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Safety of pharmacotherapy of osteoporosis in cardiology patients

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Abstract

The commonest medical conditions following menopause are osteoporosis and atherosclerotic disease. This review considers the safety of pharmacotherapy of osteoporosis in cardiology patients. Drugs used for osteoporosis treatment may have adverse effects on the cardiovascular system. This article has detailed analysed of current drug classes, such as the bisphosphonates and strontium ranelate, as well as reviewed of the controversy surrounding hormone replacement therapy (HRT) and the selective estrogen receptor modulators (SERMs). Additionally, we discuss the adverse effects on the heart of calcium and drugs influencing calcium metabolism such as vitamin D, parathormone and calcitonin. We look at the interference between osteoporosis treatment and the drugs used for atherosclerosis. Moreover, the side effects on bones of cardiology drugs are analysed. Lastly, the possible advantages of selected drugs used for cardiovascular diseases in terms of osteoporosis prevention are evaluated. (Cardiol J 2010; 17, 4: 335–343)

Key words: osteoporosis, cardiology, pharmacotherapy, complications

Introduction

Osteoporosis is a disease in which bones become fragile and more likely to break. If not prevented, or if left untreated, osteoporosis can progress painlessly until a bone breaks. These broken bones, also known as fractures, occur typically in the hip, spine, and wrist. Anyone can develop osteoporosis, but it is commonest in older women. Risk factors include: getting older, having osteopenia (low bone mass), being small and thin, having a family history of osteoporosis, being a white or Asian woman and taking certain medicines. Especially this last named concerns patients suffering from cardiac diseases. Drugs used for osteoporosis treatment may have adverse effects on the cardiovascular system. On the other hand, some cardiology drugs can provoke osteoporosis. Other cardiological treatment may prevent the loss of bone mass.

Cardiovascular side effects of drugs for osteoporosis

Bisphosphonate

An article and accompanying letter to the editor of *The New England Journal of Medicine* [1, 2] describe increased rates of serious atrial fibrillation (AF) (defined by the authors as life-threatening or resulting in hospitalization or disability) in two different studies of older women with osteoporosis treated with the bisphosphonates, zoledronic acid and alendronate. In both studies, more women who received one of the bisphosphonates (zoledronic acid: 1.3% or alendronate: 1.5%) reportedly developed serious AF as compared to women who received a placebo (zoledronic acid study: 0.5%, alendronate study: 1.0%). In both studies, the rates of all AF (serious plus non-serious) were not significantly different between groups treated with

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bisphosphonate versus placebo. These two research reports suggest a possible link between two bone-building drugs and irregular heart rhythms. The signs of a heart problem were more pronounced with zoledronic acid, a drug given as a once-a-year, 15-minute intravenous infusion. But there was a hint of similar trouble in a few women who took the leading osteoporosis pill with alendronate. There appeared to be a 50 per cent greater risk of serious heart rhythm in women who took the daily pill than among those who did not. About half of the 6,459 women took zoledronic acid, and 47 developed AF, compared with just 31 cases among the other women.

Black et al. [1] report a significant increase in the risk of serious AF adverse events (defined as events resulting in hospitalization or disability or judged to be life-threatening) associated with once--yearly infusions of intravenous zoledronic acid for the treatment of osteoporosis in post-menopausal women. However, there was no increased risk of all adverse events of AF with such infusions.

The Food and Drugs Administration (FDA), after reviewing data concerning treatment with bisphosphonates, announced in 2007 that there is potential increased risk for AF in patients with osteoporosis treated with these drugs [3]. That review involved the following bisphosphonates: alendronate, ibandronate, risedronate and zoledronic acid. In a report published in November 2008, an update to the previous communication, the FDA stated that across all studies, no clear association between overall bisphosphonate exposure and the rate of serious or nonserious AF was observed. Even increasing the dosage and duration of treatment was not associated with an increased rate of arrhythmia onset [4]. The FDA update concluded that, based on the information currently available, physicians should not alter their prescribing patterns for bisphosphonates and patients should not stop taking these drugs.

The bisphosphonates have also potentially protective effects on atherosclerosis. The study by Price et al. [5] in rats showed that the amino bisphosphonates alendronate and ibandronate inhibit warfarin-induced artery calcification, which is a sign of atherosclerosis.

