skeletal mineralisation. This suggests that mechanisms that link vascular calcification with osteoporosis may be acting in pathways not influenced by anti-resorptives.

Summary This systematic review and meta-analysis summarises the effect of anti-resorptives on vascular and valvular calcification. There is a small, positive effect of anti-resorptives on aortic stenosis, though this is of uncertain clinical importance.

Keywords Anti-resorptive · Osteoporosis · Vascular calcification

✉ Alexander J. Rodríguez
Alexander.Rodriguez@monash.edu

[1] Peninsula Health, 2 Hastings Road, Frankston, VIC 3199, Australia

[2] Department of Cardiology, Canberra Hospital, Woden, Yamba Dr, Garran, Australian Capital Territory 2605, Australia

[3] Department of Medicine, Monash Health, 246 Clayton Rd, Clayton, VIC 3168, Australia

[4] Department of Medicine, School of Clinical Sciences, Faculty of Medicine, Nursing and Health Sciences, Monash University, Monash Medical Centre, 246 Clayton Rd, Clayton, VIC 3168, Australia

[5] Monash Cardiovascular Research Centre, Monash University and Monash Heart, Monash Health, 246 Clayton Rd, Clayton, VIC 3168, Australia

[6] Department of Medicine, School of Clinical Sciences at Monash Health, Bone and Muscle Health Research Group, Monash University, Monash Medical Centre Block E, Level 5, 246 Clayton Rd, Clayton, VIC 3168, Australia

Abbreviations

SMD	Standardised mean difference
CI	Confidence interval
CVD	Cardiovascular disease
AAC	Abdominal aorta calcification
BMD	Bone mineral density
CKD	Chronic kidney disease
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
BMI	Basal metabolic index
BP	Blood pressure
DM	Diabetes mellitus
HF	Heart failure
HTN	Hypertension
AMI	Acute myocardial infarction
TIA	Transient ischaemic attack
ACEi	Angiotensin-converting enzyme inhibitor
ARB	Angiotensin receptor blocker
CAC	Coronary artery calcification
AVA	Aortic valve area
EF	Ejection fraction
IMT	Intima-media thickness
AS	Aortic stenosis

Introduction

Cardiovascular disease (CVD) and osteoporosis share many risk factors such as ageing, smoking, unhealthy diet (high sugar, high saturated fat, low protein), low levels of exercise and increased weight leading to speculation for common causative pathways [1]. One of the most frequently described links between CVD and osteoporosis is vascular calcification. Indeed, there is a strong inverse relationship between vascular calcification and bone mineral density (BMD). For example, calcification in the abdominal aorta (AAC) is associated with reduced BMD at various clinically relevant sites, and increased fracture risk at multiple clinically relevant sites [2]. The biological mechanism that drives vascular calcification is reminiscent of mineralisation of the skeleton involving calcium deposition by vascular smooth muscle cells that have undergone cellular transdifferentiation and appear phenotypically as osteoblast-like cells [3]. Given that osteoporosis treatments target well-described key drivers of bone loss, it has thus been speculated that these same treatments could favourably influence the incidence and progression of extra-skeletal mineralisation. Specifically, osteoporosis treatment targets osteoclast action (these would include the anti-resorptive agents—bisphosphonates, which mediate osteoclasts apoptosis; denosumab which is a monoclonal antibody against RANKL that inhibits bone resorption and osteoclast activity via the RANK/RANKL pathway), and osteoblast action (teriparatide is a parathyroid hormone (PTH) analogue that upregulates osteoblastogenic growth factors; romosozumab is a monoclonal antibody sclerostin antagonist that works to promote osteoblast production) [4–6]. To this end, several studies have explored the hypothesis that osteoporosis treatments could influence extra-skeletal mineralisation, albeit with heterogeneous responses [1, 7]. Much of the literature in this area has been directed towards understanding pathogenesis and treatment options in patient with chronic kidney disease (CKD). This is understandable given the burden of extra-skeletal calcification in this patient group, owing to the underlying bone and mineral disturbance from their CKD. Given that renal bone disease has its own distinct pathophysiology, there is a need to understand the overall effect of anti-osteoporosis medications in all patient groups, whose underlying bone and mineral pathophysiology could be reversed by available anti-osteoporosis treatments. A recent meta-analysis attempted to address this topic but was limited in its scope of included trials. This meta-analysis only included two trials with anti-resorptive agents which showed mixed results [8]. Another systematic review focused solely on the effect of anti-osteoporotic medications on coronary artery calcification (CAC) only and did not investigate other forms of vascular calcification and as such this study is limited by assessing only one calcification outcome [9]. Their review which included four observational studies and one randomised controlled trial (RCT) with a total of 377 patients also showed mixed results. Furthermore, very little attention is given to valvular calcification with respect to understanding extra-skeletal mineralisation in osteoporosis, despite several observational studies demonstrating potential for slower progression of valvular calcification in patients receiving anti-resorptive medications [10, 11]. It has been hypothesised that the pathophysiology behind valvular and vascular calcification belong to the same causal pathway, and for this reason, there is a need to systematically and comprehensively examine the evidence for anti-resorptive medications on extra-skeletal (valvular and vascular) calcification across indications. Therefore, we aimed to synthesise existing literature examining the effect of anti-resorptive medications on the calcification process on valves and arteries, at clinically actionable sites, in any population.

Materials and methods

Data sources and searches

We searched two databases (Medline and Embase) from inception to 15 October 2024 for relevant papers. There were no language restrictions. Studies were identified using the search strategy detailed in Supplementary Table 1. Records were then stored using a citation manager and duplicates

were removed. All titles and abstracts were screened before evaluating the eligibility of the full texts. Manual screening of cited references of eligible texts and online related article lists were also done to identify publications that were potentially relevant.

Study selection

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement, and it is registered with PROSPERO (CRD42024518650) [12]. We included studies that specifically reported any of the following outcomes: incidence and/or progression of vascular calcification (at any site) or incidence and/or progression of (any) valvular calcification (including any echocardiographic measure of such) or progression of ejection fraction. Studies were included if the trial was randomised or a controlled prospective cohort study and provided any of the above outcomes. Specific exclusion criteria included non-controlled studies, systematic reviews, reviews, conference abstracts, letters, case reports and animal or cell-based studies.

Data extraction and quality assessment

Data was extracted by a single reviewer (HZL) using a data extraction form and was checked for accuracy by another reviewer (AJR). We obtained data on the total number of enrolled patients, treatment used; comparator used; patient demographics (age, sex, basal metabolic index (BMI), blood pressure (BP), alcoholic, smoking status); medical conditions (diabetes mellitus (DM), hypertension (HTN), hyperlipidaemia, coronary artery disease, peripheral artery disease, heart failure (HF), CKD, osteoporosis, chronic liver disease, previous aortic stenosis, previous acute myocardial infarction (AMI), previous percutaneous coronary intervention, previous coronary artery bypass graft, previous stroke/transient ischaemic attack (TIA) and malignancy); medications (statins, angiotensin-converting enzyme inhibitor (ACEi)/angiotensin receptor blocker (ARB), steroids, vitamin D, calcium, phosphate binder) and osteoporotic features (baseline vertebral BMD, baseline lumbar spine BMD, baseline femoral neck BMD, previous vertebral fracture); and outcomes of interest with units of measurable change (AAC volume, CAC volume and Hu, aortic valve area and ejection fraction). Potentially relevant but missing data was sought directly from study authors via email.

Two independent reviewers (HZL and AJR) used the Cochrane Collaboration risk-of-bias tool for randomised trials to assess risk of bias [13]. This tool evaluates bias across seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias (e.g. representativeness). A judgement of low, unclear or high risk of bias was made for each domain. An overall risk of bias per study was evaluated based on the following criteria: low—all domains low; low/unclear—all domains low except for one that was unclear; unclear—greater or equal to two unclear domains; high—any domain was high. The Newcastle–Ottawa Scale was used to assess risk of bias in cohort studies [14]. This scale evaluates bias across three broad domains: selection of cohorts, comparability of cohorts and the assessment of outcome of the studies. A judgement of overall good, fair or poor quality was determined for each study according to the 'star system'. Good-quality studies were evaluated as having three or four stars in the selection domain and one or two stars in the comparability domain and two or three stars in the outcome domain. Fair quality studies were evaluated as having two stars in the selection domain and one or two stars in the comparability domain and two or three stars in the outcome domain. Poor-quality studies were evaluated as having zero or one star in the selection domain or zero stars in the comparability domain or zero or one stars in the outcome domain. For studies where there were inconsistencies between the reviewers regarding the overall risk of bias, a consensus meeting was held to resolve disagreements.

Data synthesis and analysis

Studies were suitable for meta-analysis if they initially satisfied the inclusion–exclusion criteria and reported at least one outcome of interest. Analyses were performed separately by outcome of interest. We meta-analysed data for outcomes that were reported in at least three studies. Data was pooled together in an inverse-variance model assuming random-effects (and fixed/common effects reported for completeness) where a standardised mean difference (SMD) for the overall effect estimate was obtained together with the 95% confidence interval (95% CI). For studies which examined at different anti-resorptive treatments (for example using a bisphosphonate and using denosumab), where pooled results were not provided, we reported our analysis using both treatments in separate analyses. This was done for Geers et al. (2024) where the authors looked at treatment with denosumab or alendronate and so we reported our analysis first using the denosumab data and then again using the alendronate data [15]. Heterogeneity was evaluated by calculating the tau^2 statistic (an estimate of the between-study variance) and the proportion of total variability due to between-study heterogeneity was evaluated by the I^2 statistic. All data were computed using the meta package in R (version 4.1.3). For assessment of internal validity, a leave-one-out sensitivity analysis was performed for each analysis. Finally, assessment of publication bias was done by

