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REVIEW ARTICLE

Assessment of Cardiovascular Safety of Anti-Osteoporosis Drugs

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Abstract

The incidence of osteoporosis and cardiovascular disease increases with age, and there are potentially shared mechanistic associations between the two conditions. It is therefore highly relevant to understand the cardiovascular implications of osteoporosis medications. These are presented in this narrative review. Calcium supplementation could theoretically cause atheroma formation via calcium deposition, and in one study was found to be associated with myocardial infarction, but this has not been replicated. Vitamin D supplementation has been extensively investigated for cardiac benefit, but no consistent effect has been found. Despite findings in the early 21st century that menopausal hormone therapy was associated with coronary artery disease and venous thromboembolism (VTE), this therapy is now thought to be potentially safe (from a cardiac perspective) if started within the first 10 years of the menopause. Selective estrogen receptor modulators (SERMs) are associated with increased risk of VTE and may be related to fatal strokes (a subset of total strokes). Bisphosphonates could theoretically provide protection against atheroma. However, data from randomised trials and observational studies have neither robustly supported this nor consistently demonstrated the potential association with atrial fibrillation. Denosumab does not appear to be associated with cardiovascular disease and, although parathyroid hormone analogues are associated with palpitations and dizziness, no association with a defined cardiovascular pathology has been demonstrated. Finally, romosozumab has been shown to have a possible cardiovascular signal, and therefore post-market surveillance of this therapy will be vital.

Key Points

Osteoporosis and cardiovascular disease are the potential consequences of shared mechanisms.

Anti-osteoporosis medications are associated with potential increases in cardiac risk (romosozumab, calcium supplementation, menopausal hormonal therapy), no effect on cardiac risk (vitamin D) or reduced cardiac risk (bisphosphonates).

Selective estrogen receptor modulators, such as raloxifene, and menopausal hormonal therapy are associated with increased risk of venous thromboembolic disease.

Romosozumab therapy is contra-indicated in those with a history of myocardial infarction or ischaemic stroke.

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1 Introduction

Osteoporosis is characterised by a reduction in bone mineral density and an increased risk of fractures. As with cardiovascular disease, the prevalence increases in older age so that osteoporosis and cardiovascular disease (and cardiovascular risk factors) often coexist in the same patient. Given the age group of patients with osteoporosis [1], the occurrence of cardiovascular morbidity is a significant consideration. Any interventions associated with an increased cardiovascular risk should be identified and clear guidance provided on their prescription to maximise the benefit–risk of any potential therapy. We are therefore left with a central question, namely, "To what extent are the available drug therapies for osteoporosis associated with cardiovascular adverse events?" In order to answer this question, an expert working group was convened by the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Disorders (ESCEO) and by the International Osteoporosis Foundation (IOF). The available evidence was reviewed

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on calcium supplements, vitamin D replacement, menopausal hormone therapy (MHT), selective estrogen receptor modulators (SERMs), bisphosphonates, denosumab, parathyroid hormone (PTH) analogues and romosozumab.

2 Calcium Supplementation

Inadequate calcium consumption is associated with an increased risk of fragility fracture and deterioration in bone mineral density [2]. Therefore calcium supplements can be beneficial for bone health. However, high consumption of calcium could theoretically lead to arterial and soft tissue calcification, the development of atherosclerotic plaques and cardiovascular morbidity. Although considerable current research has suggested a relationship between pharmacological calcium supplementation and the risk of heart disease, critical evaluation of this literature suggests that the observed associations may not be of clinical relevance.

Safety events can be mislabelled. This was the case in a 2006 randomised, placebo-controlled trial of calcium supplementation in osteoporosis, in which the incidence of ischaemic heart disease (IHD) in the calcium supplementation group was not significantly different to that in the placebo group (7.7% vs 7.0%, hazard ratio [HR] 1.12, 95% confidence interval [CI] 0.77–1.64). This was despite the fact that gastrointestinal adverse events were misclassified as IHD, which would potentially lead to exaggeration of the effect of calcium supplementation on cardiovascular health [3]. However, randomised placebo-controlled trials have often been powered to address the primary outcome (change in bone density or fracture), rather than cardiovascular safety. This focus serves to limit the assessment of safety-associated endpoints.