Strontium ranelate

Strontium ranelate is composed of two atoms of stable strontium (an element with properties similar to calcium) and one molecule of ranelic acid. Strontium incorporates within bone mineral by substituting for calcium ions and has also been found to stimulate alkaline phosphatase activity, which differentiates it from other drugs used in the treatment of osteoporosis. It is thought to have a dual effect on bone metabolism, increasing bone formation and decreasing bone resorption [6]. It is licensed for the treatment of post-menopausal osteoporosis to reduce the risk of vertebral and hip fractures. Strontium ranelate is not recommended in patients with severe renal impairment and should be used with caution in patients at increased risk of venous thromboembolism (VTE) [6]. In phase III studies, the annual incidence of VTE observed over four years was approximately 0.7%, with a relative risk of 1.42 ($p = 0.036$) in strontium ranelate-treated patients, as compared to placebo-treated patients. The cause of these findings is unknown. The risk for strontium ranelate appears to be less than that seen with Selective Estrogen Receptor Modulator (SERM) and hormone replacement therapy (HRT) [7]. The study by Halil et al. [8] demonstrated that after 60 days of treatment with strontium ranelate, there was no statistically significant prolongation in PFA-100 in vitro bleeding time and no statistically significant change in the critical hemostatic parameters in patients receiving strontium ranelate that led to discontinuation of the treatment. None of the subjects developed clinical VTE during the two month period of strontium ranelate treatment.

Hormone replacement therapy

Estrogen depletion has one of the most profound effects on skeletal physiology in both humans and non-human primates. A potential role for estrogen in cardiovascular disease (CVD) protection has been long suggested by the observation that women have a reduced relative CVD risk as compared to men, but that this benefit is lost after menopause, when circulating estrogen levels decrease dramatically [9]. The mechanisms by which estrogen may protect against heart disease include endothelial-mediated vascular effects, non-endothelial vascular effects, favorable lipoprotein effects, possible favorable effects on glucose and insulin homeostasis, changes in extracellular matrix and plaque stabilization, and facilitation of collateral vessel formation [10].

Until recently, HRT has been the standard treatment for osteoporosis based on the fact that sex steroids play a critical role in bone homeostasis. Both estrogens and androgens suppress bone remodeling by decreasing the number of resorption/ /formation cycles [11].

Unfortunately, the estrogen/medroxyprogesterone arm of the Women's Health Initiative (WHI)

study was terminated prematurely because of an increased risk of CVD events [12]. Two secondary prevention trials of HRT and heart disease (in patients with evidence of already established atherosclerosis), the HERS (Heart and Estrogen/Progestin Replacement Study) [13] and ERA (Estrogen Replacement and Atherosclerosis) study [14], showed no reduction in heart disease or regression of atherosclerotic plaque in users of HRT or ERT. Currently, HRT cannot be advocated for treatment or prevention of coronary artery disease.

The relationship between HRT and stroke remains uncertain. HERS and WEST (Women's Estrogen for Stroke Trial) studies showed that HRT was not significantly related to transient strokes or ischemic attacks [13, 15]. The WHI trial reported an increased risk of stroke. An analysis of 18 observational studies going back to 1980 concluded that HRT has a neutral effect on stroke [16].

Oral HRT causes a small but significant increase in venous thrombosis and pulmonary embolism. HRT doubles the risk of venous thromboembolism (VTE), with the highest risk occurring in the first year of use [17]. Advancing age, obesity and an underlying thrombophilia such as Factor V Leiden significantly increase risk. In WHI, the number of cases of VTE in placebo users per 1,000 women per year at 50–59 years was 0.8, at 60–69 years 1.9, and at 70–79 years 2.7 [17]. Randomized trial data strongly suggests that women who have previously suffered a VTE have an increased risk of recurrence in the first year of HRT use [18]. Thus previous history of VTE contraindicates oral HRT. Transdermal HRT may be associated with a lower risk [17].

