

# Bisphosphonates, atherosclerosis and vascular calcification: update and systematic review of clinical studies

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**Background:** Epidemiologic and clinical data have suggested the existence of a biologic linkage between the bone system and the vascular system. Bisphosphonates (BPs) are effective inhibitors of bone resorption and are currently considered the drugs of choice for the prevention and treatment of osteoporosis and related fractures. Data from several publications have suggested that BPs may also be effective in reducing the atherosclerotic process and vascular calcification, but the results of these studies are contrasting. This review aimed to allow a better understanding of the relationships between BPs and atherosclerosis in humans.

**Materials and methods:** Electronic databases of Pubmed-Medline, Cochrane Library and SCOPUS from inception to June 30, 2016 were searched. The full texts of the articles potentially eligible were carefully assessed and reviewed. Finally, 20 studies were found to be eligible and were included in the systematic review. All included studies were published between 2000 and 2014.

**Results:** In several studies, etidronate limited the progression of aortic and coronary calcification in hemodialysis patients, whereas the nitrogen-containing-BPs given orally did not significantly reduce vascular calcifications in patients with chronic kidney disease, kidney transplant or in those with osteoporosis. Nitrogen-containing-BPs present favorable effects both on vessel wall thickness and on arterial elasticity due to both a reduction in serum lipids and the interaction of BPs with the bone tissue, with the consequent release of bone turnover markers and cytokines into the bloodstream.

**Conclusion:** To sum up, the BPs seem to have the potential of influencing atherosclerosis and calcium homeostasis at the level of vascular walls with several possible mechanisms which may differ according to the type, potency, dosage and administration route of BPs. Additional studies are needed to specifically address the mechanism by which BP use could influence cardiovascular morbidity and mortality.

**Keywords:** bisphosphonates, atherosclerosis, vascular calcification, human studies

## Introduction

In the past, osteoporosis and atherosclerosis were considered as separate entities with a similar increasing prevalence with aging. Recently, both epidemiologic and clinical studies have outlined that patients with low bone mineral density (BMD) are at significantly greater risk of developing cardiovascular disease (CVD) as well as unexpected cardiovascular events, more severe coronary atherosclerosis and vascular calcification.<sup>1-6</sup> In addition, it is known that postmenopausal women with osteoporosis have an increased risk of developing cardiovascular events and that the increased risk is proportional to the severity of osteoporosis.<sup>7</sup> These data have also suggested

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a possible influence of drugs affecting bone metabolism on lipid and atherosclerosis mechanisms, or that drugs effective on the atherosclerosis process could also be efficacious in fracture prevention.<sup>3,4</sup> Moreover, there is growing evidence that osteoporosis and atherosclerosis share not only common risk markers such as aging, smoking, reduced physical activity and menopause in women, but also some pathophysiologic mechanisms and some genetic causes. For example, mutations with loss of function of LRP6 in humans lead to increased plasma low-density lipoprotein-cholesterol (LDL-C), hypertension and osteoporosis.<sup>8</sup>

An initial interesting theory was that CVD and osteoporosis were linked by a common denominator, such as serum lipid profile, which could act in parallel on both vascular and bone cells.<sup>9</sup> Some experimental data seemed to reinforce this concept showing an influence of lipids on osteoblasts and osteoclasts.<sup>10–12</sup> However, an interesting observational study showed that in a multiple regression analysis, lipid profile did not predict osteoporosis or fracture risk, whereas aortic calcification severity significantly explained BMD at the hip.<sup>13</sup> On the other hand, low BMD at the distal radius was found to be associated with increased risk of stroke and CVD mortality.<sup>6</sup> Several studies have reported that the progression of arterial calcification is linked with concurrent bone loss and vertebral fractures, further supporting a relationship between osteoporosis and CVD.<sup>14,15</sup> The common finding of simultaneous vascular calcification and osteoporosis in individual patients suggests that local tissue factors could have a crucial role in the regulation of mineralization and cell differentiation.<sup>16</sup> Cardiovascular calcification was conventionally viewed as an inevitable consequence of aging, but some landmark studies have demonstrated that it is a highly regulated process of mineralization which involves cellular and molecular signaling processes similar to those found in normal osteogenesis.<sup>17–20</sup> The similarity of the molecular mechanisms in osteogenesis and vascular calcification has led to the knowledge that atherosclerotic calcification is an actively regulated process, not a passive mineralization.<sup>21</sup> In fact, the mineral matrix of the plaque (hydroxyapatite) is identical to that found in bone and the process of vascular calcification, similar to bone remodeling, is a regulated process which includes both inductive and inhibitory mechanisms.<sup>22,23</sup> Moreover, mineral deposits in atherosclerotic plaque result from several different pathways involving metabolic and/or inflammatory processes.<sup>24</sup> The major factors influencing vascular atherosclerotic calcifications are listed in Table 1.

