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REVIEW

Impact of Medications for Stable Angina Pectoris on Osteoporosis: A Review of Current Evidence

Rui-Ang Wang, Chen-Xi Xu

School of Medicine, Yangzhou University, Yangzhou, Jiangsu Province, 225001, People's Republic of China

Correspondence: Chen-Xi Xu, School of Medicine, Yangzhou University, No. 136 of Jiangyang Middle Road, Hanjiang District, Yangzhou, Jiangsu Province, 225001, People's Republic of China, Tel +86 13625217622, Email xuchenxi_yu@126.com

Abstract: Stable angina pectoris (SAP) and osteoporosis (OP) are both prevalent conditions among the elderly population. Compared to SAP, the prevention and management of OP are often neglected. Furthermore, certain medications used long-term for SAP may exert significant effects on bone metabolism. This review summarizes the impact of commonly prescribed SAP medications on OP. Extensive research indicates that nitrates not only promote vascular and osteogenic coupling via the nitric oxide (NO)-cyclic guanosine monophosphate (cGMP)-protein kinase G (PKG) pathway, enhancing the osteogenic effects of estrogen and mechanical stimulation, but also regulate bone immunity through receptor-interacting protein kinase 3 (RIPK3), promoting bone remodeling. β-Blockers promote osteoblast proliferation and osteogenic differentiation of bone marrow mesenchymal stem cells (BMSCs) via the cAMP/PKA signaling pathway, stimulating bone formation, while concurrently inhibiting osteoclasts and reducing bone resorption. Statins, which inhibit 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase to regulate lipid metabolism, also upregulate bone morphogenetic protein 2 (BMP-2) expression, inducing osteogenic differentiation of BMSCs, and inhibit osteoclast differentiation and activity, thereby promoting bone formation and suppressing bone resorption. Aspirin (AS) activates osteoblasts and their precursor cells, stimulates angiogenesis, mitigates inflammatory responses, promotes bone regeneration, and accelerates bone repair. However, clopidogrel reduces osteoblast numbers via P2 receptor-mediated extracellular nucleotide signaling and promotes adipogenic differentiation of BMSCs; furthermore, its metabolism can decrease serum 25-hydroxyvitamin D levels, adversely affecting skeletal health. Calcium channel blockers (CCBs) exhibit a largely neutral effect on bone health in clinical evidence, although basic research suggests potential benefits. The heterogeneity in research findings profoundly reflects the complexity of bone metabolism and the limitations of current studies. Synthesizing the evidence, preferential consideration may be given to nitrates, β-blockers, statins, and aspirin for SAP patients with coexisting OP or at significant risk; when clopidogrel is used, enhanced monitoring of bone parameters and intensified prevention and treatment of OP are recommended.

Keywords: bone metabolism, bone mineral density, drugs, osteoporosis, stable angina pectoris

Introduction

Stable angina pectoris (SAP), the most common manifestation of ischemic heart disease, is primarily caused by coronary atherosclerosis-induced myocardial blood supply insufficiency and is associated with an annual risk of 3% to 4% for myocardial infarction or death.[1]

Osteoporosis (OP) is a systemic skeletal disorder characterized by progressive reduction in bone mineral density and deterioration of bone microarchitecture.[2] It represents a significant cause of increased disability and mortality among the elderly population. Bone metabolism relies primarily on the coordinated actions of multiple cell types, including osteoblasts, osteoclasts, and bone marrow mesenchymal stem cells (BMSCs). The loss of bone mass typically does not elicit overt symptoms, consequently leading to inadequate treatment and prevention. Data from the National Health and Nutrition Examination Survey (NHANES) 2017–2018 cycle demonstrated that approximately 12.6% of adults aged ≥50 years had OP, while 43.1% were at risk of developing the condition.[3]

Both stable angina pectoris (SAP) and osteoporosis (OP) are chronic conditions that pose significant threats to health. However, clinical attention is typically prioritized towards the management of SAP, while the associated risks of