Selective estrogen receptor modulators

The biological actions of estrogen are largely mediated by two distinct estrogen receptor isoforms, namely ERalpha and ERbeta, that are widely distributed in tissues including the cardiovascular system. Selective estrogen receptor modulators (SERMs) are a group of agents being studied for their breast cancer risk reduction effects. SERMs are non-steroidal compounds that elicit estrogen agonist effects in some tissues, such as bone, and estrogen antagonist effects in others, such as breast, through specific, high-affinity binding to the estrogen receptor. SERMs act by interacting with ER, but differ from estrogens by eliciting agonist or antagonist effects depending on the target tissue [20]. Tissue-selective SERMs may be safer agents than endogenous estrogens for cardiovascular disease. The most representative compound of this class is raloxifene, approved for osteoporosis as well as breast cancer treatment.

Raloxifene, a benzothiophene SERM that is chemically distinct from estradiol, is approved for the treatment and prevention of osteoporosis in post-menopausal women [21]. The most serious adverse effect associated with raloxifene is the approximately tripled risk of VTE [6]. Raloxifene is associated with an increased risk of venous thromboembolic events, particularly during the first four months of treatment, which is similar to the reported risk associated with hormone replacement therapy. The impact of raloxifene on cardiovascular disease is unclear, although there is evidence that it lowers fibrinogen and both total and low-density lipoprotein (LDL) cholesterol levels without increasing high-density lipoprotein (HDL) cholesterol [6]. Raloxifene mediates acute ER- and endothelium-dependent vasorelaxation in rabbit coronary arteries due to stimulation of eNOS expression [22]. Similar to estrogen, raloxifene has antiproliferative properties in vascular smooth muscle cells [23]. The MORE trial was an osteoporosis treatment trial conducted in post-menopausal women, with breast cancer risk reduction as a secondary objective [24]. Raloxifene is currently being studied for breast cancer risk reduction effects in the Continuing Outcomes Relevant to Evista® (CORE), Raloxifene Use for The Heart (RUTH), and Study of Tamoxifen and Raloxifene (STAR) clinical trials. The RUTH participants were selected based on the presence of documented coronary heart disease (50%) or multiple risk factors increasing their risk for a coronary heart disease event (50%) [25]. After an average of five years, the RUTH study showed that deaths and major heart problems were about the same in both the group receiving raloxifene and the one taking a placebo. Raloxifene users experienced one-third fewer cases of breast cancer and about half the number of invasive breast cancers [26]. Raloxifene is contraindicated in people with a history of venous thromboembolism (VTE), hepatic impairment, cholestasis, severe renal impairment, undiagnosed uterine bleeding, and endometrial cancer [6].

Besides raloxifene, there are several other SERMs such as: tamoxifene, toremifene, and fulvestrant; all are approved for breast cancer, and clomiphene is used for ovulatory dysfunction. Toremifene is potentially dangerous for cardiac patients. Toremifene is associated with a dose-dependent increase in QT interval, which carries a risk of serious cardiac arrhythmia [27]. Therefore EMEA [28] stated that toremifene must not be used

in patients with QT prolongation and also heart failure or a history of symptomatic arrhythmias. An additive effect on QT interval prolongation between toremifene and antiarrhythmic drugs class IA (quinidine, hydroquinidine, disopyramide) and class III (amiodarone, dronedarone, sotalol, dofetilide, ibutilide) cannot be excluded. Therefore co-administration of toremifene and the mentioned medications is contraindicated. There is some data indicating that another drug from the SERMs group, tamoxifene, is an agent that prolongs the QT interval and/or in some reports has been associated with torsades de pointes, but at this time there is a lack of substantial evidence for causing torsades de pointes [29].

Calcium and vitamin D supplements are generally used as an adjunct to other treatments in the management of patients with osteoporosis, based on the fact that virtually all large scale randomized controlled trials of anti-osteoporotic therapies have included calcium and vitamin D supplements as part of the treatment regimen. Calcium and vitamin D supplements do not appear to be effective in preventing fractures when used alone, except in patients at high risk of calcium and vitamin D deficiency such as the housebound elderly, or institutionalized individuals [30].

Side effects from a reasonable dose of calcium (1,000 mg/day) are very low and usually don't affect the cardiovascular system. Increased dietary calcium intake may slightly decrease blood pressure [31].