**Table 1** Factors influencing vascular atherosclerotic calcification

Factor	References	Action
BPM-2 and BPM-4	25, 26	Stimulates osteogenic differentiation by acting on Wnt pathway
MGP	27, 28	Antagonizes BMP-2 and prevents vascular calcification
Fetuin-A	29, 30	Fetuin-A accumulates at sites of vascular calcification and inhibits hydroxyapatite formation and vascular calcifications
OPG	31–38	OPG prevents RANKL from binding to its receptor OPG inhibits vascular calcification in animals; in humans, there is a positive association between OPG and CV diseases
RANKL	16, 38–41	RANKL stimulates vascular calcification
OPN	27, 42, 43	Enhancer of atherosclerosis in animals In humans, may attenuate vascular calcification
FGF23	44, 45	Reduces serum phosphate levels Biomarker of vascular calcification in CKD patients
Vitamin D	46–48	Regulates the response to inflammatory cytokines No evidence of any effects on vascular calcification
Ox-LDL	49	Induces osteogenic and apoptosis-mediated calcification of vascular cells

**Abbreviations:** BPM-2, bone morphogenetic protein-2; BPM-4, bone morphogenetic protein-4; CKD, chronic kidney disease; CV, cardiovascular; FGF23, fibroblast growth factor 23; MGP, matrix Gla-protein; OPG, osteoprotegerin; OPN, osteopontin; Ox-LDL, oxidized low-density lipoprotein; RANKL, receptor activator of nuclear factor kappa-B ligand.

## The effects of bisphosphonates on atherosclerotic plaque and vascular calcifications: experimental studies

The growing evidence that atherosclerosis and osteoporosis share several pathophysiologic mechanisms reinforces the interest in pharmacologic agents which could inhibit bone loss and also provide benefits in terms of slowing the progression of atherosclerosis. At present, only bisphosphonates (BPs), currently considered the drug of choice for the prevention and treatment of osteoporosis, could have this potential.<sup>50–52</sup> In a mouse model of glucocorticoid-induced osteoporosis, denosumab, a human monoclonal antibody targeting RANKL, reduced the progression of atherosclerosis.<sup>41</sup> Moreover, a more recent study reported that denosumab reduced spontaneous and induced calcification in an in vitro porcine valvular interstitial cell model.<sup>53</sup> However, the analysis of 2,363 postmenopausal women with osteoporosis selected from the participants in the FREEDOM study and at high risk of cardiovascular events showed a 3-year denosumab treatment had no effect on the progression of aortic calcifications or on the incidence of cardiovascular

adverse events, compared to placebo.<sup>54</sup> Also, odanacatib, a cathepsin K inhibitor, may have an anti-atherosclerotic effect; but in 2016, the development of odanacatib was discontinued after analysis discovered an increased risk of cardiovascular events.<sup>55</sup> BPs are grouped into two classes according to their chemical structure and the molecular mechanism by which they inhibit osteoclast activity (Table 2). Members of the first generation of BPs are called simple BPs (S-BPs; clodronate and etidronate), while those of the second or newer generation are called nitrogen-containing BPs (N-BPs). The latter have a high affinity for the bone tissue where they bind to and inhibit the activity of farnesyl pyrophosphate synthase, a key regulatory enzyme in the mevalonic acid pathway, leading to osteoclast apoptosis.<sup>56</sup> The first report of the effects of BPs on vascular calcification was published in the 1970s, with experiments showing inhibition of soft tissue calcification.<sup>57</sup> The accumulation of BPs in atherosclerotic arteries may be due to either their binding to calcified atheromatous lesions or their internalization into phagocytosing cells (namely, the macrophages).<sup>52</sup> Etidronate was the first BP to demonstrate the suppression of atherosclerotic lesion formation in the arteries of both rats and pigs, although there was no reduction in serum calcium and cholesterol.<sup>58,59</sup> Lomashvili et al<sup>50</sup> found that etidronate significantly reduced the calcium content in rat aortae cultured in a medium containing warfarin to induce calcification, and suggested that S-BPs may prevent calcifications by blocking the apatite crystals formation in the vessels as they do in the bone.<sup>50</sup> Clodronate at high dosages, when administered to rabbits, also significantly reduced the area of atherosclerotic lesions in the aorta, total cholesterol and total calcium concentration in the aorta.<sup>52</sup> S-BPs may directly inhibit metalloproteinases<sup>60</sup> and the expression of tumor necrosis factor- $\alpha$ , a cytokine that promotes osteoblastic differentiation of vascular cells and also inhibits calcium