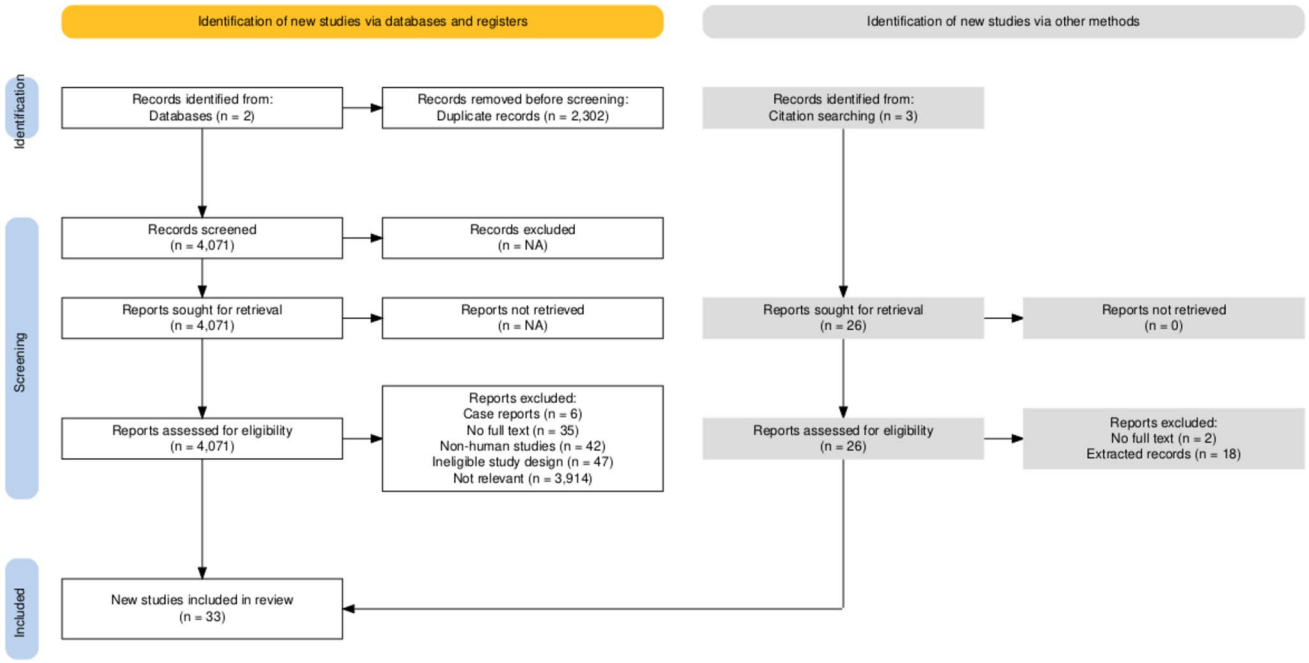


Fig. 1 PRISMA flowchart

visual inspection of a funnel plot. In certain instances, key data such as a standard deviation or error was not reported in published papers. An example of this is Hill et al. (2002) where change in coronary artery calcification (CAC) volume was recorded but the variation for the mean effect was not [16]. In such instances, these data were sought directly from authors, where no timely response was forthcoming (2-week response deadline given); the missing data was imputed from the linear prediction of a model including study mean and populations, in an effort to include as much known literature as possible to minimise publication bias (i.e. avoid exclusion of a known publication).

Results

Literature search

The literature search yielded 6373 results, and 2302 duplicates were removed, leaving 4071 records for title and abstract screening. Reports were excluded due to being irrelevant ($n=3914$), no full text ($n=35$), non-human studies ($n=42$), ineligible study design ($n=47$) and case reports ($n=6$). Additional hand searching found another six eligible articles. Overall, 33 studies [11, 15–46] were included in the qualitative analysis (Fig. 1).

Included studies

There were no restrictions to the population and we collected data on studies that included any patients (general population/community dwelling older adults) ($n=29$), patients with osteoporosis ($n=6$), patients on haemodialysis ($n=8$), patients on post-menopausal ($n=8$), patients with aortic stenosis ($n=4$), patients with type 2 DM ($n=2$), patients with CKD ($n=2$), patients at high risk for atherosclerotic aortic plaques ($n=1$), patients on bisphosphonate therapy ($n=1$), patients with pseudoxanthoma elasticum ($n=2$), patients with secondary hyperparathyroidism ($n=2$) and patients with AMI ($n=1$). Twelve studies used alendronate, eight studies used etidronate, eight studies used denosumab, three studies used ibandronate, three studies used zoledronate, two studies used risedronate, one study used calcitonin and one study used teriparatide (Table 1).

Ten studies were conducted in the United States of America (USA), seven in Japan, two in Australia, two in Netherlands, two in Spain, one in Denmark, one in Italy, two in Taiwan, one in Iran, two in the UK and one in Turkey. The smallest study included 12 patients [19] and the largest study included 141,202 patients [35]. Follow-up time varied between a minimum of 1 month and a maximum of 3.9 years (Table 2).

Table 1 Literature summary

Characteristics	All studies, *n*	Studies included in meta-analysis, *n*
Year of publication		
Pre-2010	12	5
2010–2016	8	3
2017–2024	13	7
Setting		
Any	1	0
Osteoporosis	6	4
Haemodialysis	8	5
Post-menopausal	7	2
Aortic stenosis	4	4
T2DM	2	1
CKD	1	0
Bisphosphonate therapy	1	0
Hypercholesterolaemia	1	0
Kidney transplant recipients	2	1
Pseudoxanthoma elasticum	2	1
Secondary hyperparathyroidism	2	2
Incident AMI	1	0
Region		
North America	6	4
Europe	11	3
Asia	14	8
Oceania	2	0
Number of patients		
< 100	22	11
> 100	11	4
Study design		
Cohort	19	10
Case control	1	0
RCT	13	5

AMI acute myocardial infarction, *CKD* chronic kidney disease, *RCT* randomised controlled trial, *T2DM* type 2 diabetes mellitus

Literature quality

Cohort studies were rated as good/good ($n=9$), good/fair ($n=3$), fair/fair ($n=5$) or fair/poor ($n=1$) quality by both reviewers (Supplementary Table 2). A case control study included was rated as good by both reviewers ($n=1$) (Supplementary Table 3). RCTs were rated as low/low ($n=2$), low/low-unclear ($n=5$), low-unclear/low-unclear ($n=2$) and low/high ($n=4$) risk of bias by both reviewers (Supplementary Table 4). There was some publication bias as visualised in the funnel plots (Supplementary Figs. 1–6).

Background of skeletal risk

Table 3 provides a summary of patient characteristics in terms of their background skeletal risk (baseline vertebral BMD ($n=6$), lumbar spine BMD ($n=9$), femoral neck BMD ($n=9$), previous vertebral fracture ($n=2$), vitamin D intake ($n=8$), calcium intake ($n=11$) and phosphate binder intake ($n=5$)).

Background of cardiovascular risk

Table 4 provides a summary of patient characteristics in terms of their cardiovascular risk (DM ($n=19$), HTN ($n=12$), hyperlipidaemia ($n=5$), HF ($n=2$), CKD ($n=10$), osteoporosis ($n=9$), previous MI ($n=2$), previous stroke or TIA ($n=3$)).

Outcomes of interest

Data were collected from 33 studies. Seven studies reported CAC; eight studies reported AAC; one study reported common carotid artery calcification; two studies reported mitral annulus calcification; one study reported iliac arteries calcification; one study reported lower limb arterial calcification; one study reported femoral artery calcification; one study reported total arterial calcification; nineteen reported aortic calcification (any site); five studies reported aortic valve area (AVA) (Table 2). Three studies reported ejection fraction (EF). EF is not strictly a marker of vascular/valvular calcification; we reasoned that EF would be influenced by valvular and vascular calcification and is included as an exploratory, hypothesis generating endpoint. Of interest, six studies reported on carotid intima-media thickness (IMT), but, as this represents atherosclerotic plaque not necessarily calcified, we chose to not analyse these data. Furthermore, as there was not a specific search term for IMT, we also cannot be certain that we have captured all literature reporting on osteoporosis medications and IMT.

Major findings from the included studies are described in Table 2. Etidronate resulted in less progression in coronary artery, femoral artery, thoracic and abdominal aortic calcification in seven studies [17, 19, 26, 29, 34, 41, 43]. Alendronate resulted in less progression in AAC and aortic stenosis in two studies [11, 28], and no difference in progression of CAC, aortic calcification and aortic stenosis in five studies [15, 16, 24, 30, 37]. Ibandronate resulted in no difference in AAC progression in one study [18]. Risedronate resulted in less progression in AAC and vascular calcification in two studies [23, 42]. Denosumab resulted in less progression in CAC and AAC in three studies [32, 35, 46], and no difference in AAC, aortic stenosis and CAC progression

Table 2 Study demographics

Authors, country, year	Study type	Mean time period of study	Treatment group (size/age/female %/smoker %)	Comparator group (size/age/female %/smoker %)	Population	Treatment	Comparison	Outcomes	Major finding
Hill et. al, USA, 2002	Observational study	24.1 months	56/62.0/NR/NR	56/60.0/NR/NR	Osteoporotic	Alendronate	No treatment	CAC progression—volume (change in score per month), Hu (change in score per month)	No difference in CAC progression with alendronate or control group
Nitta et. al, Japan, 2004	Observational study	388 ± 21 days	35/63.2/17/NR	21/61.3/24/NR	Haemodialysis	Etidronate	No treatment	CAC progression—CAC score change (mm^3)	Less progression in CAC with etidronate
Tanko et. al, Denmark, 2005	RCT	3 years	263/70.7/NR/21	128/70.6/NR/23	Post-menopausal	Ibandronate	Placebo	AAC progression—rate of change	No difference in AAC progression with ibandronate
Ariyoshi et. al, Japan 2006	RCT	1 year	6/NR/NR/NR	6/NR/NR/NR	Haemodialysis	Etidronate	No treatment	Aortic calcification progression—mean percentage change	Less progression in aortic calcification with etidronate
Skolnick et. al, USA, 2009	Retrospective observational study	2.4 ± 1.0 years	18/81.6/83/NR	37/82.3/70/NR	Any	Bisphosphonates, calcitonin, selective oestrogen receptor modulators	No treatment	AVA progression (cm^2/year), MAC (*n*), ejection fraction progression (%)	Less progression in aortic stenosis with osteoporosis treatment
Innasimuthu et. al, USA, 2009	Retrospective observational study	23 ± 5 months	8/NR/NR/NR	76/NR/NR/NR	Degenerative aortic stenosis	Alendronate (7), risedronate (1)	NR	AVA progression (cm^2), ejection fraction progression (%)	Less progression in aortic stenosis with bisphosphonates
Elmariah et. al, USA, 2009	Observational study	2 years	214/67.0/100/NR	3496/62.0/100/NR	On nitrogen-containing bisphosphonate (NCBP) therapy	NCBP	NR	AVC, AVRC, MAC, TAC, and CAC defined as calcification scores > 0 Hu (*n*)	Less progression in cardiovascular calcification (AVC, MAC, TAC, CAC) with NCBPs in older women
Kanazawa et. al, Japan, 2010	Observational study	1 year	13/70.4/100/NR	13/69.1/100/NR	Post-menopausal, osteoporotic, T2DM	Risedronate	No treatment	AAC progression—rate of change	Less progression in AAC with risedronate and alfacalcidol