In order to address this issue, Bolland et al. performed the Auckland Calcium Trial, which compared calcium (1 g of elemental calcium as citrate salt daily) versus placebo in 730 women over 60 months and focused on cardiovascular health as the primary outcome [4]. The results showed that there was an increased risk of myocardial infarction (MI) in the calcium group (risk ratio [RR] 2.24, 95% CI 1.20–4.17).

This was very much the 'index finding' in the investigation of calcium supplementation and cardiac risk, but there are several important issues to note. Firstly, the baseline cardiovascular status of the calcium and placebo groups was different, with the calcium group having a greater burden of cardiovascular disease than the placebo group. Secondly, there was a trend towards a reduced risk of angina in the calcium group (RR 0.71, 95% CI 0.50–1.01), which is puzzling, considering that both MI and angina can (in the case of unstable angina) sit under the bracket of 'acute coronary syndromes'. Thirdly, in this study, cardiovascular events were self-reported and then adjudicated via health records, which could introduce reporting bias. The adjudication reduced the effect size of the risk of MI, with the lower band of the 95% CI dropping to 1.01, bordering significance. These issues, together with the evidence from the Women's Health Initiative (WHI) trial of calcium and vitamin D, which found no adverse effect signal (MI/coronary death HR 1.04, 95% CI 0.92–1.18; stroke HR 0.95, 95% CI 0.82–1.10) [5], made it difficult to interpret the cardiovascular effect of calcium supplementation, and warranted further examination through data assimilation.

Fifteen calcium trials were meta-analysed, and a significantly increased risk of MI was observed (HR 1.27, 95% CI 1.01–1.59), although there was no excess risk of stroke, death or the composite endpoint in the trial-level data [6]. However, in individual patient-level analyses, there was an interaction between treatment and dietary calcium intake when the outcome of interest was MI. This interaction was observed in the patients with a spontaneous calcium intake above, but not below, the median. Thus, clarity was sought through further interrogation of the WHI calcium trial dataset in a meta-analysis together with seven other studies [7] to distil out the effect of personal supplementation alongside calcium supplementation. In those patients who were not taking over-the-counter calcium or vitamin D supplements, there was a 13% increase in the risk of cardiovascular events in those in the calcium arm (HRs from 1.13 to 1.22, p values ranging from 0.04 to 0.05) [7]. However, those who were taking over-the-counter supplements at the time of the study were at no increased risk of cardiovascular events. Calcium or calcium and vitamin D increased the risk of MI (HR 1.24, 95% CI 1.07–1.45) and the composite of MI or stroke (HR 1.15, 95% CI 1.03–1.27). The authors concluded that there was an increased risk of MI and stroke due to calcium supplementation and that this had been "obscured" in the previous WHI study by the use of personal calcium and vitamin D supplements. There are a few caveats to this assertion [8]. Firstly, if Bonferroni correction had been performed, the association with MI and stroke would be non-significant. Secondly, there was no evidence of a dose effect if supplementation was assessed in fifths of supplement intake. Thirdly, this was not a true time-to-event analysis, with more than one event allowed to count in one patient. Fourthly, the safety data were recorded in a heterogeneous fashion depending on the study and, as has been said previously, were not primary endpoints of the trials. These caveats are significant and numerous enough to call into question the findings of the above analysis, and these findings are contradicted by re-analyses and further follow-up of the WHI dataset, the results of more recent meta-analyses and by large observational studies.

Indeed a study by Prentice et al. re-examined the effect of calcium and vitamin D supplementation in the WHI clinical trial and observational study, with a specific focus on fractures, cardiovascular disease, cancer and all-cause mortality [9] and the duration of therapy. They found no associations with risks of cardiovascular disease, including MI, coronary heart disease, total heart disease or stroke. In support of this finding, at 5 years of follow-up, no significant associations were observed with any cardiovascular disease outcomes (Fig. 1) [10].

Due to the emergence of new data since the meta-analysis by Bolland et al. [6], an updated meta-analysis was performed in 2015 by Lewis et al. [11] particularly examining randomised controlled trial data comparing calcium (and vitamin D) supplements to non-treatment or placebo controls and limiting their analyses to females alone. They included 18 studies, with a total of 63,563 participants with 3390 coronary heart disease events and 4157 deaths, and found no associations between primary outcomes (coronary heart disease and mortality) or secondary outcomes (acute MI, angina and chronic coronary heart disease).