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OP are often neglected. A significant concern in the long-term treatment of SAP is the inadequate awareness regarding OP and the insufficient understanding of the potential skeletal effects of SAP medications. In clinical practice, when prescribing medications for SAP, physicians primarily focus on cardiovascular efficacy and safety, with considerably less emphasis on evaluating or informing patients about the potential implications of these drugs for skeletal health. Similarly, patient awareness regarding the potential skeletal risks or benefits associated with their prescribed medications is generally low. These limitations in awareness may consequently contribute to potentially preventable osteoporosis risk.[4]

Notably, patients with stable angina pectoris (SAP) inherently constitute a high-risk population for osteoporosis (OP), as these two conditions share significant common risk factors.[5] Advancing age is associated with progressive worsening of coronary atherosclerosis and an increased risk of myocardial ischemia. Concurrently, declining osteoblast activity coupled with relatively enhanced osteoclast activity accelerates bone loss. This association is particularly pronounced in postmenopausal women, where the precipitous decline in estrogen levels not only accelerates coronary atherosclerosis but also represents a major contributor to rapid bone loss.[6] Furthermore, SAP patients exhibit a state of chronic inflammation and oxidative stress.[7] Elevated levels of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), have been demonstrated to promote increased bone resorption.[8] The excessive reactive oxygen species generated by oxidative stress damage both vascular endothelial cells and bone cells,[9] thereby disrupting normal bone metabolism and impairing vascular nutrient supply to bone tissue, ultimately promoting the pathogenesis and progression of OP. Additionally, detrimental lifestyle factors, including smoking, excessive alcohol consumption, and physical inactivity, are closely linked to the development and progression of both conditions.[10–12] This constellation of shared pathophysiological mechanisms and exposures results in a significantly elevated risk of OP among SAP patients compared to the general population. Given the global demographic shift towards aging populations, the clinical management of comorbid SAP and OP is garnering increasing attention.[13]

Patients with stable angina pectoris (SAP) typically require long-term, often lifelong, administration of guideline-recommended medications, such as nitrates, β-blockers (BB), calcium channel blockers (CCB), statins, and antiplatelet agents (eg, aspirin and clopidogrel).[1] While primarily targeting the cardiovascular system, these drugs may also influence key bone metabolism cells—including osteoblasts, osteoclasts, and bone marrow mesenchymal stem cells (BMSCs)—and associated signaling pathways via multiple mechanisms; consequently, elucidating their long-term skeletal effects is imperative.

This review aims to synthesize existing research evidence to investigate the impact of commonly prescribed SAP medications on the development and progression of OP, thereby offering evidence-based guidance for mitigating potential skeletal risks in SAP patients and informing the development of individualized long-term therapeutic strategies.

Methods and Materials

This study aims to review the effects of commonly used drugs for stable angina pectoris (SAP) on osteoporosis (OP) and bone metabolism - related indicators. The research follows these steps:

Literature Search Strategy

Search Terms

Stable angina pectoris, Osteoporosis, bone density, fractures, nitrates, beta-blockers, calcium channel blockers, statins, aspirin, clopidogrel (both Chinese and English terms were used).

Databases

PubMed, Embase, Web of Science, Cochrane Library, China National Knowledge Infrastructure (CNKI), and Wanfang Data.

Search Period

From database establishment to January 2025.

Search Strategy

MeSH terms combined with free - text terms, linked via Boolean operators.

Inclusion and Exclusion Criteria

Inclusion Criteria

(1) Subjects: Human subjects, experimental animals, or relevant tissue models.
(2) Study Types: Randomized controlled trials (RCTs), prospective or retrospective cohort studies, case-control studies, cross-sectional studies, systematic reviews, meta-analyses.
(3) Research Focus: Studies investigating the effects of SAP-targeted agents on bone-related parameters/outcomes or elucidating their mechanisms of action.
(4) Language: Literature published in Chinese or English.
(5) Accessibility: Full-text availability.

Exclusion Criteria

(1) Subject Irrelevance: Studies not involving SAP-targeted agents or unrelated to bone-related parameters/outcomes.
(2) Study Type: Case reports, conference abstracts, commentaries, editorials.
(3) Language: Non-Chinese/non-English literature.
(4) Data Integrity: Studies with incomplete data presentation.