deposition in the atherosclerotic lesions.<sup>61</sup> Moreover, S-BPs can be metabolized by the phagocytes into non-hydrolyzable adenine-containing analogs of adenosine triphosphate,<sup>62</sup> which inhibit adenine nucleotide translocase, thus promoting the activation of caspase-3 and thereby leading to apoptosis of macrophages and osteoclasts.<sup>63</sup> Several animal studies suggest that N-BPs also may have an inhibitory effect on vascular calcification and atherosclerosis process. Alendronate and ibandronate are reported to inhibit calcification of arteries and cardiac valves in rat models of warfarin-related calcification at doses comparable to those that inhibit bone resorption, without affecting serum calcium and phosphate levels.<sup>64</sup> Moreover, in uremic rats fed with a low-protein diet, artery calcifications were prevented by treatment with ibandronate.<sup>65</sup> Another study reported that high doses of vitamin D were lethal to rats and caused excessive calcification of arteries, lungs, kidneys and cartilage; however, when subjects were given vitamin D plus ibandronate, soft tissue calcification was inhibited in all organs and death was prevented.<sup>66</sup> Moreover, in monkeys, a 2-year treatment with pamidronate inhibited the development of diet-induced atherosclerosis without significant changes in serum cholesterol and calcium.<sup>67</sup> The exact mechanism by which N-BPs inhibit vascular calcification is not fully clear. It may be by the inhibition of bone resorption, with reduced efflux of calcium and phosphate, thus limiting their availability for deposition in the vessels or their ability to influence the activity of the vascular smooth muscle cells NaPi cotransporter.<sup>68</sup> Alternatively, N-BPs may have direct effects on the vessel wall and/or crystal formation. Another possible mechanism of action of N-BPs may be a reduction in serum cholesterol levels. To sum up, the experimental studies have confirmed the ability of BPs to reduce the formation of atherosclerotic plaques and to inhibit vascular calcifications. In animal studies, etidronate was the more potent inhibitor of vascular calcifications.

**Table 2** Different potential effects of simple bisphosphonates and nitrogen-containing bisphosphonates on vascular calcification

Simple bisphosphonates	Nitrogen-containing bisphosphonates
Inhibit metalloproteinases	Reduce efflux of calcium and phosphate
Inhibit TNF- $\alpha$	Influence the activity of the vascular smooth muscle cell NaPi cotransporter
Promote osteoblastic differentiation of vascular cells	Direct effects on the vessel wall
Inhibit calcium deposition in the atheromatous lesions	Direct effects on formation of crystals on the vessel wall, such as pyrophosphate
Promote the activation of caspase-3 and induce apoptosis of osteoclasts	Induce osteoclast apoptosis by inhibiting the farnesyl pyrophosphate synthase

**Abbreviation:** TNF- $\alpha$ , tumor necrosis factor alpha.

## The effects of BPs on atherosclerotic plaque and vascular calcifications: a systematic review of clinical studies

This review aimed to collect and synthesize the available data, in order to allow a better understanding of the relationships between BPs and atherosclerosis/vascular calcifications in humans.

## Materials and methods

A literature review was conducted from inception to June 30, 2016. Pubmed-Medline, Cochrane Library and SCOPUS databases were searched using the following search terms

(“bisphosphonates” or “etidronate” or “alendronate” or “risedronate” and so on) AND (“atherosclerosis” or “atherosclerotic plaque” or “cholesterol” or “vascular calcification”).