Taking calcium with a β-blocker (such as atenolol) may interfere with blood levels of both the calcium and the β-blocker [32]. Study results are conflicting, however. Similarly, it has been reported that calcium may reverse the therapeutic effects as well as the side effects of calcium channel blockers (such as verapamil) often prescribed for the treatment of high blood pressure [33]. These study results are also controversial. People taking verapamil or another calcium channel blocker along with calcium supplements should probably have their blood pressure checked regularly. A class of medications known as bile acid sequestrants (including cholestyramine, colestipol, and colesevelam), used to treat high cholesterol, may interfere with normal calcium absorption and increase the loss of calcium in the urine [34]. Supplementation, therefore, with calcium and vitamin D may be recommended by healthcare provider. High levels of calcium may increase the likelihood of a toxic reaction to digoxin, a medication used to treat irregular heart rhythms [35]. On the other hand, low levels of calcium cause this medication to be ineffective. People who are taking digoxin should have blood calcium levels monitored closely. Two different classes of diuretics interact with calcium in opposite ways: thiazide diuretics such as hydrochlorothiazide can raise calcium levels in the blood, while loop diuretics, such as furosemide and bumetanide, can decrease calcium levels [36].

Vitamin D promotes the absorption of calcium and phosphorus. It regulates how much calcium remains in blood and how much is deposited in bones and teeth. This high prevalence of hypovitaminosis D might contribute to osteoporosis. Insufficient vitamin D levels have been linked to heart failure [37]. Studies have already shown that vitamin D can lower inflammation by increasing levels of anti-inflammatory messengers like the cytokine named IL-10 (interleukin-10) [38]. A 2006 analysis of vitamin D metabolism suggested that vitamin D may be directly involved in cholesterol reduction [39]. Adequate vitamin D levels may be important for decreasing the risk of high blood pressure [40]. But lastly, a completed study by Hsia et al. [41] has shown that calcium/vitamin D supplementation neither increased nor decreased coronary or cerebrovascular risk in generally healthy post-menopausal women over a seven-year use period. Excess vitamin D, on the other hand, can accelerate bone resorption and also some cardiac side effects. The symptoms of vitamin D toxicity are a result of hypercalcemia (an elevated level of calcium in the blood) caused by increased intestinal calcium absorption. In humans, manifestations of vitamin D toxicity include hypercalcemia, hypercalciuria, nausea, anorexia, lethargy, mental disturbances, ectopic soft tissue calcification, including vascular calcification and nephrocalcinosis, and renal failure. The induction of hypercalcemia by toxic levels of vitamin D may precipitate cardiac arrhythmia in patients on digitalis [42]. Rajasree et al. [43] showed elevated risk of ischemic heart disease when 25hydroxyvitamin D_3 ($25D_3$) was above 89 ng/mL. In an animal study [44], the amino bisphosphonate ibandronate prevents vitamin D toxicity and inhibits vitamin D-induced calcification of arteries, cartilage, lungs and kidneys. The following medications, used by cardiology patients, should not be taken at the same time as vitamin D because they can decrease the intestinal absorption of vitamin D: cholestyramine, colestipol, orlistat, mineral oil, and the fat substitute Olestra.

Parathormone (PTH). Parathyroid hormone is the most important endocrine regulator of calcium and phosphorus concentration in extracellular fluid. This hormone is secreted from cells of the parathyroid glands and finds its major target cells in

bone and kidney. Another hormone, parathyroid hormone-related protein, binds to the same receptor as parathyroid hormone and has major effects on development. The influence of parathyroid hormone on the cardiovascular system is unclear. Data collected on uremic rats indicates that heart cell is a target organ for PTH and may have receptors for the hormone; PTH increases beating rate of heart cells and causes early death of cells; PTH effect appears to be due to calcium entry into heart cells; the locus of action through which PTH induces calcium entry is different from that for catecholamines; and uremic serum has no effect unless it contains PTH. Data suggests that myocardial damage may occur in uremia due to prolonged exposure to very high blood levels of PTH, and assign new dimensions to PTH toxicity in uremia [45]. A study by Ogino et al. [46] suggests that the physiologically important functions of parathyroid hormone-related protein are chronothropy and vascular dilatation rather than inotropy.