Literature Screening Process

Following the literature search strategy, duplicate records were removed using EndNote X9 reference management software supplemented by manual reference tracing. Two investigators independently screened titles and abstracts according to the predefined inclusion and exclusion criteria. Full texts of preliminarily eligible studies were retrieved, after which both investigators independently performed full-text assessment for final eligibility. Disagreements during screening were resolved through discussion or adjudication by the corresponding author. Ultimately, 62 core publications were included: nitrates (n=12), β-blockers (n=14), calcium channel blockers (CCB, n=12), statins (n=10), aspirin (n=7), and clopidogrel (n=7). Among these 62 publications, 39 were preclinical studies and 23 were clinical studies.

Analytical Approach

The analysis proceeded through four sequential phases: First, study findings and evidence were systematically synthesized according to drug classes. Second, preclinical evidence was integrated to elucidate potential mechanisms of action underlying pharmacological interventions. Third, clinical research outcomes were consolidated to comprehensively evaluate the potential therapeutic benefits and skeletal risks associated with each drug category, with emphasis on presenting predominant perspectives to inform clinical decision-making. Finally, comparative analysis was conducted to identify discrepancies across studies and examine contentious issues, including exploration of potential contributing factors.

Potential Effect of Commonly Used Drugs in SAP on Osteoporosis

Nitrates (Organic Nitrates)

Nitrates are classified as organic nitrate compounds and exert their effects through the release of nitric oxide (NO), with commonly used agents including nitroglycerin and isosorbide mononitrate (ISMO).[14]

NO serves as a multifunctional signaling molecule with diverse physiological roles. Extensive research has demonstrated that NO contributes to blood pressure reduction, improvement of vascular endothelial function, enhancement of exercise capacity, reversal of metabolic syndrome, and cognitive function improvement.[15] The underlying mechanisms involve modulation of mitochondrial respiration, activation of metabolic regulatory pathways, and the reduction of oxidative stress.[16] Disruptions in oxidative stress balance and dysfunction of the nitric oxide synthase system can lead to endothelial dysfunction and a subsequent decrease in NO bioavailability, which has been implicated in the occurrence of various diseases. Consequently, therapeutic strategies aimed at restoring redox homeostasis and supplementing NO and other biologically active nitrogen oxides have been proposed as potential treatment approaches.[17]

The NO-cyclic guanosine monophosphate-protein kinase G signaling pathway plays a key role in maintaining bone homeostasis. In bone tissue, NO activates this pathway, facilitates the coupling of angiogenesis and osteogenesis, and

accelerates bone repair.[18] Additionally, NO mediates the osteogenic response to mechanical stimulation and estrogen to some extent.[19] By modulating receptor-interacting serine/threonine-protein kinase 3, NO reduces lipid metabolism and monocyte necrosis. Furthermore, Pan et al reported that NO derived from nitrates inhibits monocyte apoptosis in bisphosphonate-related osteonecrosis of the jaw, modulates the bone immune microenvironment, and promotes bone remodeling following injury.[20]

Given the significant role of NO in bone metabolism, several clinical studies have examined the effects of nitrate therapy on BMD. Some studies have reported positive outcomes. For instance, a randomized trial demonstrated that ISMO administration led to increased bone formation and reduced bone resorption in postmenopausal women.[21] In this study, women who received 20 mg of ISMO daily exhibited a 45.4% reduction (95% CI, 25.8–64.9) in urinary N-terminal telopeptide, a marker of bone resorption, along with a 23.3% increase (95% CI, 8.9–37.8) in serum bone-specific alkaline phosphatase (ALP), a marker of bone formation.