Table 2 (continued)

Authors, country, year	Study type	Mean time period of study	Treatment group (size/age/female %/smoker %)	Comparator group (size/age/female %/smoker %)	Population	Treatment	Comparison	Outcomes	Major finding
Toussaint et. al, Australia, 2010	RCT	18 months	25/66.0/32/NR	25/59.1/36/NR	CKD	Alendronate	Placebo	Aortic calcification progression (Hu)	No difference in aortic calcification progression with alendronate or placebo
Aksoy et. al, USA, 2012	Retrospective observational study	10 years	219/75.8/NR/NR	219/75.9/NR/NR	Post-menopausal	Bisphosphonates	No treatment	AVA progression	No difference in aortic stenosis progression with bisphosphonates or control group
Kawahara et. al, Japan, 2013	RCT	1 year	36/59.4/42/NR	72/61.1/NR/NR	Hypercholesterolaemia	Etidronate	Atorvastatin Atorvastatin and etidronate	Thoracic and AAC progression—percentage change	Less progression in thoracic and AAC with etidronate and atorvastatin
Samelson et. al, USA, 2014	RCT	36 months	843/74.0/100/48	782/74.0/NR/45	Post-menopausal, osteoporotic	Denosumab	Placebo	AAC progression—mean change in aortic calcification score	No difference in AAC progression with denosumab or placebo
Okamoto et. al, Japan, 2014	Observational study	1 year	5/52.8/80/NR	7/52.9/57/NR	Kidney transplant recipients	Alendronate	No treatment	AAC progression—percentage change	Less progression in AAC with alendronate
Kranenburg et. al, Netherlands, 2018	RCT	1 year	37/57.0/51/NR	37/57.0/51/NR	Pseudoxanthoma elasticum	Etidronate	Placebo	Femoral artery calcification—percentage change; carotid IMT progression (mm)	Less progression in femoral artery calcification and carotid IMT with etidronate
Iseri et. al, Japan, 2019	RCT	1 year	46/71.4/NR/NR	0/NR/NR/NR	Haemodialysis	Denosumab; Alendronate	NR	Adverse events (*n*)	No difference in CAC and carotid IMT with denosmab or alendronate
Passeri et. al, Italy, 2019	Observational study	1 year	20/70.0/100/NR	10/70.0/100/NR	Post-menopausal	Zoledronate; Teriparatide	No treatment	Carotid IMT progression (mm)	Less progression in carotid IMT with zoledronate compared to teriparatide

Table 2 (continued)

Authors, country, year	Study type	Mean time period of study	Treatment group (size/age/female %/smoker %)	Comparator group (size/age/female %/smoker %)	Population	Treatment	Comparison	Outcomes	Major finding
Chen et. al, Taiwan, 2020	Observational study	6 months	21/62.1/86/NR	21/54.8/57/NR	Haemodialysis and secondary hyperparathyroidism	Denosumab	No treatment	CAC progression—volume (mm^3), Hu	Less progression in CAC with denosumab
Alishiri et. al, Iran, 2020	Observational study	2 years	37/69.6/100/NR	33/68.7/100/NR	Aortic stenosis and osteoporotic	Alendronate	No treatment	AVA progression (cm^2), ejection fraction progression (%)	Less progression in aortic stenosis with alendronate
Cai et. al, Australia, 2020	RCT	3 years	234/72.3/100/NR	268/72.7/100/NR	Post-menopausal and osteoporotic	Zoledronate	Placebo	AAC changes > 0 (n)	No difference in AAC progression with zoledronate or placebo
Bartstra et. al, Netherlands, 2020	RCT	1 year	37/57.0/51/NR	37/57.0/51/NR	Pseudoxanthoma elasticum	Etidronate	Placebo	Common carotid artery, coronary arteries, aorta, iliac arteries, arteries of the legs and total arterial calcification changes—percentage change	Less progression in total arterial, carotid siphon, thoracic and AAC with etidronate
Mazzucchelli et. al, Spain, 2020	Case control	14 years	23, 590/66.8/27/NR	117,612/66.8/27/NR	Incident AMI	Alendronate; Ibandronate; Risedronate	NR	Incident AMI	No difference in AMI risk with alendronate, ibandronate or risedronate
Suzuki et. al, Japan, 2021	Observational study	30 months	28/65.9/25/NR	30/68.1/23/NR	Haemodialysis	Denosumab	No treatment	Aortic arch calcification changes—percentage change	Less aortic arch calcification with denosumab
Pawade et. al, United Kingdom, 2021	RCT	24 months	100/72.5/21/NR	50/72.0/20/NR	Aortic stenosis	Denosumab; Alendronate	Placebo	AVA progression (cm^2)	No difference in aortic stenosis progression with denosumab or alendronate or placebo
Saito et. al, Japan, 2022	Observational study	1 year	13/72.0/38/NR	0/NR/NR/NR	Haemodialysis and osteoporotic	Denosumab	NR	CAC score progression	Progression in thoracic and CAC with romosozumab

Table 2 (continued)

Authors, country, year	Study type	Mean time period of study	Treatment group (size/age/female %/smoker %)	Comparator group (size/age/female %/smoker %)	Population	Treatment	Comparison	Outcomes	Major finding
Koshiyama et. al, Japan, 2000	Observational study	1 year	57/62.6/77/NR	57/60.8/70/NR	Osteopenia and T2DM	Etidronate	No treatment	Carotid IMT progression (mm)	Decrease in carotid IMT with etidronate
Delibasi et. al, Turkey, 2007	Retrospective observational study	13 ± 2 months	71/59.9/100/30	0/NR/NR/NR	Post-menopausal	Alendronate	NR	Carotid IMT progression (mm)	No difference in carotid IMT with alendronate or no treatment
Hashiba et. al, Japan, 2006	Observational study	35 months	12/63.2/NR/NR	9/67.7/NR/NR	Haemodialysis	Etidronate	No treatment	AAC progression	Less progression in AAC with etidronate
Torregrosa et. al, Spain, 2010	RCT	12 months	52/47.4/17/NR	49/50.7/22/NR	Kidney transplant recipients	Risedronate	No treatment	Vascular calcification score change	Less vascular calcifications with risedronate
Hashiba et. al, Japan, 2004	Observational study	12 months	8/69.5/NR/NR	10/62.1/NR/NR	Haemodialysis	Etidronate	No treatment	AAC progression	Less progression in AAC with etidronate
Celiloglu et. al, Turkey, 2008	Observational study	12 months	39/NR/100/NR	33/NR/100/NR	Osteoporosis	Alendronate	No treatment	Carotid IMT (mm)	Decrease in carotid IMT with alendronate
Gonnelli et. al, Italy, 2013	RCT	12 months	30/66.4/100/17	30/67.0/100/13	Post-menopausal and osteoporotic	Zoledronate	Ibandronate	Carotid IMT (mm)	Greater decrease in carotid IMT with zoledronate compared to ibandronate
Geers et. al, United Kingdom, 2024	RCT	24 months	100/72.5/21/NR	50/72.0/20/NR	Aortic stenosis	Denosumab; Alendronate	Placebo	CAC progression—Hu, aortic calcification progression	Denosumab or alendronate are not associated with CAC or aortic calcification progression
Chen et. al, Taiwan, 2024	Observational study	6 months	24/59.4/83/NR	21/54.8/57/NR	Haemodialysis and secondary hyperparathyroidism	Denosumab	No treatment	CAC progression—volume (mm^3), Hu	Less progression in CAC with denosumab

AAC abdominal aortic calcification, *AMI* acute myocardial infarction, *AVA* aortic valve area, *AVC* aortic valve calcification, *AVRC* aortic valve ring calcification, *CAC* coronary artery calcification, *IMT* intima-media thickness, *MAC* mitral annulus calcification, *NR* not reported, *RCT* randomised controlled trial, *TAC* thoracic aorta calcification

Table 3 Background of skeletal risk

Authors, country, year	Baseline vertebral BMD, g/cm^2 (treatment/control)	Baseline lumbar spine BMD, g/cm^2 (treatment/control)	Baseline femoral neck BMD, g/cm^2 (treatment/control)	Previous vertebral fracture (treatment/control)	Vitamin D intake (treatment/control)	Calcium intake (treatment/control)	Phosphate binder intake (treatment/control)
Hill et. al, USA, 2002	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR
Nitta et. al, Japan, 2004	0.941 ± 0.125/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR
Tanko et. al, Denmark, 2005	NR/NR	2.5 mg oral: 0.827 ± 0.099 20 mg oral: 0.841 ± 0.112 0.5 mg IV: 0.791 ± 0.099 1.0 mg IV: 0.796 ± 0.095/oral: 0.797 ± 0.118 IV: 0.796 ± 0.091	2.5 mg oral: 0.717 ± 0.103 20 mg oral: 0.726 ± 0.093 0.5 mg IV: 0.706 ± 0.094 1.0 mg IV: 0.721 ± 0.089/ Oral: 0.701 ± 0.102 IV: 0.711 ± 0.086	NR/NR	Yes/yes	Yes/yes	NR/NR
Ariyoshi et. al, Japan 2006	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR
Skolnick et. al, USA, 2009	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	9/12	NR/NR
Innasimuthu et. al, USA, 2009	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR
Elmariah et. al, USA, 2009	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR
Kanazawa et. al, Japan, 2010	NR/NR	0.744 ± 0.127/0.919 ± 0.124	0.558 ± 0.056/0.637 ± 0.081	NR/NR	13/0	0/0	NR/NR
Toussaint et. al, Australia, 2010	1/1	0.40 ± 1.48/0.37 ± 2.11	− 1.28 ± 0.98/ − 1.26 ± 1.38	NR/NR	NR/NR	5/6	1/1
Aksoy et. al, USA, 2012	NR/NR	NR/NR	NR/NR	NR/NR	146(67)/151(69)	179(82)/180(82)	NR/NR
Kawahara et. al, Japan, 2013	NR/NR	0.85 ± 0.06/atorvastatin: 0.85 ± 0.06 Combination: 0.85 ± 0.07	0.64 ± 0.08/atorvastatin: 0.63 ± 0.07 Combination: 0.64 ± 0.10	NR/NR	NR/NR	NR/NR	NR/NR
Samelson et. al, USA, 2014	NR/NR	0.733 (0.063)/0.738 (0.077)	0.731(0.098)/0.715 (0.101)	201(24)/175(22)	843/782	843/782	NR/NR
Okamoto et. al, Japan, 2014	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR
Kranenburg et. al, Netherlands, 2018	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR
Iseri et. al, Japan, 2019	NR/NR	Denosumab: 0.876 (0.716–1.139) Alendronate: 0.797 (0.735–0.919)/NR	Denosumab: 0.496 (0.440–0.580) Alendronate: 0.523 (0.477–0.564)/NR	Denosumab: 10 Alendronate: 7/NR	NR/NR	NR/NR	NR/NR
Passeri et. al, Italy, 2019	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR
Chen et. al, Taiwan, 2020	NR/NR	0.74 ± 0.04/0.91 ± 0.04	0.47 ± 0.03/0.64 ± 0.03	NR/NR	NR/NR	21/21	21/21
Alishiri et. al, Iran, 2020	NR/NR	NR/NR	NR/NR	NR/NR	37/33	37/33	NR/NR
Cai et. al, Australia, 2020	NR/NR	0.64(0.09)/0.66 (0.07)	0.53(0.06)/0.54 (0.06)	NR/NR	NR/NR	NR/NR	NR/NR
Bartstra et. al, Netherlands, 2020	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR
Mazzucchelli et. al, Spain, 2020	NR/NR	NR/NR	NR/NR	NR/NR	582/3084	583/3185	NR/NR
Suzuki et. al, Japan, 2021	−0.84/−0.85	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR
Pawade et. al, United Kingdom, 2021	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR
Saito et. al, Japan, 2022	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	4/NR	7/NR
Koshiyama et. al, Japan, 2000	0.769(0.017)/0.987 (0.034)	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR
Delibasi et. al, Turkey, 2007	0.765 ± 0.016/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR
Hashiba et. al, Japan, 2006	2.36 ± 0.11/2.17 ± 0.20	NR/NR	NR/NR	NR/NR	7/3	NR/NR	7/5