## Study selection

Studies were excluded if they were not available; they were on children, animals, in vitro or experimental studies, case reports, case series, letters to editor, comments, review articles; they were published in languages other than English; and they did not fulfill the objective of this review. Original studies were included if they met the following inclusion criteria: 1) being a clinical study; 2) investigating the impact of BPs on atherosclerosis, vascular calcification or serum cholesterol and 3) presentation of sufficient information on the study parameters at baseline and at the end of follow-up. Exclusion criteria were: 1) non-interventional studies; 2) observational and cross-sectional studies and 3) study duration of <6 months.

Eligible studies were reviewed and the following data were extracted: 1) first author’s name; 2) year of publication; 3) study design; 4) study duration; 5) number of subjects in BP and control groups; 6) intervention assigned to the control group (placebo, non-active treatment or active treatment); 7) outcome measurements evaluated and 8) baseline and end-study values for the study parameters.

## Characteristics of included studies

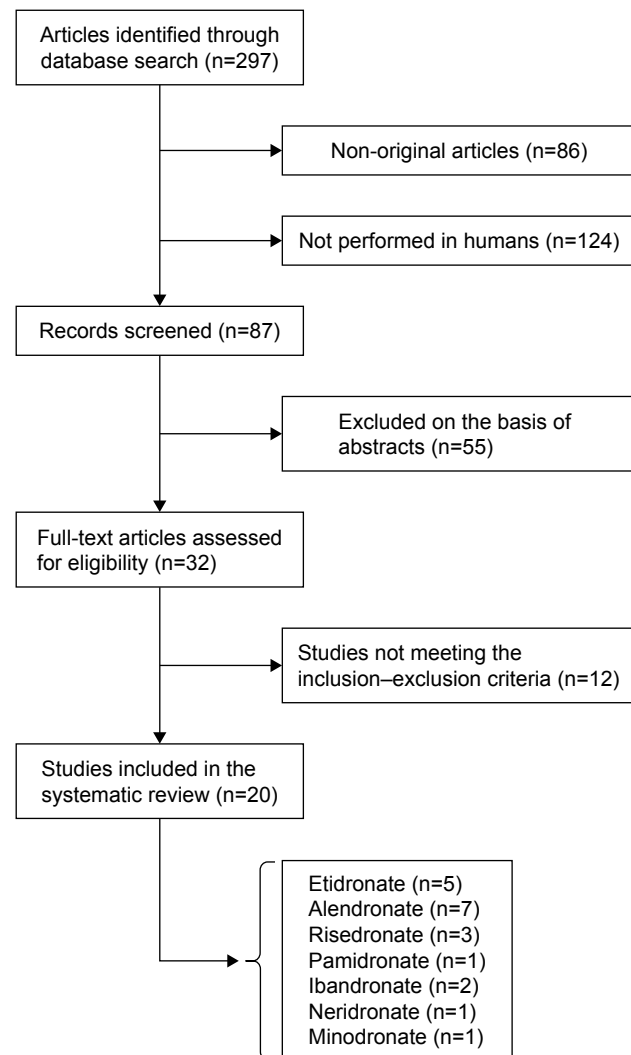
After the multiple database search, 297 published studies were identified and the abstracts reviewed. The study selection process is shown in Figure 1. The full text of the 32 articles potentially eligible were carefully assessed and reviewed. Finally, 20 studies were found to be eligible and were included in the systematic review.

## Results

The characteristics of the 20 studies included in the systematic review are presented in Table 3. The included studies were published between 2000 and 2014. Similar to animal experiments, which reported conflicting results for BP treatment of atherosclerosis and related vascular calcification, there have been varying responses in clinical studies.

### Effects of BPs an intima–media thickening and serum cholesterol

More than a decade ago, Adami et al firstly reported a significant reduction in LDL-C and an increase in high-density lipoprotein-cholesterol (HDL-C) in postmenopausal women treated with intravenous (i.v.) neridronate, whereas no significant changes were observed in total cholesterol.<sup>69</sup>



**Figure 1** Flow chart of the studies identified and included in the review.

Significant reductions in LDL-C were also reported by other two clinical studies carried out, respectively, in patients treated with i.v. pamidronate for Paget’s bone disease and in patients with smouldering multiple myeloma treated with zoledronic acid.<sup>70,71</sup> More recently, Gonnelli et al reported that in postmenopausal osteoporotic women, a 1-year treatment with both zoledronate (a single yearly injection) and ibandronate (a 3-monthly injection) induced similar changes in lipid profile by increasing HDL-C and reducing LDL-C and resulted in a reduction of intima–media thickness (IMT) at the carotid artery; however, in the latter study, no significant changes in total cholesterol were observed.<sup>72</sup> These positive effects of i.v. N-BPs on lipids have not yet been confirmed by the majority of studies carried out with N-BPs or S-BPs given orally. In particular, a study by Luckish et al carried out on osteoporotic women with at least one cardiovascular risk factor treated with risedronate 35 mg weekly for 6 months reported a significant improvement in artery elasticity, but