However, findings from a one-year double-blind, randomized, placebo-controlled trial indicated that organic nitrates did not produce clinically significant effects on BMD or bone loss in postmenopausal women.[22] Additionally, a meta-analysis conducted by Liu et al, which included four group studies and two randomized controlled trials, examined the association between nitrate use and fracture risk.[23] Group studies indicated no significant relationship between nitrate use and overall fracture risk (RR = 0.97; 95% CI, 0.94–1.01; I2 = 31.5%) or hip fracture risk (RR = 0.88; 95% CI, 0.76–1.02; I2 = 74.5%). Furthermore, two randomized controlled trials comparing nitrate therapy with alendronate demonstrated similar effects on lumbar BMD (WMD = 0.00; 95% CI, −0.01–0.02; I2 = 0.0%).

With the advancement of bone immunology, it has been proposed that nitrates not only influence conventional bone cell signaling pathways but also regulate cytokines within the bone immune microenvironment, potentially affecting BMD indirectly.[24] These findings indicate that nitrates contribute to the modulation of specific pathophysiological mechanisms and support normal bone function.[25] However, the overall impact of nitrates on BMD, osteoporosis, and bone metabolism remains inconclusive. Further high-quality, large-scale studies are required to clarify their effects and clinical implications.

Beta-Blocker

BBs are widely used in the management of SAP due to their ability to reduce heart rate, myocardial contractility, and blood pressure by blocking cardiac β_1-AR, thereby decreasing myocardial oxygen consumption.[26] Additionally, these agents exert varying degrees of blockade on β_2-AR and β_3-AR.[27] In recent years, advancements in pharmacological research have provided new insights into the effects of BBs on bone metabolism and bone mass.

Studies indicate that catecholamines released by sympathetic nerves bind to β-ARs located on the surface of osteoblasts and osteoclasts. Activation of β_2-AR inhibits osteoblast proliferation and bone formation via the cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA) signaling pathway while at the same time promoting osteoclast maturation and activity, resulting in increased bone resorption.[28,29] Additionally, β_2-AR and β_3-AR play significant roles in the osteogenic differentiation and regulation of BMSCs. Activation of β-ARs by the sympathetic nervous system inhibits osteogenesis in BMSCs via the cAMP/PKA pathway, whereas beta-blockers counteract this effect and promote osteogenesis.[30]

Experimental studies support this hypothesis. In an in vitro study, the non-selective beta-blocker propranolol enhanced the osteogenic differentiation and migration of rat BMSCs while inhibiting osteoclast formation through β-AR blockade.[31] Currently, β_2-AR is considered the primary regulator of bone metabolism, although β_1-AR and β_3-AR have also been implicated in bone formation, though the precise mechanisms remain unclear. Notably, selective β_1-AR blockers have demonstrated promising results in osteoporosis management.

A study using an ovariectomized rat model found that metoprolol, a selective β_1-AR blocker, significantly increased the gene expression of osteoblast markers, enhanced ALP activity, promoted calcium mineralization, and reversed osteoporosis-related declines in BMD, bone microstructure integrity, and biomechanical properties, indicating a significant anti-osteoporotic effect.[32]

Clinical studies have further corroborated these findings. Selective β_1-AR blockers, including atenolol and nebivolol, have been associated with reductions in serum collagen type I C-telopeptide, a bone resorption marker (19.5% and 20.6%, respectively; $p < 0.01$), along with significant increases in distal radius BMD (3.6% and 2.9%, respectively; $p <$

0.01 and $p < 0.05$).[33] Additionally, the use of selective β_1-AR blockers in postmenopausal women has been linked to increased lumbar BMD.[34] Song et al also reported a reduction in fracture risk among patients over 65 years of age who were treated with β_1-AR blockers.[35]

Collectively, these findings indicate a strong association between the use of selective beta-blockers and increased BMD, as well as a reduced risk of fractures.[36] However, some studies have reported no significant effects of BBs on bone formation or BMD improvement.[37–39] The current evidence remains insufficient to support the use of BB as a therapeutic option for osteoporosis.

Calcium Antagonists

CCBs alleviate myocardial oxygen supply-demand imbalance by inhibiting calcium ion influx into cells, thereby reducing myocardial contractility, dilating coronary and peripheral blood vessels, and improving myocardial metabolism. Given the key role of calcium ions in bone metabolism, the potential effects of CCBs on bone health have been an area of increasing research interest.