Table 3 (continued)

Authors, country, year	Baseline vertebral BMD, g/cm^2 (treatment/control)	Baseline lumbar spine BMD, g/cm^2 (treatment/control)	Baseline femoral neck BMD, g/cm^2 (treatment/control)	Previous vertebral fracture (treatment/control)	Vitamin D intake (treatment/control)	Calcium intake (treatment/control)	Phosphate binder intake (treatment/control)
Torregrosa et. al, Spain, 2010	NR/NR	NR/NR	NR/NR	NR/NR	52/49	52/49	NR/NR
Hashiba et. al, Japan, 2004	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR
Celiloglu et. al, Turkey, 2008	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR
Gonnelli et. al, Italy, 2013	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR
Geers et. al, United Kingdom, 2024	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR
Chen et. al, Taiwan, 2024	NR/NR	0.76 ± 0.19/0.91 ± 0.18	0.50 ± 0.16/0.64 ± 0.12	NR/NR	NR/NR	24/21	24/21

BMD bone mineral density, *IV* intravenous, *NR* not reported

in three studies [15, 27, 37]. Zoledronate resulted in no difference in AAC progression in one study [33].

Meta-analysis

Fifteen studies, including a total of 2344 patients, had data available for meta-analysis (Fig. 2A–E). Specifically, studies that reported aortic calcification (any site) were not able to be analysed as varying units of measurements were used, for example, reporting on a percentage of the cohort that experience regression/progression of calcification as opposed to some measure of change in calcification. Therefore, we focused our analysis on outcomes for which units of measurable change were reported for a more targeted and clinically relevant analysis. Other studies not included were due to a lack of control group or specific results that were required for analysis. Parameters like mitral annular calcification and pulse wave velocity were unable to be analysed due to a lack of sufficient data.

Abdominal aorta calcification

Six studies, including 1815 patients, reported on change in AAC as an outcome of anti-resorptive therapy [23, 27, 28, 34, 36, 41]. Suzuki included patients on haemodialysis and treated them with denosumab; Hashiba included patients on haemodialysis and treated them with etidronate; Bartstra included patients with pseudoxanthoma elasticum and treated them with etidronate; Okamoto included patients with kidney transplant and treated them with denosumab; Samelson included post-menopausal and osteoporotic patients and treated them with denosumab as a secondary analysis of a larger fracture reduction trial; Kanazawa included patients who were post-menopausal, were osteoporotic and had type 2 diabetes mellitus. When pooled together, the rates of AAC progression were similar (SMD = −0.45 [95% confidence interval −0.99 to 0.08, tau^2 = 0.33; n = 935; I^2 = 84%; Fig. 2A]), where SMD represents the difference in the change in vascular outcome (AAC) between treatment and control groups. Focusing specifically on patients on etidronate, four studies with a total of 1721 patients studied the effects of etidronate on change in AAC [23, 27, 28, 36]. When pooled together, the rates of AAC progression were similar (SMD = −0.41 [95% confidence interval −1.24 to 0.41, tau^2 = 0.58, n = 889; I^2 = 89%; Fig. 2B]). Focusing specifically on haemodialysis patients, four studies with a total of 1736 patients, studied the effects of haemodialysis on change in AAC [23, 27, 28, 34]. When pooled together, the rates of AAC progression were similar (SMD = −0.08 [95% confidence interval 0.31 to 0.16, tau^2 = 0.019, n = 898; I^2 = 2%; Fig. 2C]).

Coronary artery calcification (volume)

Four studies, including 239 patients, reported on change in volume of CAC (CAC-volume) as an outcome of anti-resorptive therapy [16, 19, 32, 34]. Chen included patients who were on haemodialysis and had secondary hyperparathyroidism and treated them with denosumab; Hill included osteoporotic patients and treated them with alendronate; Ariyoshi included patients on haemodialysis and treated them with etidronate; Bartstra included patients with pseudoxanthoma elasticum and treated them with etidronate. When pooled together, the rates of CAC-volume progression were similar (SMD = −1.19 [95% confidence interval −2.92 to 0.55, tau^2 = 2.96; n = 120; I^2 = 91%; Fig. 2A]), where SMD represents the difference in the change in vascular

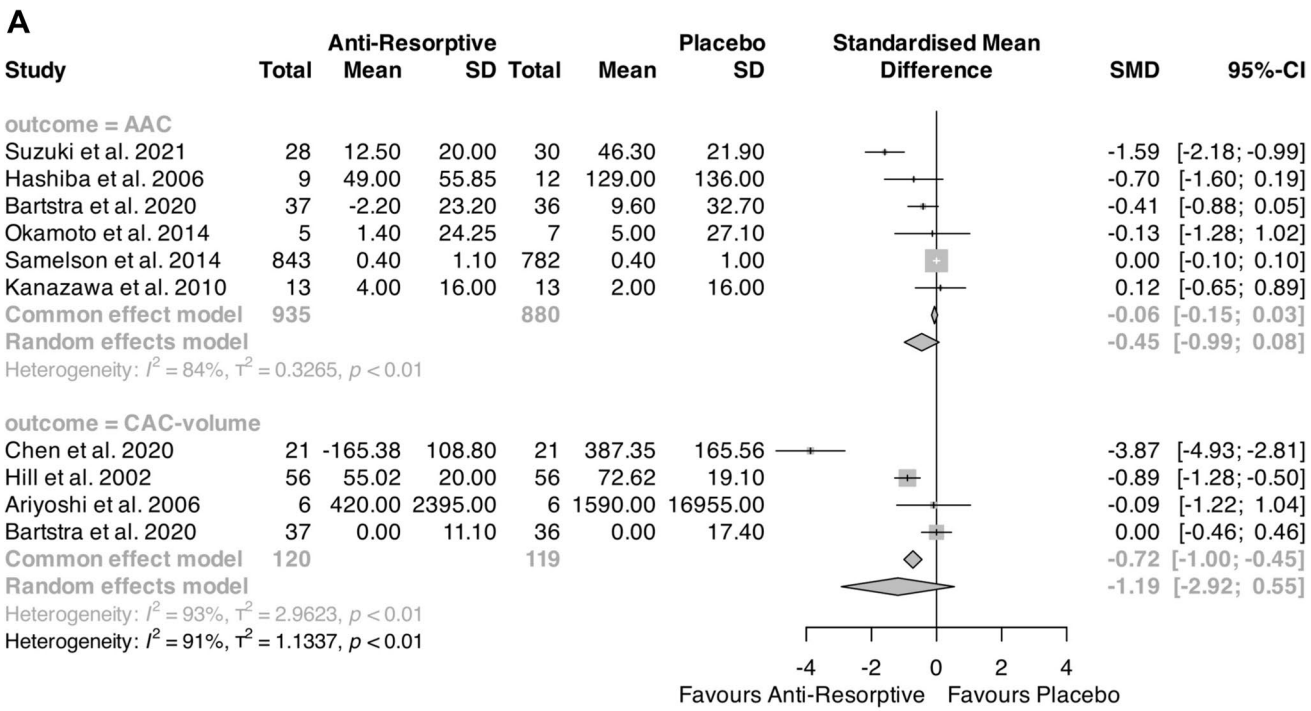
Table 4 Background of cardiovascular risk

Authors, country, year	DM (treatment/control)	HTN (treatment/control)	HLD (treatment/control)	HF (treatment/control)	CKD (treatment/control)	Osteoporosis (treatment/control)	Previous MI (treatment/control)	Previous stroke or TIA (treatment/control)
Hill et. al, USA, 2002	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	56/56	NR/NR	NR/NR
Nitta et. al, Japan, 2004	8/NR	NR/NR	NR/NR	NR/NR	NR/NR	35/NR	NR/NR	NR/NR
Tanko et. al, Denmark, 2005	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	263/NR	NR/NR	NR/NR
Ariyoshi et. al, Japan 2006	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	6/NR	NR/NR	NR/NR
Skolnick et. al, USA, 2009	5/8	18/33	NR/NR	NR/NR	NR/NR	18/6	NR/NR	NR/NR
Innasimuthu et. al, USA, 2009	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	8/NR	NR/NR	NR/NR
Elmariah et. al, USA, 2009	20(9)/461(13)	80(37)/1449(41)	100(47)/1432(41)	NR/NR	NR/NR	214/NR	NR/NR	NR/NR
Kanazawa et. al, Japan, 2010	13/13	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR
Toussaint et. al, Australia, 2010	14/15	23/25	NR/NR	NR/NR	25/25	NR/NR	NR/NR	NR/NR
Aksoy et. al, USA, 2012	34(16)/30(14)	98(45)/97(44)	74(34)/7(32)	NR/NR	5(2.3)/5(2.3)	NR/NR	NR/NR	NR/NR
Kawahara et. al, Japan, 2013	26/atorvastatin: 26 Combination: 26	10/atorvastatin: 11 Combination: 9	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR
Samelson et. al, USA, 2014	217(25.7)/203 (26.0)	692(82.1)/652 (83.4)	542(64.3)/525 (67.1)	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR
Okamoto et. al, Japan, 2014	2/3	4/5	NR/NR	NR/NR	5/7	NR/NR	NR/NR	NR/NR
Kranenburg et. al, Netherlands, 2018	NR/NR	NR/NR	NR/NR	NR/NR	0/0	NR/NR	Treatment: 113 (13.4) Control: 94 (12.0)/ Treatment: 113 (13.4) Control: 94 (12.0)	NR/NR
Iseri et. al, Japan, 2019	Denosumab: 20 Alendronate: 9/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR
Passeri et. al, Italy, 2019	NR/NR	Zoledronate: 5 Teriparatide: 6/5	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR
Chen et. al, Taiwan, 2020	3/2	19/20	NR/NR	NR/NR	21/21	NR/NR	NR/NR	NR/NR