**Table 3** Main characteristics of the 20 studies included in the review

Study	Treatment	Duration (months)	Subjects (n)	Outcomes evaluated	Randomized	Results: changes in outcomes
Koshiyama et al <sup>74</sup>	Etidronate 200 mg for 2 weeks every 3 months No treatment	12	T2DM with osteopenia (57) T2DM (57)	Carotid artery IMT Lipids	No	IMT=↓0.038 mm T-C=↓0.8 mg/dL; HDL-C=↓2.6 mg/dL; TG=↓22.3 mg/dL IMT=↑0.023 mm T-C=5.4 mg/dL; HDL-C=1.7 mg/dL; TG=↓14.5 mg/dL
Delibasi et al <sup>77</sup>	Alendronate 70 mg/week	13	PM women with OP (71)	Carotid artery IMT Lipids	No	IMT=↓0.022 mm LDL-C=1 mg/dL; HDL-C=1 mg/dL; TG=↓3 mg/dL
Luckish et al <sup>73</sup>	Risedronate 35 mg/week	6	PM women with OP (68)	Large AEI Small AEI	No	AEI=↑1.68 mL/mmHg AEI=↑0.64 mL/mmHg
Celligloglu et al <sup>75</sup>	Alendronate 70 mg/week No treatment	12	PM women with OP (39) PM women (40)	Carotid artery IMT Lipids	Yes	IMT=↓0.025 mm T-C=↓3.5 mg/dL; LDL-C=↓13.3 mg/dL; HDL-C=2.7 mg/dL; TG=↓7.8 mg/dL IMT=↑0.020 mm T-C=↓2.1 mg/dL; LDL-C=↓3.7 mg/dL; HDL-C=0.7 mg/dL; TG=0 mg/dL
Kanazawa et al <sup>76</sup>	Risedronate 2.5 mg daily No treatment	12	T2DM with osteoporosis (13) T2DM controls (13)	PS AACSS	Yes	PS=↑1.25; AACSS=no changes PS=↑3.47; AACSS=↑1.0 Th=↑0.1; Ab=↓0.18
Kawahara et al <sup>79</sup>	Etidronate 400 mg for 2 weeks every 3 months Atorvastatin 20 mg Atorvastatin + etidronate	12	Hypercholesterolemia (36) Hypercholesterolemia (35) Hypercholesterolemia (37)	MR vessel maximal wall thickness (mm) at Th and Ab Lipids	Yes	T-C=↓6.9 mg/dL; LDL-C=↓7.2 mg/dL; HDL-C=1 mg/dL; TG=↓2.4 mg/dL Th=↓0.52; Ab=↓0.04 T-C=↓75.5 mg/dL; LDL-C=↓66.5 mg/dL; HDL-C=4.3 mg/dL; TG=↓52.4 mg/dL Th=↓0.54; Ab=↓0.39
Gonnelli et al <sup>72</sup>	Zoledronate 5 mg/year Ibandronate 3 mg every 3 months	12	PM women with OP (30) PM women with OP (30)	Carotid artery IMT Lipids	Yes	IMT=↓0.041 mm T-C=↓8.9 mg/dL; LDL-C=↓10 mg/dL; HDL-C=3.9 mg/dL; TG=↓5.3 mg/dL IMT=↓0.030 mm T-C=↓5.3 mg/dL; LDL-C=↓9.6 mg/dL; HDL-C=4.6 mg/dL; TG=↓3.5 mg/dL Δ=3.1% Δ=↓1.0%
Igase et al <sup>78</sup>	Alendronate 35 mg/week Minodronate 5 mg/month	12	PM women with OP (19) PM women with OP (19)	Brachial-ankle PWV	Yes	T-C=↓1.9 mg/dL; LDL-C=↓7.3 mg/dL; HDL-C=6.2 mg/dL; TG=↓6.9 mg/dL
Adami et al <sup>69</sup>	Neridronate 50 mg i.v. every 2 months No treatment	12	PM women with OP (44) PM women with OP (43)	Lipids	Yes	T-C=3.8 mg/dL; LDL-C=3.9 mg/dL; HDL-C=0.1 mg/dL; TG=↓1.1 mg/dL