Animal studies have provided insights into the influence of CCBs on bone metabolism. One study reported that after five weeks of oral amlodipine administration, osteoprotegerin levels in the experimental group of mice increased approximately fivefold, while receptor activator for nuclear factor-κB ligand levels increased tenfold compared to controls. These findings indicate that amlodipine may accelerate fracture healing by stimulating bone formation, promoting callus remodeling, and enhancing osteoblast activity.[40] Additionally, amlodipine inhibits osteoclast activity and suppresses parathyroid hormone secretion, resulting in improved femoral BMD in hypertensive male rats.[41] Other studies have demonstrated that cilnidipine reduces bone loss in estrogen-deficient female rats by inhibiting sympathetic activity and the renin-angiotensin-aldosterone system through the blockade of N-type calcium channels on sympathetic nerve cell membranes.[42] Zhang et al further reported that felodipine decreased osteolysis in ovariectomized mice by inhibiting mitogen-activated protein kinase phosphorylation.[43] Karakus et al observed that lacidipine and amlodipine enhanced the gene expression of osteogenic markers, including runt-related transcription factor 2 (Runx2) and type I collagen 1A1, in a rat model of ovariectomy-induced osteoporosis.[44]

However, contrasting findings have also been reported. Wen et al found that nifedipine significantly reduced ALP activity and mineralized nodule formation, while also downregulating the expression of osteogenic markers such as osteocalcin, bone sialoprotein, and Runx2.[45] These effects led to inhibited osteogenic differentiation of BMSCs and induced osteoblast apoptosis.

Despite numerous preclinical studies highlighting the positive effects of CCBs on various aspects of bone metabolism, clinical evidence remains limited and inconsistent. For instance, Ay et al reported that amlodipine administration for 12 weeks led to increased vitamin D levels, which play a crucial role in calcium absorption and bone metabolism.[46] This indicates that amlodipine exerts indirect benefits on bone health by enhancing vitamin D status. In a long-term follow-up study of 22,180 patients using data from the Veterans Affairs and Medicare databases in the United States, Puttnam et al found that CCB use was associated with a lower risk of hip and pelvic fractures (HR = 0.79; 95% CI, 0.63–0.98; $p = 0.04$), indicating a potential protective effect on bones.[47]

Conversely, findings from a national cohort study in Sweden did not establish a clear relationship between amlodipine or felodipine use and hip fracture risk.[48] Similarly, other studies have reported no significant relationship between CCB use and BMD or bone strength.[49,50] Furthermore, a Mendelian randomization analysis indicated that CCBs may have detrimental effects on bone health.[51]

The discrepancies among these studies may be attributed to differences in study populations, dosages, treatment durations, observation parameters, and assessment methodologies. To clarify the potential effects of CCBs on bone metabolism, future research should focus on large-scale, multicenter, and standardized clinical studies with rigorous methodologies and long-term follow-up.

Statins

Statins are widely prescribed for the management of SAP. Along with their well-established role in inhibiting cholesterol biosynthesis, statins exert anti-inflammatory, antioxidant, antiproliferative, anti-apoptotic, cell cycle regulatory, and immunomodulatory effects, primarily through the inhibition of 3-hydroxy-3-methylglutaryl-CoA reductase.[52]

Regarding bone metabolism, statins upregulate the expression of bone morphogenetic protein 2, promote the differentiation of BMSCs into osteoblasts, and suppress the differentiation and activity of osteoclasts.[53,54] These findings indicate that statins influence bone metabolism through dual mechanisms—enhancing bone formation and inhibiting bone resorption.

Animal studies have provided evidence supporting the osteogenic effects of statins.[55] One study demonstrated that simvastatin and lovastatin significantly increased serum calcium levels, upregulated osteogenic gene expression, improved BMD, and enhanced biomechanical properties, particularly in trabecular bone, in ovariectomized rats ($p < 0.05$). Another study investigating the effects of simvastatin on bone microstructure and mechanical properties in ovariectomized mice reported significant increases in bone volume fraction, trabecular bone number, connectivity density, and trabecular tissue density in the experimental group compared to the control group ($p < 0.05$).[56] These findings indicate that certain statins contribute positively to bone metabolism and enhance bone quality.