Table 4 (continued)

Authors, country, year	DM (treatment/control)	HTN (treatment/control)	HLD (treatment/control)	HF (treatment/control)	CKD (treatment/control)	Osteoporosis (treatment/control)	Previous MI (treatment/control)	Previous stroke or TIA (treatment/control)
Alishiri et. al, Iran, 2020	10/10	NR/NR	NR/NR	0/0	NR/NR	37/33	NR/NR	NR/NR
Cai et. al, Australia, 2020	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR
Bartstra et. al, Netherlands, 2020	NR/NR	NR/NR	NR/NR	NR/NR	0/0	NR/NR	NR/NR	NR/NR
Mazzucchelli et. al, Spain, 2020	6398/19,460	12,157/50,503	11,045/41,217	876/2967	900/2817	NR/NR	NR/NR	1574/6171
Suzuki et. al, Japan, 2021	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR
Pawade et. al, United Kingdom, 2021	Denosumab: 12 Alendronate: 11/12	Denosumab: 35 Alendronate: 38/41	Denosumab: 34 Alendronate: 22/35	NR/NR	Denosumab: 6 Alendronate: 4/2	0/0	NR/NR	Denosumab: 9 Alendronate: 5/6
Saito et. al, Japan, 2022	6/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR
Koshiyama et. al, Japan, 2000	57/57	28/25	NR/NR	NR/NR	NR/NR	NR/NR	Denosumab: 8 Alendronate: 5/4	3/5
Delibasi et. al, Turkey, 2007	0/NR	NR/NR	NR/NR	NR/NR	0/NR	NR/NR	NR/NR	NR/NR
Hashiba et. al, Japan, 2006	3/2	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR
Torregrosa et. al, Spain, 2010	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR
Hashiba et. al, Japan, 2004	3/4	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR
Celiloglu et. al, Turkey, 2008	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR
Gonnelli et. al, Italy, 2013	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR
Geers et. al, United Kingdom, 2024	Denosumab: 12 Alendronate: 11/12	Denosumab: 35 Alendronate: 38/41	Denosumab: 34 Alendronate: 22/35	NR/NR	Denosumab: 6 Alendronate: 4/2	0/0	NR/NR	Denosumab: 9 Alendronate: 5/6
Chen et. al, Taiwan, 2024	NR/NR	NR/NR	NR/NR	NR/NR	24/21	NR/NR	NR/NR	NR/NR

CKD chronic kidney disease, *DM* diabetes mellitus, *HF* heart failure, *HLD* hyperlipidaemia, *HTN* hypertension, *MI* myocardial infarction, *NR* not reported, *TIA* transient ischaemic attack



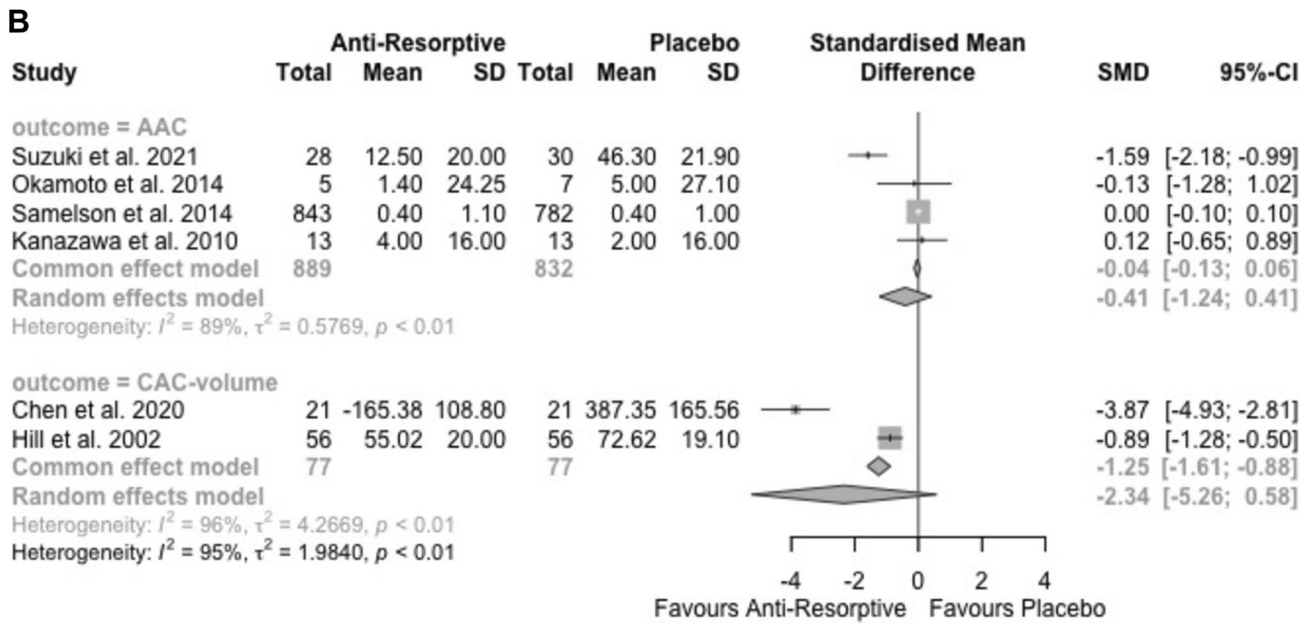


Fig. 2 **A** Forest plot of standardised mean difference for change in abdominal aortic calcification (AAC) and coronary artery calcification (volume) (CAC-volume). **B** Forest plot of standardised mean difference for change in abdominal aortic calcification (AAC) and coronary artery calcification (volume) (CAC-volume) in patients on etidronate. **C** Forest plot of standardised mean difference for change in abdominal aortic calcification (AAC) and coronary artery calcification (volume) (CAC-volume) in patients on haemodialysis. **D** Forest plot of standardised mean difference for change in coronary artery calcification (Hu) (Geers et al. (denosumab users)) and coronary artery calcification (Hu) (Geers et al. (alendronate users)). **E** Forest plot of standardised mean difference for change in aortic valve area/aortic stenosis (AVA-AS) and change in ejection fraction (EF)

outcome (CAC-volume) between treatment and control groups. Focusing specifically on patients on etidronate, two studies with a total of 154 patients studied the effects of etidronate on change in CAC (CAC-volume) [16, 32]. When pooled together, the rates of CAC-volume progression were similar (SMD = −2.34 [95% confidence interval −5.26 to 0.58, tau^2 = 4.27, n = 77; I^2 = 96%; Fig. 2B]). Focusing specifically on haemodialysis patients, four studies with a

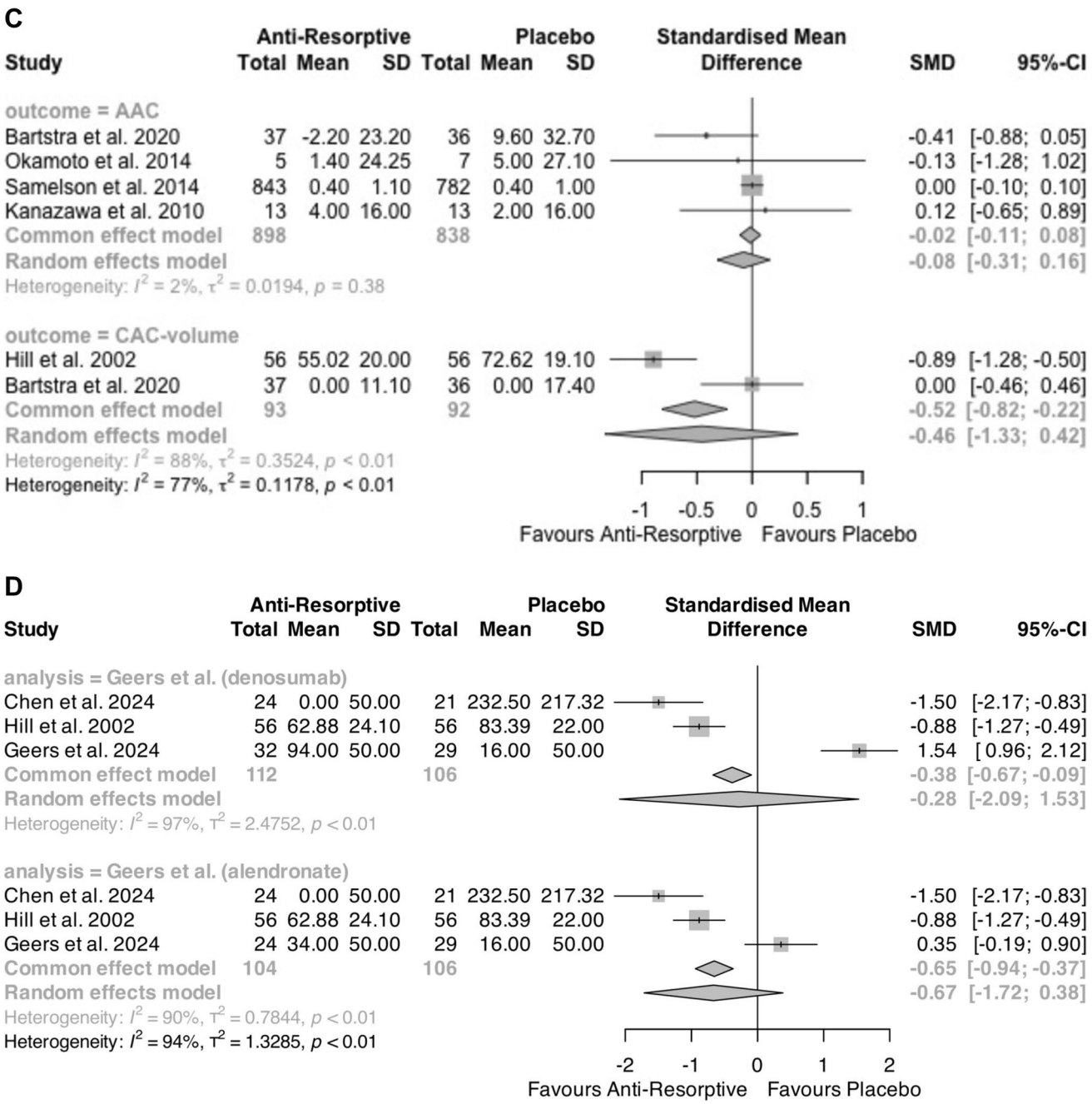


Fig. 2 (continued)

total of 185 patients studied the effects of haemodialysis on change in CAC (CAC-volume) [16, 34]. When pooled together, the rates of CAC-volume progression were similar (SMD = −0.46 [95% confidence interval −1.33 to 0.42, tau^2 = 0.0.35, n = 93; I^2 = 88%; Fig. 2C]).