Further observational studies have found no increased cardiovascular risk with calcium supplementation. A study using the UK Biobank (a cohort of 500,000 men and women in the UK, aged 40–69 years at baseline) showed incident cardiovascular disease in the 10.6% of women and 2.6% of men who took calcium supplements [12]. Subsets of patients on calcium supplements alone were compared to those on calcium and vitamin D, and no effect was observed in the incidence of MI, IHD or any cardiovascular outcomes over the 5–10 years of follow-up. Within such observational studies, there are potential epidemiological issues, including confounding by indication, time-varying confounding, depletion of susceptible subjects and over-the-counter use of calcium and vitamin D, which is common in the UK. One explanation for the apparent confusion in this area may be in the definition of cardiovascular events. However, even a large study including coronary artery computed tomography (CT) scans and a mean of 7 years of supplements in ~ 750 women (aged 50–59 at baseline) demonstrated no association [13].

The most recent meta-analysis at the time of writing was performed in 2019 by Yang et al. Their meta-analysis of 42 studies (26 prospective cohort studies and 16 randomised controlled trials) of calcium intake, in which cardiovascular disease outcomes were recorded, showed that dietary calcium intake of up to 1500 mg/day had no significant effect on the risk of cardiovascular disease as a whole or on stroke in isolation [14]. However, there was an 8% increased risk when MI was examined alone (RR 1.08, 95% CI 1.02–1.15). It should be noted that none of the contributing relative risks on a study level were significant and the majority of studies were observational, representing a lower quality of evidence.

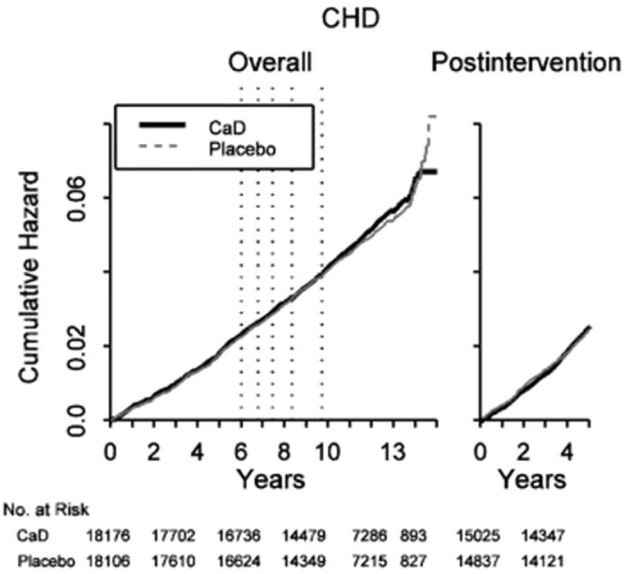

Fig. 1 Results taken from the Women's Health Initiative (WHI) trial of calcium and vitamin D (CaD) showing the cumulative hazard of coronary heart disease (CHD) against time. Intervention (left) and post-intervention (right) follow-up are depicted. There was no significant difference in the rates of CHD between the CaD and placebo arms [10]

There appears to be no convincing signal for cardiovascular disease due to calcium [9, 10], even when taken without concurrent vitamin D supplementation. Moreover, although the theory of increased calcium deposition within blood vessels exists, there are no data available that provide chemical evidence of this effect [8, 15]. Indeed, calcium intake, whether from supplementation or directly from diet, reduces blood pressure [16], improves lipid profile [17] and leads to transient increases in extracellular and serum calcium and thence a short-lived decrease in PTH [18], none of which are overtly deleterious to the cardiovascular system. Indeed the blood pressure and lipid effects may well be beneficial.

To conclude, calcium supplements and oral calcium intake of 1000 mg daily appear to reduce fracture risk, particularly in institutionalised compared to community-dwelling individuals, but there is no evidence for cardiovascular adverse events [9]. There is uncertainty regarding the cardiovascular risk of a high daily intake of calcium (in excess of 1200–1500 mg daily). However, given that higher intakes do not have a proven skeletal benefit, excessive calcium intake should be avoided in any case.

3 Vitamin D

Cholecalciferol (D_3) (referred to here as vitamin D unless otherwise stated) has a plethora of functions, with vitamin D receptors found in nearly all the tissues of the human body.

In the cardiovascular system, vitamin D has effects on the vascular wall, renin-angiotensin system and cardiac muscle.

In the context of osteoporosis, current guidance recommends vitamin D replacement of 800 international units (IU) daily in postmenopausal women at an increased risk of fragility fracture, those at an increased risk of vitamin D deficiency and those symptomatic of low vitamin D [19].