Teriparatide is a recombinant form of parathyroid hormone, used in the treatment of advanced osteoporosis. Teriparatide can possibly influence the heart by changing calcium metabolism and in that way interfere with cardiac drugs. The study by Benson et al. [47] showed that teriparatide, 20 mg subcutaneously, does not alter the cardiac effect of digitalis. The assessment of effects of an acute dose of teriparatide on blood pressure and heart rate (pulse rate) showed that teriparatide was safe and well tolerated in subjects with mild or moderate heart failure. The drug was not associated with changes in supine or standing hemodynamic parameters, QT or other ECG abnormalities. In an open-label, non-randomized study performed in 14 women with hypertension, teriparatide 40 μg was administered alone and in combination with atenolol or with a long-acting calcium channel antagonist. Results showed an increase in peak pulse rate and decrease in nadir blood pressure. Neither calcium channel antagonists nor atenolol potentiate the blood response associated with teriparatide. In a single blind, randomized, two-period crossover study, the effects of a 20 μg subcutaneous dose of teriparatide on cardiac conduction and re-polarization were evaluated. Results showed that teriparatide was associated with a small but statistically significant decrease in average standing SBP compared to placebo, a slight increase in average pulse rate, relative to placebo, but approximately three and two beats per minute in the standing and supine positions, respectively and small, statistically significant decreases in RR and QT intervals, but no changes in PR and QRS.

A global analysis of ECG data obtained from five clinical studies of 118 subjects has been performed. The results did not show apparent adverse effects on ECG intervals with single subcutaneous doses of teriparatide in amounts of 20, 40 and 80 μg. No effect on the PR and QRS intervals was observed; however, dose-related shortenings in the RR, QT and QTc intervals were observed. A modest and not significant increase in heart rate was also observed [48].

Calcitonin is an osteoclast inhibitor which is effective in preventing post-menopausal bone loss and the secondary prevention of vertebral fractures in post-menopausal osteoporosis. Synthetic salmon calcitonin has the same effects as the natural human hormone and is used to prevent bone breakdown. There is no evidence that calcitonin causes severe side effects on the cardiovascular system. Very rare reactions such as elevation of blood pressure or tachycardia, hypotonia and collapse have been observed due to anaphylactic-type reactions [49].

The influence of cardiologic pharmacotherapy on osteoporosis

Heparin

Osteoporosis is a well-recognized complication of long-term heparin therapy [50, 51]. About one third of patients have subclinical reductions in bone density, but only 2% to 3% of those receiving protracted heparin therapy develop symptomatic fractures [52, 53].

In heparin-treated rats, histomorphometric analysis of the distal third of femurs demonstrated a significant loss of cancellous bone accompanied by increased numbers of osteoclasts, and decreased numbers of osteoblasts, lining the trabecular bone surface. Biochemical markers of bone turnover supported these findings. This suggests that heparin causes bone loss not only by increasing osteoclastic bone resorption, but also by decreasing osteoblastic bone formation [54, 55]. Treatment was associated with a 45% decrease in the number of osteoblasts and an 81% decrease in the amount of unmineralized collagen (osteoid) lining the cancellous bone surface. Furthermore, heparin increased osteoclast surface by 58%, indicating that heparin causes bone loss both by decreasing the rate of bone formation and by increasing bone resorption [54].

A study performed in rats by Shaughnessy et al. [56] suggests that heparin-induced osteoporosis is not rapidly reversible because heparin is seques-

tered in bone for an extended period. Heparin causes cancellous bone loss by influencing bone remodeling rather than growth. Similarly in humans, heparin-induced reduction in bone density is not rapidly reversible. In 61 pre-menopausal women treated with long-term heparin therapy, compared to age-matched controls, there were no significant differences in mean radial and spinal bone densities, but a significantly greater proportion of women who had received heparin two years previously had bone densities below a predefined minimal level [57]. Sequestration of heparin in bone provides a plausible explanation for these results.

The site of heparin sequestration in bone is unknown. Heparin has been reported to bind to endothelial cells and macrophages, as well as to a variety of plasma proteins. The sequestration of heparin within the bone microenvironment may explain the lack of recovery of bone loss over the 28-day study period after heparin therapy was stopped [56]. Such binding can also explain heparin's poor bioavailability at low doses and the variable anticoagulant response that it produces when used therapeutically [58].