(Continued)



Table 3 (Continued)

Study	Treatment	Duration (months)	Subjects (n)	Outcomes evaluated	Randomized	Results: changes in outcomes
Montagnani et al <sup>70</sup>	Pamidronate 60 mg i.v. every 3 months No treatment	9	Paget's disease (20) Paget's disease (12)	Lipids	No	T-C=-5.7 mg/dL; LDL-C=-6.6 mg/dL; HDL-C=4.5 mg/dL; TG=-2.2 mg/dL T-C=-1.5 mg/dL; LDL-C=-1.2 mg/dL; HDL-C=0.6 mg/dL; TG=7.0 mg/dL
Gozzetti et al <sup>71</sup>	Zoledronate 4 mg i.v. every 2 months No treatment	6	Multiple myeloma (16) Multiple myeloma (10)	Lipids	Yes	T-C=-2.8 mg/dL; LDL-C=-3.4 mg/dL; HDL-C=2.5 mg/dL; TG=-3.0 mg/dL T-C=-0.2 mg/dL; LDL-C=-2.0 mg/dL; HDL-C=-1.4 mg/dL; TG=13 mg/dL
Iwamoto et al <sup>80</sup>	Alendronate 5 mg daily Raloxifene 60 mg daily	12	PM women with OP (61) PM women with OP (61)	Lipids	Yes	T-C=-2.1 mg/dL; LDL-C=0.4 mg/dL; HDL-C=-0.4 mg/dL; TG=-3.4 mg/dL T-C=-3.9 mg/dL; LDL-C=-7.7 mg/dL; HDL-C=5.1 mg/dL; TG=7.4 mg/dL CAC=-0.307.6 mm <sup>3</sup>
Nitta et al <sup>81</sup>	Etidronate 200 mg daily for 14 days every 3 months	9	Hemodialysis patients (35)	CAC by CT	No	ACS: oral 2.5 mg daily=↑0.510; oral 20 mg=↑0.713
Tankó et al <sup>87</sup>	Oral ibandronate (2.5 mg daily or 20 mg intermittently for 12 days every 3 months) Ibandronate i.v. (0.5 mg or 1.0 mg i.v. every 3 months) Placebo	36	PM women with OP (93) PM women with OP (170) PM women with OP (128)	ACS by lateral X-ray	Yes	ACS: i.v. 0.5 mg=↑0.615; i.v. 1 mg=↑0.597 ACS: placebo=↑0.615
Hashiba et al <sup>83</sup>	Etidronate orally 200 mg on the days of dialysis (3/week) No treatment	23	Hemodialysis patients (12) Hemodialysis patients (9)	ACA by CT Lipids	Yes	ACA=↑149 mm <sup>2</sup> T-C=13 mg/dL; LDL-C=4.6 mg/dL ACA=↑129 mm <sup>2</sup>
Ariyoshi et al <sup>82</sup>	Etidronate 400 mg daily for 6 months No treatment	12	Hemodialysis patients (8) Hemodialysis patients (6)	ACS by CT	Yes	T-C=2.0 mg/dL; LDL-C=-0.7 mg/dL ACS=↓650 mm ACS=↑610 mm
Toussaint et al <sup>85</sup>	Alendronate 70 mg/week No treatment	18	CKD stages 3-4 CKD stages 3-4	PWV; AVC	Yes	AVC=↑70 HU; PWV= no changes AVC=↑149 HU; PWV= no changes
Torregrosa et al <sup>86</sup>	Risedronate 35 mg/week No treatment	12	Kidney transplant patients (52) Kidney transplant patients (49)	VCS by X-ray	Yes	VCS=↑0.27 VCS=↑0.43
Okamoto et al <sup>84</sup>	Alendronate 35 mg/week No treatment	24	Kidney transplant recipient (5) Kidney transplant recipient (7)	ACI by CT	Yes	ACI=↑1.4% ACI=↑5%
Hill et al <sup>88</sup>	Alendronate 10 mg daily No treatment	24	OP patients (56) OP patients (56)	CAC by CT	No	CAC=↑2.1% CAC=↑2.7%