There are safety issues associated with both an excess and a deficiency of vitamin D. Overloading with unusually high doses of vitamin D can precipitate hypercalcaemia and hypercalciuria. High extracellular calcium concentration in the context of primary hyperparathyroidism or vitamin D overdose-dependent prolonged hypercalcaemia, vitamin D toxicity or any other cause of prolonged hypercalcaemia is associated with arrhythmias (including ventricular premature beats, PR interval prolongation, shortening of the QT and broadening of the QRS complex) and calcification (of the arterial wall and soft tissues, including the myocardium) [20, 21]. There are observational data from Scandinavian registries [22], supported by murine studies [23], that suggest a reverse J-shaped association between cardiovascular risk and serum 25-hydroxy vitamin D levels, with increased cardiovascular risk with lower (12.5 nmol/L) and higher (125 nmol/L) extremes.

However, a 3-year randomised controlled trial of high-dose vitamin D (up to 10,000 IU per day over 3 years) demonstrated no difference in tibial arterial calcification [24]. On the other hand, a meta-analysis of observational data has shown that if a patient is vitamin D deficient, insufficient or inadequate there is an increased risk of cardiovascular adverse events [25]. Whether this is a causal association remains in question, as the same finding has not been borne out in Mendelian randomisation [25]. A participant-level meta-analysis of vitamin D intervention studies for cardio-metabolic outcomes found no effect of vitamin D on systolic blood pressure or glycated haemoglobin (HbA1c), although there was a reduction in low-density lipoprotein cholesterol of −0.10 mmol/L (95% CI −0.20 to −0.00), −0.10 mmol/L (95% CI −0.18 to −0.02) and −0.07 mmol/L (95% CI −0.14 to −0.00) for subgroups with < 75, < 100 and < 125 mmol serum levels of vitamin D, respectively [26].

Data from the UK Biobank suggest that there is no association between calcium and vitamin D supplementation and incident ischaemic cardiovascular events or death [12].

The Vitamin D and Omega-3 Trial (VITAL) randomised over 25,000 individuals (mean age 67 years, 50.6% women) who received either 2000 IU per day of vitamin D or placebo (and either omega-3 supplementation or placebo). Participants were followed up for a median of 5.3 years. Investigators found that there was no association between cardiovascular disease and vitamin D supplementation [27].

However, vitamin D supplementation does not appear to prevent cardiovascular disease. The Vitamin D Assessment (ViDA) study in New Zealand included about 5000 participants (aged 65.9 years, 41.9% women) who were randomised to vitamin D_3, 100,000 IU per month (including a 200,000 IU loading dose at baseline) and followed up for 3.3 years. Vitamin D did not protect against cardiovascular disease [28], but vitamin D supplementation improved arterial function in those with vitamin D deficiency.

The most recent meta-analysis investigating the effect of vitamin D supplementation on cardiovascular disease included 21 randomised controlled trials (including VIDA and VITAL), with more than 83,000 individuals, and, once again, found that vitamin D supplementation did not confer cardiovascular protection [29]. It should be noted that many of these individuals were healthy and not osteoporotic.

In conclusion, at the usual dosages of vitamin D (800 IU daily) used to prevent vitamin D deficiency in patients with osteoporosis [30], there is no evidence for increased cardiovascular events. Findings of a protective effect are largely from observational datasets, and these have not been borne out in randomised controlled trials with cardiovascular disease as the primary or co-primary outcome or in Mendelian randomisation studies. The association between low vitamin D and cardiovascular disease may therefore be an epiphenomenon or potentially be due to differences in reference ranges [31].

4 Menopausal Hormonal Therapy

Current evidence suggests that MHT is an effective therapy for fracture prevention in the early menopause, with reductions in hip and vertebral fractures [32].

The postmenopausal state is inherently associated with a greater risk of cardiovascular disease than the pre-menopausal state. This was observed in women aged 40–50 years at the advent of the Framingham cohort with a higher incidence of coronary heart disease and cardiovascular events [33–35].

It is important to understand the history and chronology of the investigation of cardiovascular disease and MHT, which can be divided into four phases.