Clinical evidence also supports the association between statin use and improved bone health. A retrospective cohort study found that statin therapy was associated with a reduced risk of hip fracture (HR = 0.78; 95% CI, 0.64–0.94). This protective effect was particularly evident in women aged 50–64 years, with hazard ratios approaching 0.35 for both males and females, though no significant association was observed in older adults. Furthermore, women in the 50–64 age group who received statins had a lower risk of vertebral fractures (HR = 0.70; 95% CI, 0.50–0.99), whereas no such effect was noted in males.[57] Additional studies have reported that statin use reduces the risk of osteoporosis, hip fractures, and vertebral fractures.[58,59]

A meta-analysis incorporating data from 33 clinical trials, comprising of 314,473 statin users and 1,349,192 controls, conducted a comprehensive evaluation of fracture risk, BMD, and bone metabolism markers. Statin therapy was associated with increased BMD and OC levels, reduced fracture risk, and a more pronounced effect in males compared to females.[60] However, in one study, there was no significant effect of statins on overall fracture risk.[61]

Antiplatelet Drugs

Aspirin (AS)

Aspirin is a commonly used antiplatelet agent that irreversibly inhibits cyclooxygenase-1, leading to reduced thromboxane A_2 production and effective inhibition of platelet aggregation. Recent research has highlighted its potential benefits in bone metabolism.

AS activates various cytokines and mediators involved in osteoclast, osteoblast, and progenitor cell function, thereby promoting bone regeneration, stimulating angiogenesis, and accelerating bone repair.[62] Studies indicate that AS enhances the migration, proliferation, and differentiation of bone marrow stromal cells while also reducing the inflammatory response of macrophages, significantly promoting bone formation.[63] Additionally, it has been reported to induce the osteogenic differentiation of adipose-derived stem cells.[64]

Animal studies further support these findings. AS mitigates the inhibitory effects of TNF-α on chondrogenesis in BMSCs by stabilizing Yes-associated protein (YAP).[65] In another study, mice treated with three different doses of AS exhibited significantly increased trabecular bone thickness, trabecular bone number, BMD, maximum compressive load of the lumbar spine, and three-point bending load of the femoral axis compared to control groups.[66]

Human studies have also demonstrated a positive association between AS use and bone health, particularly at low doses. Xie et al reported that low-dose AS (< 100 μg/mL), commonly prescribed for thrombosis prevention, enhances osteoblast-driven osteogenesis in a COX-dependent manner while inhibiting osteoclast activity, thereby contributing to the maintenance of bone mass and quality.[67]

A cross-sectional study of 15,560 adults aged 50–80 years examined differences in BMD between individuals taking low-dose AS and those not using AS.[68] The findings from the study indicated that BMD at multiple skeletal sites was higher in the low-dose AS group, with significant differences observed at the total femur (β = 0.019, 95% CI, 0.004–0.034), femoral neck (β = 0.017, 95% CI, 0.002–0.032), intertrochanteric region (β = 0.025, 95% CI, 0.007–0.043), and lumbar vertebra L1 (β = 0.026, 95% CI, 0.006–0.046). These differences were independent of age and sex.

In summary, AS, particularly at low doses, has demonstrated potential benefits in maintaining and improving BMD, providing a promising avenue for osteoporosis prevention and treatment. However, further research is required to elucidate the optimal dosage, underlying mechanisms, and long-term safety of AS in the context of bone health. Future studies should focus on large-scale, well-controlled trials to confirm these findings and establish clinical guidelines for the use of AS in osteoporosis management.

Clopidogrel

Clopidogrel is a $P2Y_{12}$ receptor antagonist that inhibits adenosine diphosphate-mediated platelet aggregation and is widely prescribed to reduce the risk of SAP attacks, particularly due to its relatively lower incidence of gastrointestinal adverse effects.