Coronary artery calcification (Hu)

Three studies, including 218 patients, reported on change in volume of CAC (CAC-Hu) as an outcome of anti-resorptive therapy [15, 16, 46]. Chen included patients who were on haemodialysis and had secondary hyperparathyroidism and treated them with denosumab; Hill included osteoporotic patients and treated them with alendronate; Geers included patients with aortic stenosis and treated them with either denosumab or alendronate. When pooled together, the rates of CAC-Hu progression were similar (when including those treated with denosumab in Geers et al.) (SMD = −0.28 [95% confidence interval −2.09 to 1.53, tau^2 = 2.48; n = 112; I^2 = 97%; Fig. 2D]) and CAC-Hu (when including those

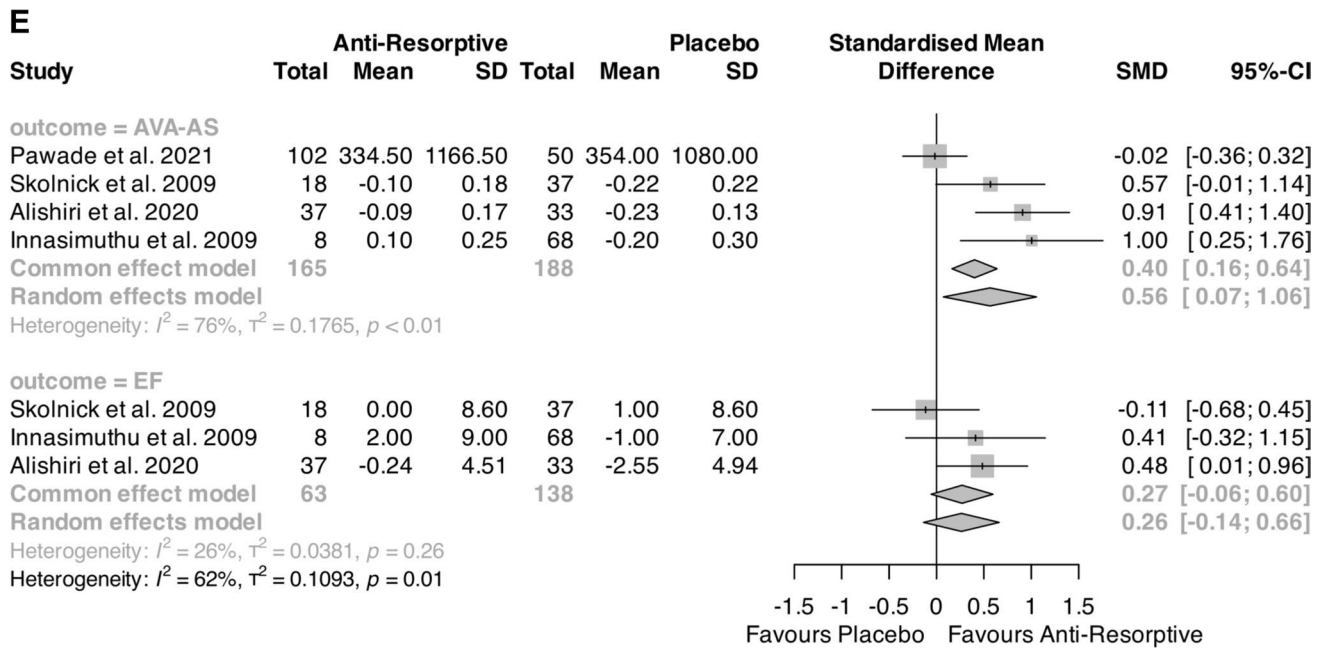


Fig. 2 (continued)

treated with alendronate in Geers et al.) (SMD = −0.67 [95% confidence interval −1.72 to 0.38, tau^2 = 0.784; n = 104; I^2 = 94%; Fig. 2D]), where SMD represents the difference in the change in vascular outcome (CAC-Hu) between treatment and control groups.

Aortic valve area (aortic stenosis)

Four studies, including 353 patients, reported on change in aortic valve area or aortic stenosis (AVA-AS) as an outcome of anti-resorptive therapy [11, 20, 21, 37]. Skolnick had no specific exclusion criteria for the population and treated the patients with bisphosphonates, calcitonin or selective oestrogen receptor modulators; Pawade included patients with aortic stenosis and treated them with denosumab or alendronate, but helpfully provided data for 'any antiresorptive use'; Alishiri included patients with aortic stenosis and osteoporosis and treated them with alendronate; Innasimuthu included patients with aortic stenosis and treated them with alendronate or risedronate. When pooled together, there was a significant small increase in AVA-AS (SMD = 0.56 [95% confidence interval 0.07 to 1.06, tau^2 = 0.18; n = 165; I^2 = 76%; Fig. 2E]), where SMD represents the difference in the change in vascular outcome (AVA-AS) between treatment and control groups. This means that the rate of progression in stenosis was marginally slower in those on anti-resorptives.

Ejection fraction

Three studies, including 201 patients, reported on percentage change in EF as an outcome of anti-resorptive therapy [11, 20, 21]. Skolnick had no specific exclusion criteria for the population and treated the patients with bisphosphonates, calcitonin or selective oestrogen receptor modulators; Innasimuthu included patients with aortic stenosis and treated them with alendronate or risedronate; Alishiri included patients with aortic stenosis and osteoporosis and treated them with alendronate. When pooled together, there was no increase in EF (SMD = 0.26 [95% confidence interval −0.14 to 0.66, tau^2 = 0.038; n = 63; I^2 = 62%; Fig. 2E]).

Sensitivity analysis

To account for clinical heterogeneity (e.g. study populations and interventions trialled), a leave-one-out sensitivity analysis was conducted for the above outcomes (Supplementary Table 5). Exclusion of Samelson only resulted in an overall significant reduction in AAC. Exclusion of any study except Hill resulted in an overall significant reduction in CAC-volume. Exclusion of any study except Hill resulted in an overall significant reduction in CAC-Hu (Geers et al. (denosumab users) and Geers et al. (alendronate users)) and overall significant increase in AVA-AS. Exclusion of Skolnick only resulted in an overall significant increase in EF.

Discussion

In this systematic review and meta-analysis, we attempted to evaluate whether anti-resorptive medications could influence the incidence or progression of various measures of vascular and valvular calcification. We demonstrated that there was significant, small favourable effect on AVA and non-significant, small favourable effects on AAC, CAC (volume), CAC (Hu) and EF associated with anti-resorptive use. A recent review also concluded that there is currently insufficient evidence to support the correlation between anti-resorptive use and CAC which we have again demonstrated but have extended on these previous findings by quantifying the putative association and inclusion of a broader range of indications to explore whether specific indications influence the overall outcome [9]. Taken together, these results indicate that the putative mechanisms that have been hypothesised to link vascular calcification with osteoporosis may be acting in pathways not influenced by anti-resorptives. Therefore, it could be speculated that interventions that target the shared causative pathways of both osteoporosis and vascular calcification (such as smoking, inflammation) may be more likely to yield favourable effects on both outcomes. While there is a small magnitude positive effect of anti-resorptive use on aortic stenosis, the clinical significance is still uncertain.

It should be noted that we did demonstrate small, significant favourable effects on AVA and small, non-significant favourable effects on AAC, CAC (volume), CAC (Hu) and EF. The small number of studies and patients enrolled in the included studies possibly account for the weak findings and one may speculate that inclusion of further and larger trials may alter outcomes and thus further research is warranted to explore this possibility.

In the case of bisphosphonates (which accounts for the majority of included trials), there is plausible biological evidence for them having favourable effects on vascular calcification. Bisphosphonates inhibit the farnesyl pyrophosphate synthase enzyme which acts downstream of HMG-CoA reductase in the malonate pathway of cholesterol synthesis [47]. Statins (inhibitors of HMG-CoA reductase) have well described effects on reducing plaque burden and clinical outcomes; thus, it is assumed that bisphosphonates would deliver similar benefit. Indeed, a secondary analysis of a large fracture reduction trial demonstrated reduced myocardial infarction mortality in those treated with zoledronate [48]. However, the results of our meta-analysis and previous meta-analysis of statins on calcification outcomes do not support this as the mechanism [49–51]. We observed a subtle difference in the effect of anti-resorptives on CAC versus AAC, where the effect was more pronounced in CAC. This could possibly reflect a small study effect (epiphenomenon). However, further analysis was done focusing on the effect of etidronate also showed a more positive effect in CAC. As etidronate is a non-nitrogen-containing-bisphosphonate, the main mode of action is slightly different—interfere with the mitochondrial adenosine diphosphate (ADP)/adenosine triphosphate (ATP) translocase [52]. However, during the process, it binds to hydroxyapatite crystals which helps in ectopic mineralisation that potentially reducing vascular and valvular calcification [34]. It has also been shown to reduce arterial calcification in patients with pseudoxanthoma elasticum [34, 53]. Furthermore, in a trial examining etidronate in thoracic and abdominal plaques, there appeared to be differential effects of the bisphosphonate on these sites [26]. Etidronate appeared to reduce abdominal plaques (distal vessel) but have little impact on thoracic plaques (proximal). We speculate that a similar phenomenon may be occurring, albeit with the associations reversed. That is to say, more proximal vessels such as the coronary vessels are being favourably altered, while the distal vessels such as the abdominal aorta are not. This could be related to the different vessel architecture/cellular constituents between the aorta and the coronaries and how bisphosphonates interact with them [54]. A separate analysis was also done to look at the effects of anti-resorptives on patients undergoing haemodialysis considering the extra-skeletal burden in CKD patients. Though insignificant, CAC was more favourable to anti-resorptives compared to AAC.