The first phase (pre-2002) was characterised by the supposition that the benefits of MHT outweighed the risks, and it was widely used for prevention and treatment of menopausal symptoms. It was therefore one of the most prescribed medications at the time, peaking in 2001, with 40% of postmenopausal women using MHT [36, 37]. Observational studies of the time suggested a potential benefit to cardiac health (with up to a 50% reduction in coronary heart disease). However, more recently, these studies have been heavily criticised due to methodological flaws [38].

The second phase was marked in 2002 by the publication of data from the WHI. This study included postmenopausal

females aged 50–79 who had taken MHT for a mean of 5.2 years. Those women with an intact uterus ($n = 16,608$) were randomised to placebo or combination MHT (conjugated equine estrogens [CEE] and medroxy-progesterone acetate [MPA]) due to the risks of endometrial cancer associated with unopposed estrogen use. Those in the combination MHT arm had an increased risk of coronary heart disease (HR 1.29, 95% CI 1.02–1.63), stroke (HR 1.41, 95% CI 1.07–1.85) and pulmonary embolism (HR 2.13, 95% CI 1.39–3.25) [39]. Those who had undergone hysterectomy ($n = 10,739$) were randomised to placebo or CEE alone. In the CEE-only arm, an increased risk of stroke only was observed (HR 1.39, 95% CI 1.10–1.77) [39]. This signal of increased cardiovascular and thromboembolic risk with combination MHT and increased risk of stroke with both combination and CEE-only MHT prompted a statement that MHT led to an increased risk of cardiovascular disease "irrespective of age, ethnicity or health" and was followed by a wave of research into the safety of MHT. The usage of MHT was significantly affected, with reduced use of oral formulations [40] and an increase in transdermal MHT [41]. Nevertheless, it should be acknowledged that the previous observational studies were in younger participants, who largely had menopausal symptoms, which the majority in the WHI study did not, and the age of the WHI participants was older than the mean age of menopause in Europe or North America, 51 years [37].

It is therefore appropriate that the third phase of MHT investigation was marked by analysis of the age-stratified data (into age ranges of 50–59, 60–69 and 70–79 years) from the WHI study [41], which led to some interesting and practice-influencing findings. In the original WHI study, 16,608 participants received combined MHT. Women in their 70s had an increased absolute risk of coronary heart disease, venous thromboembolism (VTE) and stroke compared to women in their 50s [42–44]. Women in their 60s had an increased risk of VTE and stroke (though not coronary heart disease) compared to women in the youngest age group, and the highest cardiovascular event risk was for VTE, which increased with increasing age [42]. The results for the 50–59 years age group (or for those less than 10 years since the menopause) can be seen in Fig. 2, which shows an increased risk of VTE and stroke, but apparent benefit regarding coronary artery disease and overall mortality.

In the unopposed estrogen group ($n = 10,739$), younger women (aged 50–59 years) were at a low absolute risk of all adverse events, although the highest risk was associated with VTE, which, similar to the findings of the combined MHT group, increased with increasing age [45, 46]. The highest absolute risk of a cardiovascular adverse event was associated with thrombotic (ischaemic) stroke in the 60–69 and 70–79 years age groups [46].

When all women taking MHT were analysed together, regardless of hormonal constituents of MHT, the absolute risk of all cardiovascular adverse events was low in the youngest group (50–59 years) (absolute excess risk − 6 per 10,000 person-years), but higher in the 70–79 years age subset (absolute excess risk 17 per 10,000 person-years) [47]. The risk of stroke did not vary significantly with age, although it was increased in those patients taking hormone therapy (HR 1.32, 95% CI 1.12–1.56).

These findings had two main effects. Firstly, it shifted the adverse effects of concern away from coronary heart disease and towards thromboembolic disease (comprising VTE and embolic stroke) [48]. Secondly, it spawned the concept of a window of opportunity in which to use MHT, which became a theory named the 'Timing Hypothesis'. This hypothesis was also supported by non-human primate randomised controlled trials, which found that estrogen replacement reduced atherosclerosis if provided soon after ovariectomy (though not if commenced years later) [49].