Recent studies have identified the widespread expression of the $P2Y_{12}$ receptor in both bone and bone marrow, providing a theoretical basis for exploring the effects of clopidogrel on skeletal health. Clopidogrel has been shown to regulate osteoblast and osteoclast activity through extracellular nucleotides that signal via P2 receptors.[69] Its administration has been associated with a reduction in osteoblast number and viability, leading to decreased bone formation and lower BMD.[70] Additionally, clopidogrel promotes the differentiation of precursor cells into adipocytes, increasing adipocyte numbers and disrupting normal bone marrow function.[71] These changes not only impair bone nutrient supply and metabolism but also interfere with bone development and repair processes.

Furthermore, the metabolism of clopidogrel in the liver and kidneys has been linked to decreased circulating levels of 25-hydroxyvitamin D, which negatively impacts bone health.[72] A reduction in 25-hydroxyvitamin D levels compromises calcium absorption and utilization, thereby affecting bone mineralization and further contributing to the deterioration of bone strength and quality.

In vitro studies have demonstrated that clopidogrel inhibits both osteoblast and osteoclast proliferation and differentiation while at the same time promoting adipocyte formation.[73] However, given that clopidogrel requires hepatic enzymatic activation to exert its effects, in vivo studies provide a more accurate representation of its physiological impact.[74] Animal studies have reported that long-term clopidogrel administration results in significantly reduced BMD, decreased trabecular bone volume, and lower serum levels of bone formation markers. Collectively, these findings indicate that clopidogrel disrupts bone homeostasis by inhibiting the $P2Y_{12}$ receptor signaling pathway, indicating that prolonged use may have detrimental effects on bone health.

Clinical data further support these observations. A national cohort study conducted in Denmark found that clopidogrel treatment was strongly associated with an increased risk of fractures, particularly osteoporotic fractures, with the highest risk observed in individuals receiving treatment for more than one year.[75] Although clinical research on the effects of clopidogrel on bone metabolism remains limited, the available evidence underscores the need for further investigation.

Discussion

Numerous studies have demonstrated that nitrate compounds not only promote vascular-bone formation coupling via the NO-cGMP-PKG pathway, enhancing the bone anabolic effects of estrogen and mechanical stimulation, but also regulate bone immunology through RIPK3, thereby facilitating bone remodeling. β-blockers promote osteoblast proliferation and osteogenic differentiation of bone marrow stromal cells (BMSCs) via the cAMP/PKA signaling pathway, stimulating bone formation while simultaneously suppressing osteoclasts and reducing bone resorption. Statins inhibit HMG-CoA reductase to modulate lipid metabolism and concurrently upregulate BMP-2 expression, inducing osteogenic differentiation of BMSCs, and reducing osteoclast differentiation and activity, which benefits skeletal health. Atorvastatin (AS) activates osteoblasts and their progenitor cells, stimulates angiogenesis, mitigates inflammatory responses, promotes bone regeneration, and accelerates bone repair. However, clopidogrel, which mediates extracellular nucleotide signaling via P2 receptors, may reduce osteoblast numbers and promote adipogenic differentiation of BMSCs. Its metabolism in the kidneys and liver can also lead to decreased serum levels of 25-hydroxyvitamin D, exerting detrimental effects on bone health. Calcium channel blockers (CCBs) yield conflicting findings: animal studies suggest potential skeletal benefits, whereas clinical evidence is largely neutral, indicating no significant impact on bone.

However, the current body of evidence still faces significant challenges. The discrepancies and inconsistencies among study findings are primarily attributed to the inherent complexity of bone metabolism and the limitations inherent in existing research. The heterogeneity in outcome measures (eg, bone turnover markers [BTMs], bone mineral density [BMD], fracture incidence) complicates direct comparisons across studies. Furthermore, variations in study populations (including factors such as age, sex, ethnicity, underlying comorbidities, and cohort size), differences in drug dosage and treatment duration, and the use of diverse detection methodologies collectively contribute to the heterogeneity of results and may confound their interpretation.