**Abbreviations:** AACs, abdominal aortic calcification scores; Ab, abdominal; ACA, aortic calcification area; ACI, aortic calcification index; ACS, aortic calcification score; AEI, artery elasticity index; AVC, aortic vascular calcification; CAC, coronary artery calcification; CKD, chronic kidney disease; CT, computed tomography; HDL-C, high-density lipoprotein cholesterol; HU, Hounsfield units; IMT, intima-media thickness; i.v., intravenous; LDL-C, low-density lipoprotein cholesterol; MR, magnetic resonance; OP, osteoporosis; PM, postmenopausal; PS, plaque score at carotid artery; PWV, pulse wave velocity; T2DM, type 2 diabetes mellitus; T-C, total cholesterol; TG, triglycerides; Th, thoracic; VCS, vascular calcification score.

no change in HDL-C and LDL-C levels.<sup>73</sup> Koshiyama et al<sup>74</sup> investigated the effect of etidronate on carotid IMT in patients with type 2 diabetes and reported that at the end of a 12-month treatment, IMT was significantly reduced in the etidronate group with respect to control participants. Also, the study by Celiloglu et al reported that in postmenopausal osteoporotic women, a 1-year treatment with alendronate significantly reduced carotid IMT with respect to controls.<sup>75</sup> Moreover, in a study carried out on Japanese women with diabetes and postmenopausal osteoporosis, a 1-year therapy with risedronate (2.5 mg/day) along with alfacalcidol (1 mg/day) significantly reduced the progression of atherosclerotic plaques at the carotid arteries and abdominal aorta.<sup>76</sup> On the contrary, the study by Delibasi et al reported that in postmenopausal osteoporotic women, a 13-month treatment with alendronate did not evidence any changes in carotid IMT or serum levels of lipids.<sup>77</sup> Also, the study by Igase et al reported that in a Japanese population, a 1-year treatment with alendronate (35 mg/week) did not improve arterial stiffness.<sup>78</sup> Some studies reported that a 12-month treatment with etidronate<sup>74,79</sup> or alendronate<sup>75</sup> induced a nonsignificant reduction in total and LDL-C, along with a nonsignificant increase in HDL-C. Moreover, Kawahara et al, in a prospective randomized study carried out in hypercholesterolemic patients, reported that atorvastatin plus etidronate combination therapy was significantly more effective ( $P < 0.001$ ) in reducing atherosclerotic plaques in the abdominal aorta than both atorvastatin and etidronate monotherapy.<sup>79</sup> In the same study, the atorvastatin plus etidronate combination therapy showed a reduction of the atherosclerotic plaques in thoracic aorta similar to that of atorvastatin monotherapy.<sup>79</sup> On the contrary, a Japanese study carried out on osteoporotic women treated with a reduced dose of alendronate (5 mg/day) did not find any changes in cholesterol levels.<sup>80</sup> To sum up, the majority of human studies have reported a reduction of IMT at the carotid artery, whereas data on arterial stiffness and the atherosclerotic plaques are inconclusive. Moreover, N-BPs seem to improve the lipid profile only when given i.v.

### Effects of BPs on vascular calcification

Nitta et al reported that in hemodialysis patients, etidronate at a dose of 200 mg/day for 2 weeks every 90 days significantly reduced coronary artery calcifications, assessed by spiral computed tomography, and serum levels of osteoprotegerin.<sup>81</sup> In another study carried out on hemodialysis patients, etidronate (400 mg/day for 6 months) decreased aortic calcifications by 65%, whereas aortic calcifications markedly increased in controls.<sup>82</sup> Another Japanese study carried out on hemodialysis patients reported that etidronate (200 mg on

days of dialysis for 23 months) protected against progression of aortic calcifications, whereas these significantly increased in the control group.<sup>83</sup> A 2-year weekly treatment with alendronate in kidney transplant recipients was effective in preventing the progression of aortic calcifications with respect to control patients (1.4% vs 5%,  $P = ns$ ).<sup>84</sup> Moreover, in a study carried out in end-stage chronic kidney disease (CKD) patients, an 18-month treatment with alendronate significantly decreased the progression of aortic calcification with respect to placebo.<sup>85</sup> Similarly, Torregrosa et al reported that 1-year treatment with risedronate (35 mg/week) did not significantly influence the progression of vascular calcifications in kidney transplant patients.<sup>86</sup> Another clinical study involved osteoporotic women receiving oral or i.v. ibandronate for 3 years; at the end of the study period, the effect on BMD was positive, whereas no difference was detected in the rate of aortic calcification change.<sup>87</sup> Moreover, the study by Hill et al assessing coronary artery calcification, measured by spiral computed tomography scans, in patients treated with alendronate 10 mg daily for 2 years matched to a cohort of reference subjects did not find any significant differences between the two groups.<sup>88</sup> To sum up, etidronate markedly reduced progression of vascular calcifications, but most of these studies were carried out in patients with CKD or in hemodialysis. The effects of N-BPs given orally on the vascular calcifications were modest and inconclusive.