The development of atherosclerotic plaques is known to increase with increasing age, and it may well be that the delivery of MHT to those with established atherosclerotic disease, predominantly after the age of 60 years, may not have the same protective effects against the development of plaques as in younger women under the age of 60, or within 10 years of the menopause. Indeed, with the advance of atherosclerotic plaques, there is a loss of estrogen receptor expression (ERα and ERβ) in the vasculature, which leads to a loss of estrogen-related vasculoprotection and an increase in the pro-inflammatory effects of exogenous estrogens, which could lead to worsening of vasculopathology [49, 50]. There is therefore a possible biochemical and histopathological mechanism behind the 'Timing Hypothesis', and it was further investigated through two randomised controlled trials: the Kronos Early Estrogen Prevention Study (KEEPS) [51] and Early Versus Late Intervention Trial With Estradiol (ELITE) [52]. KEEPS found a mixed effect on biomarkers of cardiovascular risk, but no detectable effect of MHT (oral and transdermal estrogens combined with oral progesterone vs placebo) on either the advancement or retardation of atherosclerotic progression (as measured by carotid artery intima-media thickness) in 'recently menopausal' women [51]. ELITE randomised 643 healthy women to oral 17β-estradiol and progesterone vaginal gel or placebo, stratified according to time since the menopause. Again, using carotid artery intima-media thickness, they found no significant difference between MHT and placebo in those > 10 years since the menopause, but a significantly lower carotid intima-media thickness (CIMT) change in those on MHT compared to placebo in those < 6 years since the menopause [52]. This supports the 'Timing Hypothesis' and suggests

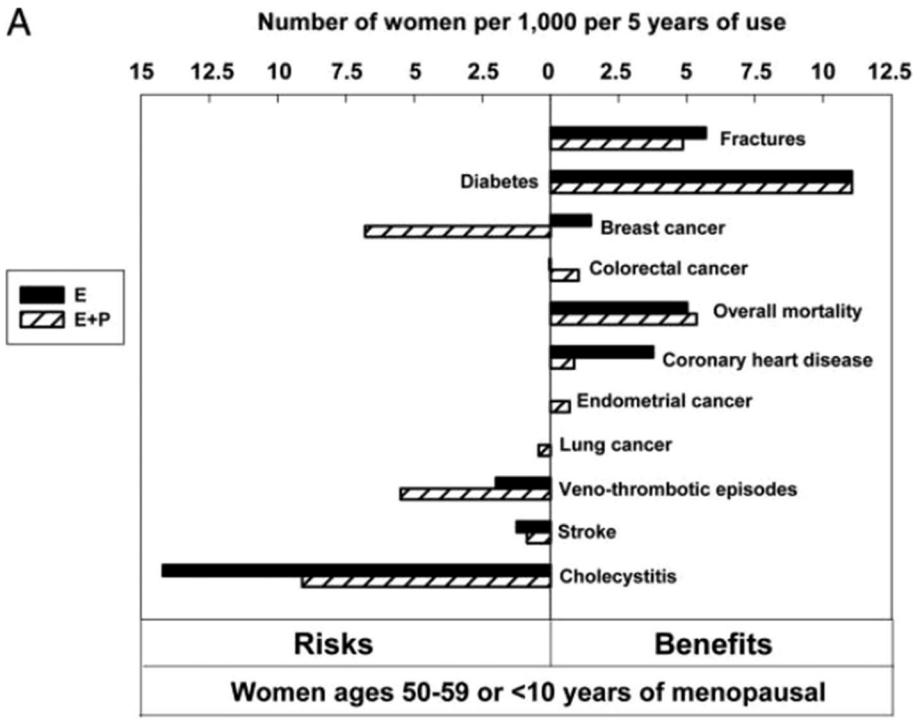

Fig. 2 The risk–benefit profile for estrogenic and combined menopausal hormone therapy in numbers of women (aged 50–59 years, or less than 10 years since the menopause) per 1000 per 5 years of use. Looking specifically at the cardiovascular risks, risks of venous thromboembolism and stroke are increased through the use of both combined and estrogen-only formulations, although there appears to be a protective effect on coronary heart disease and overall mortality [48]

that a window of opportunity for the use of MHT exists in those < 10 years since the menopause.

This is relevant when considering the initial findings of the WHI study, in which the participants were typically over the age of 60 years [39]. This would place the participants in an older age category when, potentially, atherosclerotic disease is already more advanced and the advantages of MHT, in a cardiovascular respect, are lost.

Regarding stroke, the risk of ischaemic stroke with MHT may be solely related to oral route of administration, with lower oral doses associated with lower risk and transdermal administration associated with low risk or no risk at all [53, 54].

Considering VTE, observational studies and possible biological mechanisms suggest a lower risk of VTE with low-dose transdermal therapy [55] and some progestogens (MPA, norpregnane derivatives and continuous combined regimens) may be associated with a greater risk of VTE in oral MHT users [53]. The risk of VTE may therefore be affected by the estrogenic route of administration, the dosage of progestogen and the type of progestogen used [48, 56]. Indeed, the effect of progestogens depends on their downstream mineralocorticoid and androgenic effects.