To elucidate the precise impact of commonly used SAP medications on OP, the following types of future studies are warranted:

(1) Large-Scale Prospective Cohort Studies: Long-term follow-up of SAP patients to precisely quantify the associations between different types, dosages, and durations of SAP medications and bone mineral density (BMD), bone turnover markers, and fracture risk, with strict adjustment for confounding factors.

(2) Mechanism-Validating Randomized Controlled Trials (RCTs): Long-term RCTs designed with bone health as the primary endpoint, conducted in specific populations (eg, postmenopausal women). These should verify mechanisms of drug action identified in basic research, assess their actual effects on BMD, bone microstructure, and fracture rates, and explore dose-response relationships.

(3) Biomarker and Personalized Medicine Research: Utilizing multi-omics technologies (genomics, transcriptomics, proteomics) integrated with clinical data to identify biomarkers capable of predicting individual patient skeletal responses (beneficial or adverse) to specific medications, thereby guiding precision therapy.

(4) Drug Interaction Studies: Investigating the combined effects of commonly used SAP drug combinations on bone metabolism. This includes assessing whether concomitant use of anti-osteoporosis medications (eg, bisphosphonates) can effectively mitigate the adverse skeletal effects of potentially bone-detrimental drugs (eg, clopidogrel).

Conclusion

Understanding the impact of commonly used SAP medications on OP is crucial for optimizing SAP management. This reflects a paradigm shift in clinical decision-making from single-disease management towards patient-centered holistic health management. Most SAP patients belong to a high-risk population for OP due to underlying pathophysiological factors such as aging and chronic inflammatory states. For SAP patients with osteopenia, prioritizing medications such as nitrates, beta-blockers, statins, and aspirin can yield synergistic dual protective effects for both cardiac and skeletal health. Given the potential adverse impact of clopidogrel on bone health, its selection necessitates rigorous assessment of the risk-benefit ratio and the initiation of prophylactic bone health management strategies. For medications with controversial effects, such as calcium channel blockers (CCBs), individualized evaluation is required, along with targeted bone health monitoring and early intervention measures. Neglecting these impacts may induce or exacerbate OP.

The complexity of bone metabolism not only presents challenges for clinical pharmacotherapy but also delineates future research directions. By integrating data from basic and clinical research, and employing advanced detection technologies and analytical methods to elucidate the underlying mechanisms by which SAP medications affect bone metabolism, we can develop more precise and personalized management strategies for the skeletal health of SAP patients.

Abbreviations

ALP, Alkaline Phosphatase; AS, Aspirin; β-AR, Beta-Adrenergic Receptor; BB, Beta-Blockers; BMD, Bone Mineral Density; BMSCs, Bone Marrow Mesenchymal Stem Cells; BMP, Bone Morphogenetic Protein; BTMs, Bone Turnover Markers; cAMP, cyclic Adenosine Monophosphate; CCB, Calcium Channel Blocker; cGMP, cyclic Guanosine Monophosphate; CI, Confidence Interval; CNKI, China National Knowledge Infrastructure; COX-1, Cyclooxygenase-1; HMG-CoA, 3-Hydroxy-3-Methylglutaryl-Coenzyme A; HR, Hazard Ratio; IL-6, Interleukin-6; ISMO, Isosorbide Mononitrate; MeSH, Medical Subject Headings; NHANES, National Health and Nutrition Examination Survey; NO, Nitric Oxide; OP, Osteoporosis; PKA, Protein Kinase A; PKG, Protein Kinase G; RCTs, Randomized Controlled Trials; RIPK3, Receptor-Interacting Protein Kinase 3; Runx2, Runt-Related Transcription Factor 2; RR, Relative Risk; SAP,

Stable Angina Pectoris; TNF-α, Tumor Necrosis Factor-alpha; WMD, Weighted Mean Difference; YAP, Yes-Associated Protein.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval

This study did not involve human or animal subjects, and thus, no ethical approval was required. The authors confirm that this review was conducted in accordance with the principles of academic integrity and research ethics.

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Disclosure

The authors declare that they have no competing interests in this work.

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