We demonstrated small, non-significant effects on EF. EF is not a direct marker of vascular/valvular calcification but was included as an exploratory, hypothesis-generating endpoint as the calcific burden on valvular or coronary structures would negatively impact EF. Analysis of effects of anti-osteoporosis medications on ejection fraction is included opportunistically in the setting of our primary aim. We hypothesise that peripheral vascular calcification (e.g. AAC) would affect total peripheral resistance, augmenting afterload which may promote ventricular remodelling, ultimately resulting in dilated cardiomyopathy. As such, EF may be preserved in this instance, but may predispose to declines in EF in untreated disease (such as advancing atherosclerotic disease). Hence, any small effect of anti-resorptives on EF may thus be reflective of an overall mixed effect of differing homeostatic forces. There might be a small reduction in total peripheral vascular resistance that would occur from a reduced peripheral vascular calcification burden together with a preserved EF due to left ventricular hypertrophy and improved myocardial perfusion from reduced coronary calcification burden. It should be noted, however, that heart failure and ejection fraction itself have multiple aetiologies and contributing factors and this may account for why no meaningful change in response to anti-resorptive treatment (assumed to the reduce calcification) was observed.

Our study also demonstrated small, significant favourable effects on change in aortic stenosis (there was a slower progression of valvular disease in patients on anti-resorptives

compared with those who were not), but the clinical significance is uncertain. This reflects the possibility that anti-resorptives act on the same pathway and have the same effect on valvular and vascular calcification. Previous animal studies also showed that bisphosphonates were able to inhibit vascular and valvular calcification [55]. Interestingly, there is a recent case report of an older osteoporotic women experiencing rapid progression of previously very stable aortic stenosis after commencing an anabolic agent (a parathyroid hormone analogue), suggestive of direct mineral metabolism effect on the pathophysiology of valvular calcification [56]. PTH results in increased renin secretion, reactive-oxygen species production and endothelin levels which could all result in hypertension and induce valvular stiffening, contributing to valvular calcification [57].

Previous meta-analyses on this topic had showed differing findings. Meta-analyses in 2016 and 2017 demonstrated that bisphosphonates were able to reduce arterial wall calcification. Kranenburg further found that bisphosphonates were also able to reduce the risk of cardiovascular mortality and all-cause mortality [58, 59]. In our meta-analysis, we revealed that anti-resorptive therapy provided significant, small favourable effects on AVA and non-significant, small favourable effects on AAC, CAC (volume), CAC (Hu) and EF. This contrasts with the meta-analyses mentioned. More clinical trials with a long follow-up period need to be conducted to reasonably conclude the role of anti-resorptive therapy in vascular calcification—further understanding the relationship between anti-resorptive therapy and valvular/vascular calcification may allow clinicians to better tailor osteoporosis therapies to individual patient risk factors and comorbidities, particularly those pertaining to valvular/vascular calcification.

While our review focused mainly on anti-resorptive medications, there has been ongoing discussions about the utility of vitamin D and its role in vascular calcification. In fact, vitamin D and CVDs have a U-shaped association between them [60, 61]. With insufficient vitamin D, it triggers a pro-inflammatory reaction which causes stress on the endothelium, leading to calcification or through inhibition of vascular smooth muscle cell (VSMC) into osteoclast-like cells [60, 61]. Excessive vitamin D instead causes calcification through differentiation of VSMC into osteoblast-like cells or with concomitant increases in calcium and phosphate [60, 61]. Hence, the biphasic actions of vitamin D make it especially vital to ensure patients have a healthy level of vitamin D to prevent vascular calcification and CVDs.

Our study has some limitations. Despite inclusion of many studies (33), only 15 of the papers had data included in the final meta-analysis totalling 2344 patients. Therefore, there is potentially a large amount of un-analysed, already published data and so overall findings are incomplete from this perspective. We urge and encourage custodians of these data to consider reporting on these outcomes. Also, the relatively small sample size of our data analysis may not be entirely reflective of the total population using anti-resorptives that may be at risk of vascular/valvular calcification. The wide confidence intervals of our results confirm this probable data limitation. In addition, as we placed no restrictions on study populations, our study extracted data from a heterogeneous cohorts (for example, pseudoxanthoma elasticum). This could potentially skew our dataset as different populations could have different risk factors that put them at increased risk of osteoporosis or valvular/vascular calcification or indeed have differing responses to anti-resorptives. However, we believe that inclusion of this diversity of cohorts only serves to increase the generalisability of our findings. Another further limitation was the heterogeneity of outcomes included. As there are few studies published that directly address the topic of anti-resorptive effects on valvular/vascular calcification in randomised settings, we collected a variety of outcomes that could be considered subclinical markers of valvular/vascular calcification in an effort to collect as much relevant data as possible. Random effects models were employed in an attempt to overcome this heterogeneity which generates conservative estimates. Some of the data collected were used for secondary analyses to affirm the primary outcomes that were statistically significant. For instance, EF was reported as an exploratory endpoint which had a non-significant small increase. This may be due to the vastly differing aetiologies of heart failure that are not directly related to extra skeletal calcification. There was also substantial heterogeneity in the outcomes for and changes in AAC, CAC (volume), CAC-Hu (Geers et al. (denosumab users) and Geers et al. (alendronate users)) and AVA ($tau^2 = 0.33$, 2.96, 2.49, 0.784 and 0.18, respectively). We also performed leave-one-out sensitivity analyses to explore small study effects and indication specific effects. Furthermore, some of the published papers had missing data that we were unable to collect. For example, some of the standard deviations (SDs) had to be imputed based on the mean of the studies included in the analysis. Data on the background of patients with osteoporosis were also limited. Hence, future studies could aim to include relevant information such as DEXA measurements, previous fractures and use of vitamin D or calcium, so that a deeper analysis could be undertaken to look at risk factors or any potential new associations linking risk factors, anti-resorptive medications and valvular/vascular calcification. Lastly, the follow-up of patients included in the analyses was relatively short, ranging from 6 months to 2 years. As calcification is a long and slow process that takes several years, the data obtained from these studies could potentially lead to misleading results. Different studies also used differing methods of measurement for calcification which may have a big measurement error in comparison with real changes that occur in the human body.

In conclusion, this systematic review and meta-analysis identified non-significant, marginal effects of osteoporosis

medications on markers of vascular calcification and significant, marginal effects of osteoporosis medications on valvular calcification; but studies were limited by small sample sizes, short follow-up durations, heterogeneous populations and outcome reported limiting interpretation about whether a true effect can be seen. Given significant biological evidence for osteoporosis mechanisms being involved in extra-skeletal calcification, our data would do well to be corroborated in future trials with larger sample size with longer follow-up times in cohorts representative of those taking osteoporosis medications and at risk of valvular/vascular calcification.

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Author contribution HZL and AJR designed the study and developed the study protocol and tools. HZL and AJR were responsible for data collection. HZL, KL, RH, NN, PRE and AJR analysed data and wrote the manuscript. All authors contributed to the conceptualization of the research questions, interpretation of the results and manuscript writing. All authors read and approved the final manuscript.

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Data availability Data used for this study can be accessed upon request from the Principal Investigator (Dr. Alexander J. Rodríguez) at Alexander.Rodriguez@monash.edu.

Declarations

Conflict of interest None.

References

1. Seeto AH, Tadrous M, Gebre AK, Lewis JR, Fink HA, Ebeling PR et al (2023) Evidence for the cardiovascular effects of osteoporosis treatments in randomized trials of post-menopausal women: a systematic review and Bayesian network meta-analysis. Bone 167:116610
2. Gebre AK, Sim M, Rodríguez AJ, Hodgson JM, Blekkenhorst LC, Szulc P et al (2021) Abdominal aortic calcification is associated with a higher risk of injurious fall-related hospitalizations in older Australian women. Atherosclerosis 328:153–159
3. Cannata-Andía JB, Carrillo-López N, Messina OD, Hamdy NAT, Panizo S, Ferrari SL et al (2021) Pathophysiology of vascular calcification and bone loss: linked disorders of ageing? Nutrients 13(11):3835
4. Kim B, Cho YJ, Lim W (2021) Osteoporosis therapies and their mechanisms of action (Review). Exp Ther Med 22(6):1379
5. Vall H, Patel P, Parmar M (2024) Teriparatide. StatPearls. Treasure Island (FL): StatPearls Publishing. Copyright © 2024, StatPearls Publishing LLC
6. Krupa KN, Parmar M, Delo LF (2024) Romosozumab. StatPearls. Treasure Island (FL): StatPearls Publishing. Copyright © 2024, StatPearls Publishing LLC
7. Seeto AH, Abrahamsen B, Ebeling PR, Rodríguez AJ (2021) Cardiovascular safety of denosumab across multiple indications: a systematic review and meta-analysis of randomized trials. J Bone Miner Res 36(1):24–40
8. Murali S, Smith ER, Tiong MK, Tan SJ, Toussaint ND (2023) Interventions to attenuate cardiovascular calcification progression: a systematic review of randomized clinical trials. J Am Heart Assoc 12(23):e031676
9. Saunders SL, Chaudhri K, McOrist NS, Gladysz K, Gnanenthiran SR, Shalaby G (2024) Do bisphosphonates and RANKL inhibitors alter the progression of coronary artery calcification? A systematic review. BMJ Open 14(9):e084516
10. Sterbakova G, Vyskocil V, Linhartova K (2010) Bisphosphonates in calcific aortic stenosis: association with slower progression in mild disease–a pilot retrospective study. Cardiology 117(3):184–189
11. Alishiri G, Heshmat-Ghahdarijani K, Hashemi M, Zavar R, Farahani MM (2020) Alendronate slows down aortic stenosis progression in osteoporotic patients: An observational prospective study. J Res Med Sci 25:65
12. Matthew JP, Joanne EM, Patrick MB, Isabelle B, Tammy CH, Cynthia DM et al (2021) The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 372:n71
13. Julian PTH, Douglas GA, Peter CG, Peter J, David M, Andrew DO et al (2011) The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 343:d5928
14. Stang A (2010) Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 25(9):603–605
15. Geers J, Bing R, Pawade TA, Doris MK, Daghem M, Fletcher AJ et al (2024) Effect of denosumab or alendronate on vascular calcification: secondary analysis of SALTIRE2 randomized controlled trial. J Am Heart Assoc 13(18):e032571
16. Hill JA, Goldin JG, Gjertson D, Emerick AM, Greaser LD, Yoon HC et al (2002) Progression of coronary artery calcification in patients taking alendronate for osteoporosis. Acad Radiol 9(10):1148–1152
17. Nitta K, Akiba T, Suzuki K, Uchida K, Watanabe R, Majima K et al (2004) Effects of cyclic intermittent etidronate therapy on coronary artery calcification in patients receiving long-term hemodialysis. Am J Kidney Dis 44(4):680–688
18. Tankó LB, Qin G, Alexandersen P, Bagger YZ, Christiansen C (2005) Effective doses of ibandronate do not influence the 3-year progression of aortic calcification in elderly osteoporotic women. Osteoporos Int 16(2):184–190
19. Ariyoshi T, Eishi K, Sakamoto I, Matsukuma S, Odate T (2006) Effect of etidronic acid on arterial calcification in dialysis patients. Clin Drug Investig 26(4):215–222
20. Skolnick AH, Osranek M, Formica P, Kronzon I (2009) Osteoporosis treatment and progression of aortic stenosis. Am J Cardiol 104(1):122–124
21. Innasimuthu AL, Katz WE (2011) Effect of bisphosphonates on the progression of degenerative aortic stenosis. Echocardiography 28(1):1–7