### Discussion

The interest in the relationships between BPs and atherosclerosis has recently shown a further increase after the publication of the results of the HORIZON study which reported a 28% reduction in mortality in hip fracture patients treated with an annual i.v. dose of zoledronic acid.<sup>89</sup> In another study, Kang et al revealed that patients who received BP therapy for osteoporotic fracture had a lower hazard of myocardial infarction during the 2-year follow-up period with respect to controls.<sup>90</sup> Moreover, two recent studies have reported that oral BPs reduce mortality in osteoporotic patients and that the reduction in mortality could be mainly due to cardiovascular and cerebrovascular deaths.<sup>91,92</sup> On the contrary, a recent meta-analysis by Kim et al<sup>93</sup> indicated that commonly prescribed BPs do not provide any clinically important benefits or harm with regard to cardiovascular events. The analysis of the studies included in this systematic review seems to suggest a positive effect of BPs on the progression of both atherosclerotic plaque and vascular calcifications. First of all, it is important to emphasize that this review has some limitations primarily resulting from the small sample size of most studies. Thus, insufficient data were available

to allow separate analysis of the effects of BPs in different patient subgroups. Moreover, most of these studies were of suboptimal quality in terms of providing adequate description of allocation concealment and the lack of the use of double blinding, thus leading to possible overestimation of BP benefit.

Several studies have shown that etidronate limited the progression of aortic and coronary calcification in hemodialysis patients.<sup>81–83</sup> Instead, the N-BPs given orally (alendronate, risedronate and ibandronate) did not significantly reduce vascular calcifications either in patients with CKD<sup>85</sup> and kidney transplant<sup>86</sup> or in patients with osteoporosis<sup>88</sup> and hypercholesterolemia.<sup>79</sup> However, at present, the clinical use of etidronate should be considered with caution because this agent can cause impaired bone mineralization, which may lead to osteomalacia and to an increased risk of stress fractures. Moreover, particular attention is required when using BPs in CKD and hemodialysis patients because in these patients, BPs may excessively reduce bone turnover, ultimately aggravating adynamic bone disease. Several studies have reported that BPs, especially N-BPs, present favorable effects both on vessel wall thickness and on the parameters of arterial elasticity and stiffness.<sup>72–76,79</sup> A possible mechanism of action of N-BPs may be a slowing down of the formation of atherosclerotic plaques due to a reduction in serum lipids, which are considered responsible for the triggering of atherosclerosis progression. In fact, the majority of studies found a reduction in total and LDL-C along with a mild increase in HDL-C,<sup>69–72,74</sup> whereas other studies did not report any changes.<sup>77,80</sup> These controversial data may suggest that the effect of BPs on lipids depends on the administration route, with a more favorable effect found when given i.v. However, literature data suggest that the changes in lipids alone are not sufficient to explain the positive effect on atherosclerosis. Moreover, BPs, especially N-BPs, could have an indirect effect on atherosclerotic manifestations due to the interaction of BPs with the bone tissue, with the consequent release of bone turnover markers, bone-related hormones and cytokines (such as osteocalcin, fibroblast growth factor 23, osteoprotegerin and so on) into the bloodstream. As confirmation, a recent study reported that osteocalcin and fibroblast growth factor 23 were independent predictors of carotid IMT in postmenopausal women treated with zoledronate.<sup>72</sup>

To sum up, the BPs seem to have the potential of influencing atherosclerosis and calcium homeostasis at the level of vascular walls with several possible mechanisms which may differ according to the type, potency, dosage and administration route of BPs. However, until the present time, it is

not yet clear which of these above-mentioned mechanisms may be the most important in humans and additional studies are needed to specifically address the mechanism by which BPs use could influence cardiovascular morbidity and mortality.

## Disclosure

The authors report no conflicts of interest in this work.

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