The fourth phase is characterised by reflections on the story of MHT thus far, which has been aptly expressed in the following statement by Manson et al: "The reluctance to treat menopausal symptoms has derailed and fragmented the clinical care of midlife women, creating a large and unnecessary burden of suffering" [57]. This is a sobering thought, although when safety concerns exist, it is absolutely right that interventions should be withheld whilst further information is gathered.

The benefit/risk balance for MHT is most favourable in younger, recently postmenopausal women [58, 59] (those who are less than 60 years old or within 10 years of the onset of the menopause), in the context of menopausal symptoms and low baseline risk of breast cancer, cardiovascular and cerebrovascular events and venous thromboembolic disease [59, 60]. MHT reduces fracture risk in populations unselected for low bone mineral density, but the evidence for long-term persisting benefits after cessation of treatment is limited [39, 58]. International guidance on MHT varies, with a global consensus statement in 2016 recommending that MHT could be commenced for women aged less than 60 years (or within 10 years of the menopause) for the reduction of fracture risk, whereas other guidelines have suggested that a reduction in fracture should be viewed as an additional benefit in the context of treatment of menopausal symptoms [59, 61]. Although transdermal preparations are associated with a lower risk of VTE, any beneficial effects on fracture risk are yet to be proven [59].

In conclusion, while guidelines differ in the approach to skeletal health as a primary treatment indication, there is a general consensus that MHT has an important role in younger, recently postmenopausal women with low baseline risk of breast cancer, cardiovascular and cerebrovascular events and venous thromboembolic disease for the treatment of menopausal symptoms, in which context, its positive effects on bone health are an additional and welcome benefit.

5 Tibolone

Tibolone is a synthetic steroid with estrogenic, progestogenic and androgenic properties used primarily for the treatment of postmenopausal osteoporosis and postmenopausal symptoms and was the subject of the Long-Term Intervention on Fractures with Tibolone (LIFT) study, a randomised, placebo-controlled trial. Over a median 34 months of treatment, compared to placebo, tibolone was associated with a reduced risk of vertebral fracture (70 cases vs 126 cases per 1000 person-years; relative hazard 0.55, 95% CI 0.41–0.74) and a reduced risk of nonvertebral fracture (122 cases vs 166 cases per 1000 person-years; relative hazard 0.74, 95% CI 0.58–0.93), but an increased risk of stroke (relative hazard 2.19, 95% CI 1.14–4.23), which led to the discontinuation of the study by the safety board [60].

6 Selective Estrogen Receptor Modulators

The major SERM used in the treatment of osteoporosis is raloxifene, although bazedoxifene (which may be combined with conjugated estrogens) and lasofoxifene (which has a limited distribution in parts of Europe) are included in this drug class.

SERMs have potential effects on lipid profile [61], inflammatory mediators [62], platelet function [63], coagulation [61] and glucose metabolism [64], although none of these effects are consistently demonstrated in the basic scientific literature. Although vasodilatory effects have been observed [65], there is no effect on blood pressure in clinical studies [66]. Significant associations with cardiovascular disease have been observed in trials and, latterly, in meta-analysis.

One such meta-analysis demonstrated a significant increase in the risk of venous thromboembolic disease (including deep venous thrombosis [DVT] and pulmonary emboli [PE]) from the analysis of nine trials (24,523 postmenopausal women), with an increased odds of any VTE (odds ratio [OR] 1.62, 95% CI 1.25–2.09), DVT (OR 1.54, 95% CI 1.13–2.11) and PE (OR 1.91, 95% CI 1.05–3.47) [67] associated with raloxifene usage. Similar associations are observed with lasofoxifene (with a dose-related increase in cumulative incidence of VTE) [68], and there was a trend towards an increased risk of VTE with bazedoxifene (RR 1.56, 95% CI 0.92–2.64). The increased risk of VTE with SERMs is therefore supported by the current literature. However, with coronary artery disease, there has been more conjecture.

The Multiple Outcomes of Raloxifene Evaluation (MORE) study was a randomised, placebo-controlled trial, and in a subset of women at high cardiac risk (cardiovascular risk score ≥ 4), raloxifene appeared to be protective against coronary events over 4 years (RR 0.60, 95% CI 0.38–0.95) [69]. However, after 8 years of follow-up, there was no protective or detrimental effect of raloxifene [70].