22. Elmariah S, Delaney JA, O'Brien KD, Budoff MJ, Vogel-Claussen J, Fuster V et al (2010) Bisphosphonate use and prevalence of valvular and vascular calcification in women MESA (The Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol 56(21):1752–1759
23. Kanazawa I, Yamaguchi T, Hayashi K, Takase H, Shimizu T, Sugimoto T (2010) Effects of treatment with risedronate and alfacalcidol on progression of atherosclerosis in postmenopausal women with type 2 diabetes mellitus accompanied with osteoporosis. Am J Med Sci 339(6):519–524
24. Toussaint ND, Lau KK, Strauss BJ, Polkinghorne KR, Kerr PG (2010) Effect of alendronate on vascular calcification in CKD stages 3 and 4: a pilot randomized controlled trial. Am J Kidney Dis 56(1):57–68
25. Aksoy O, Cam A, Goel SS, Houghtaling PL, Williams S, Ruiz-Rodriguez E et al (2012) Do bisphosphonates slow the progression of aortic stenosis? J Am Coll Cardiol 59(16):1452–1459
26. Kawahara T, Nishikawa M, Kawahara C, Inazu T, Sakai K, Suzuki G (2013) Atorvastatin, etidronate, or both in patients at high risk for atherosclerotic aortic plaques: a randomized, controlled trial. Circulation 127(23):2327–2335
27. Samelson EJ, Miller PD, Christiansen C, Daizadeh NS, Grazette L, Anthony MS et al (2014) RANKL inhibition with denosumab does not influence 3-year progression of aortic calcification or incidence of adverse cardiovascular events in postmenopausal women with osteoporosis and high cardiovascular risk. J Bone Miner Res 29(2):450–457
28. Okamoto M, Yamanaka S, Yoshimoto W, Shigematsu T (2014) Alendronate as an effective treatment for bone loss and vascular calcification in kidney transplant recipients. J Transplant 2014:269613
29. Kranenburg G, de Jong PA, Bartstra JW, Lagerweij SJ, Lam MG, Ossewaarde-van Norel J et al (2018) Etidronate for prevention of ectopic mineralization in patients with pseudoxanthoma elasticum. J Am Coll Cardiol 71(10):1117–1126
30. Iseri K, Watanabe M, Yoshikawa H, Mitsui H, Endo T, Yamamoto Y et al (2019) Effects of denosumab and alendronate on bone health and vascular function in hemodialysis patients: a randomized, controlled trial. J Bone Miner Res 34(6):1014–1024
31. Passeri E, Mazzaccaro D, Sansoni V, Perego S, Nano G, Verdelli C et al (2019) Effects of 12-months treatment with zoledronate or teriparatide on intima-media thickness of carotid artery in women with postmenopausal osteoporosis: a pilot study. Int J Immunopathol Pharmacol 33:2058738418822439
32. Chen CL, Chen NC, Wu FZ, Wu MT (2020) Impact of denosumab on cardiovascular calcification in patients with secondary hyperparathyroidism undergoing dialysis: a pilot study. Osteoporos Int 31(8):1507–1516
33. Cai G, Keen HI, Host LV, Aitken D, Laslett LL, Winzenberg T et al (2020) Once-yearly zoledronic acid and change in abdominal aortic calcification over 3 years in postmenopausal women with osteoporosis: results from the HORIZON Pivotal Fracture Trial. Osteoporos Int 31(9):1741–1747
34. Bartstra JW, de Jong PA, Kranenburg G, Wolterink JM, Isgum I, Wijsman A et al (2020) Etidronate halts systemic arterial calcification in pseudoxanthoma elasticum. Atherosclerosis 292:37–41
35. Mazzucchelli R, Rodríguez-Martín S, García-Vadillo A, Crespí-Villarías N, Gil M, Rodriguez-Miguel A et al (2020) Risk of acute myocardial infarction among new users of bisphosphonates: a nested case–control study. Osteoporos Int 31(12):2403–2412
36. Suzuki S, Suzuki M, Hanafusa N, Tsuchiya K, Nitta K (2021) Denosumab recovers aortic arch calcification during long-term hemodialysis. Kidney Int Rep 6(3):605–612
37. Pawade TA, Doris MK, Bing R, White AC, Forsyth L, Evans E et al (2021) Effect of denosumab or alendronic acid on the progression of aortic stenosis: a double-blind randomized controlled trial. Circulation 143(25):2418–2427
38. Saito T, Mizobuchi M, Kato T, Suzuki T, Fujiwara Y, Kanamori N et al (2023) One-year romosozumab treatment followed by one-year denosumab treatment for osteoporosis in patients on hemodialysis: an observational study. Calcif Tissue Int 112(1):34–44
39. Koshiyama H, Nakamura Y, Tanaka S, Minamikawa J (2000) Decrease in carotid intima-media thickness after 1-year therapy with etidronate for osteopenia associated with type 2 diabetes1. J Clin Endocrinol Metab 85(8):2793–2796
40. Delibasi T, Emral R, Erdogan MF, Kamel N (2007) Effects of alendronate sodium therapy on carotid intima media thickness in postmenopausal women with osteoporosis. Adv Ther 24(2):319–325
41. Hashiba H, Aizawa S, Tamura K, Kogo H (2006) Inhibition of the progression of aortic calcification by etidronate treatment in hemodialysis patients: long-term effects. Ther Apher Dial 10(1):59–64
42. Torregrosa JV, Fuster D, Gentil MA, Marcen R, Guirado L, Zarraga S et al (2010) Open-label trial: effect of weekly risedronate immediately after transplantation in kidney recipients. Transplantation 89(12):1476–1481
43. Hashiba H, Aizawa S, Tamura K, Shigematsu T, Kogo H (2004) Inhibitory effects of etidronate on the progression of vascular calcification in hemodialysis patients. Ther Apher Dial 8(3):241–247
44. Celiloglu M, Aydin Y, Balci P, Kolamaz T (2009) The effect of alendronate sodium on carotid artery intima-media thickness and lipid profile in women with postmenopausal osteoporosis. Menopause 16(4):689–693
45. Gonnelli S, Caffarelli C, Maggi S, Rossi S, Siviero P, Gandolini G et al (2013) The assessment of vertebral fractures in elderly women with recent hip fractures: the BREAK Study. Osteoporos Int 24(4):1151–1159
46. Chen C-L, Liou E-S, Wu M-T (2024) Denosumab decreases epicardial adipose tissue attenuation in dialysis patients with secondary hyperparathyroidism and low bone mass. Cardiorenal Med 14(1):113–122
47. Martin TJ (2000) Bisphosphonates - mechanisms of action. Aust Prescr 23(6):130–132
48. Reid IR, Horne AM, Mihov B, Stewart A, Garratt E, Wong S et al (2018) Fracture prevention with zoledronate in older women with osteopenia. N Engl J Med 379(25):2407–2416
49. Shahraki MN, Jouabadi SM, Bos D, Stricker BH, Ahmadizar F (2023) Statin use and coronary artery calcification: a systematic review and meta-analysis of observational studies and randomized controlled trials. Curr Atheroscler Rep 25(11):769–784
50. Zhao Y, Nicoll R, He YH, Henein MY (2016) The effect of statins therapy in aortic stenosis: meta-analysis comparison data of RCTs and observationals. Data Brief 7:357–361
51. Lai R, Ju J, Lin Q, Xu H (2020) Coronary artery calcification under statin therapy and its effect on cardiovascular outcomes: a systematic review and meta-analysis. Front Cardiovasc Med 7:600497
52. Grey A, Reid IR (2006) Differences between the bisphosphonates for the prevention and treatment of osteoporosis. Ther Clin Risk Manag 2(1):77–86
53. Ferrante EA, Cudrici CD, Rashidi M, Fu YP, Huffstutler R, Carney K et al (2024) Pilot study to evaluate the safety and effectiveness of etidronate treatment for arterial calcification due to deficiency of CD73 (ACDC). Vasc Med 29(3):245–255

54. Teronen O, Heikkilä P, Konttinen YT, Laitinen M, Salo T, Hanemaaijer R et al (1999) MMP inhibition and downregulation by bisphosphonates. Ann N Y Acad Sci 878:453–465
55. Price PA, Faus SA, Williamson MK (2001) Bisphosphonates alendronate and ibandronate inhibit artery calcification at doses comparable to those that inhibit bone resorption. Arterioscler Thromb Vasc Biol 21(5):817–824
56. Solomon A, Birkenfeld S (2021) Rapid progression of aortic stenosis after initiation of teriparatide treatment: a case report. Cardiovasc Endocrinol Metab 10(1):56–58
57. Rossi GP (2011) Hyperparathyroidism, arterial hypertension and aortic stiffness: a possible bidirectional link between the adrenal cortex and the parathyroid glands that causes vascular damage? Hypertens Res 34(3):286–288
58. Caffarelli C, Montagnani A, Nuti R, Gonnelli S (2017) Bisphosphonates, atherosclerosis and vascular calcification: update and systematic review of clinical studies. Clin Interv Aging 12:1819–1828
59. Kranenburg G, Bartstra JW, Weijmans M, de Jong PA, Mali WP, Verhaar HJ et al (2016) Bisphosphonates for cardiovascular risk reduction: a systematic review and meta-analysis. Atherosclerosis 252:106–115
60 Wang J, Zhou JJ, Robertson GR, Lee VW (2018) Vitamin D in vascular calcification: a double-edged sword? Nutrients 10(5):652
61. Zittermann A (2014) Vitamin D and cardiovascular disease. Anticancer Res 34(9):4641–4648