Low molecular weight heparin

Low molecular weight heparin (LMWH) may carry a lower risk of osteoporosis than unfractionated heparin (UFH). Dalteparin, 5,000 anti-Xa U sc, was compared with UFH, 10,000 U sc bid, for three to six months in 80 patients with deep vein thrombosis. Six of the 40 patients who received UFH developed spinal fractures, compared to one patient receiving dalteparin [59]. Some data indicates a dose-dependent decrease in cancellous bone volume. In rats treated with UFH or the LMWH tinzaparin (0.5 to 1.0 μg) for 32 days, UFH caused significantly greater cancellous bone loss than LMWH [55]. Although UFH and LMWH decreased osteoblast and osteoid surface similarly, only UFH increased osteoclast surface. Both UFH and LMWH reduced serum alkaline phosphatase, consistent with reduced bone formation, while there is a transient increase in urinary type 1 collagen cross-linked pyridinoline, consistent with an increase in bone resorption. Whereas UFH decreases cancellous bone volume both by decreasing the rate of bone formation and increasing the rate of bone resorption, LMWH causes less osteopenia, decreasing only the rate of bone formation [8]. Unlike heparin, only > 50-fold higher concentrations of the LMWH preparations enoxaparin, dalteparin, tinzaparin, and ardeparin than used clinically were needed to stimulate bone resorption at concentrations usually used for prophylaxis and treatment of the thromboembolism [60]. Another LMWH, fondaparinux, does not appear to have a negative effect on bone metabolism. Therefore, fondaparinux may be a safe and effective alternative to UFH and LMWH in women who require anticoagulation during pregnancy [61].

Warfarin

Vitamin K is an essential factor for the synthesis of plasma-clotting proteins. Because γ-carboxylation of specific glutamic acid residues is also required for activation of osteocalcin and other bone matrix proteins [62], vitamin K antagonists might increase the risk of osteoporotic fractures. There are two mechanisms by which warfarin use could predispose to osteoporotic fractures: directly, by γ-carboxylation in osteocalcin and other bone matrix proteins; and indirectly, because patients taking warfarin may limit their dietary intake of foods rich in vitamin K. In utero, vitamin K antagonists interfere with bone formation. During the first trimester, exposure to warfarin causes embryopathy that includes nasal hypoplasia and epiphyses stippling [63]. Children who receive long-term vitamin K antagonist therapy have reduced bone density [64]. A low vitamin K concentration is associated with reduced bone mineral density (BMD) [65]. Clinical trials support the role of vitamin K in maintaining bone health. In randomized, controlled trials of osteoporotic women, participants randomized to receive vitamin K_2 (menatetrenone, 45 mg/day) had slower loss of bone mineral density and a reduced risk of subsequent osteoporotic fractures than control women [66, 67].

Warfarin is the vitamin K antagonist, prescribed to millions of people worldwide to decrease their risk of clotting. In a retrospective study of 14,564 patients with AF, long-term use of warfarin was associated with a 25% increased risk of osteoporotic fracture [68]. In contrast, use of warfarin for less than one year had no significant association with osteoporotic fracture. Among those with long-term use, warfarin was most strongly associated with vertebral fractures. Carabello et al. [69] has found that long-term exposure to oral anticoagulation is associated with an increased risk of vertebral and rib fractures.

Clinicians should carefully assess anticoagulated patients for osteoporosis risk, monitor BMD, and refer them to dietitians for dietary and supplement advice on bone health. Epidemiological studies and clinical trials consistently indicate that vitamin K has a positive effect on bone mineral

density and decreases fracture risk. Typical dietary intakes of vitamin K are below the levels associated with better BMD and reduced fracture risk; thus issues of increasing dietary intakes, supplementation, and/or fortification arise. Anticoagulants that do not affect vitamin K metabolism are now available and make clinical trials feasible to address the question of whether coumarins adversely affect bone [70].

Acenocumarol

The study by Wawrzyńska et al. [71] has shown a distinct and progressive decrease in BMD in patients on prolonged anticoagulation with the Vitamin K antagonist acenocumarol. They also compared oral anticoagulants to LMWH and found that BMD is more evident in patients on LMWH therapy.

When prescribing Vitamin K antagonists, especially to elderly patients at high risk of falling, physicians should instruct them to have adequate intake of calcium and vitamin D, exercise regularly, wear stable shoes, use walking aids, and discontinue unnecessary medications.

Beta-blockers

Beta-adrenergic antagonists have a protective effect on bone density and risk of fracture. Gage et al. [68] found that patients prescribed β-adrenergic antagonists had a 16% reduction in subsequent osteoporotic fracture. The association between hyperthyroidism and osteoporotic fractures suggests that part of the possible benefit of β-adrenergic antagonists could be mediated via the known inhibition of thyroxine [72].

Thiazide diuretics

Thiazide diuretics are often used to treat high blood pressure, but they may also protect against age-related bone loss by reducing the amount of calcium expelled in urine. A study performed by Schoofs et al. [73] has shown that people aged over 55 who took thiazide diuretics for a year or more had about a 50% lower risk of suffering a potentially debilitating hip fracture than those who never took diuretics. This protective effect disappears within four months after use is discontinued.

Calcium channel blockers

Calcium channel blockers are an important group of vasodilators in the treatment of hypertension and coronary artery disease. There is no evidence that calcium channel blockers cause osteoporosis. It affects the calcium channels in the muscles not the levels of calcium in blood.

Statins

Low bone mineral density has also been associated with vascular diseases or atherosclerosis. Observational studies found that the risk of fractures was approximately half as high in people taking statins as in nonusers [74]. At the same time, people taking non-statin lipid-lowering drugs had approximately the same risk as nonusers. On the other hand, LaCroix et al. [75], analyzing data from more than 90,000 post-menopausal women, found no link between statin use and risk of hip fractures. However, few women in this study had used statins for more than three years. Therefore, the findings do not rule out the possibility that long-term statin use might reduce fracture risk.

Statins appear to enhance osteoblastic activity by both increasing expression of bone morphogenetic protein-2, a stimulator of osteoblast differentiation, and diminishing osteoclast activity by preventing prenylation and activation of key intracellular proteins [76]. The mechanism of this effect is unclear because it is impossible to separate antiresorptive and anabolic effects *in vitro*.

Currently available statins, which are designed for lipid-lowering, may be suboptimal for treating osteoporosis; however, insights from studies may lead to development of similar molecules that more effectively promote bone formation and inhibit resorption [76].

Closing remarks

Most drugs used for the treatment of osteoporosis are safe for cardiology patients. Bisphosphonates can rarely provoke events of AF. Strontium ranelate is not recommended in patients with severe renal impairment and should be used with caution in patients at increased risk of VTEs.

Hormone replacement therapy has not been proven to be beneficial in primary and secondary prevention of coronary heart disease; in fact, it may result in a slightly increased rate of CHD. HRT should not be initiated for women with existing heart disease. HRT increases in thromboembolic events mainly in the first year of use. The relationship between HRT and stroke remains uncertain. HRT initiation and continuation should be based on: established non-coronary benefits and risks, possible coronary benefits and risks, patient preference.

Treatment with raloxifene was associated with: increased risk of VTEs, no effect on all-cause mortality, no effect on all strokes, increased risk of death due to stroke. The risk-benefit balance should be considered in women at risk for stroke. Based on the RUTH trial, raloxifene should not be used

for the primary or secondary prevention of cardiovascular disease.

Vitamine D, parathormone and calcitonin influence calcium metabolism, and thus may lead to cardiac rhythm disturbances as well as interfere with some cardiological drugs.

Cardiology drugs such as statins, β-adrenergic antagonists and thiazides may provide an added benefit to the treatment of osteoporosis, a common disorder, implying a significant public health benefit, while significantly reducing cardiovascular events.

Unfortunately, long-term heparin therapy can cause osteoporosis. LMWHs may carry a lower risk of osteoporosis than UFH. Osteoporosis is a well-recognized complication of treatment with the vitamin K antagonist such as warfarin and acenocumarol. Clinicians should carefully assess anticoagulated patients for osteoporosis risk, refer them to dietitians for dietary and supplement advice on bone health, and instruct them to discontinue unnecessary medications.

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