In the Raloxifene for the Use of the Heart (RUTH) trial, there was no demonstrable cardiac benefit of raloxifene compared to placebo; neither was there a significant difference in mortality rates, cardiovascular disease or stroke [71]. However, those in the raloxifene arm were at an increased risk of fatal stroke (HR 1.49, 95% CI 1.00–2.24; absolute risk increase 0.7 per 1000 woman-years). A similar trend was observed with lasofoxifene (although the HR did not reach significance: HR 2.39, 95% CI 0.84–6.78), potentially supporting a class effect [72].

In conclusion, there appears to be a significant increase in the risk of VTE with SERMs, and this should guide clinical practice. There is no evidence to support the use of raloxifene for cardiac benefit in women at high risk for cardiovascular disease, and there may be an increased risk of fatal stroke with SERMs, but not overall strokes, cardiovascular disease or mortality rate.

7 Bisphosphonates

When examining the cardiovascular safety of the bisphosphonates, the key issues are the possible association with atrial fibrillation and the potential atherosclerotic protection afforded by this group of anti-osteoporosis interventions.

The cardioprotective effects of bisphosphonates are debated [73, 74]. Animal studies in pigeons fed an atherogenic diet demonstrated a reduction in atherosclerotic plaque size and percentage with a non-nitrogen bisphosphonate, etidronate [75]. A study in monkeys has also demonstrated reduction in diet-induced atherosclerosis following treatment with anti-calcifying agents, including bisphosphonates, independent of changes in circulating lipid profiles [76].

Other mechanisms for the potential cardiovascular benefit of bisphosphonates include improvement of arterial elasticity, decrease in systemic vascular resistance and carotid artery intima-media thickness [77], inhibition of the mevalonate pathway (preventing ischaemia-induced myocardial remodelling and cardiac function) [78], inhibition of intravascular calcification [79] and a decrease in circulating γδ T cells, which are known to stimulate atherosclerotic progression [80].

These findings from animal studies are interesting, but it must be noted that they could be potentially due to dose effects, as higher doses were used in animal models than are utilised in clinical trials and practice. Indeed, the evidence discussed below pertains to the doses used in the context of osteoporosis, which are lower than those employed within the context of oncology.

The present analysis concerns doses used in the treatment of osteoporosis. Regarding the mortality and morbidity data from the early phase 3 controlled trials for risedronate, there is a discernible trend towards reduced cardiovascular mortality, though not on overall mortality, in those treated with risedronate compared to placebo [81]. However, a closer examination reveals a more mixed picture. The rates of cardiovascular adverse events (rather than mortality), coronary artery disease and stroke were numerically very similar for placebo, 2.5 mg risedronate and 5 mg risedronate, with no significant difference seen. When focussing on any cardiovascular mortality, the protective effect of risedronate was only observed in the 2.5-mg group (RR 0.69, 95% CI 0.49–0.99) and not in those taking 5 mg (RR 0.84, 95% CI 0.60–1.17). A similar picture was seen with stroke mortality for the 2.5-mg (RR 0.36, 95% CI 0.17–0.78) and 5-mg (RR 0.64, 95% CI 0.34–1.20) groups. There was no protective effect observed for mortality from coronary artery disease, which, given the proposed biological mechanisms for bisphosphonate cardiovascular protection, would be suspected to be the most amenable pathology to treatment.

Zoledronic acid was the subject of the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) trial [82], which found similar rates of cardiovascular events and stroke, although there was a reduction of 28% in all-cause mortality in the zoledronic acid group (9.8% mortality vs 13.3% mortality, $p = 0.01$) [83]. In the Fracture Prevention with Zoledronate in Older Women with Osteopenia trial [84] (in osteopenic rather than osteoporotic older women with an 18-month interval in zoledronic acid administration), the HR for MI in the zoledronic acid group was 0.60 (95% CI 0.36–1.00) and the rate ratio was 0.58 (95% CI 0.35–0.94). For a pre-specified composite cardiovascular endpoint (sudden death, MI, coronary artery revascularisation or stroke), the HR was 0.76 (95% CI 0.53–1.08) and the rate ratio was 0.72 (95% CI 0.53–0.98) [85].

The absence of a true cardiovascular benefit of bisphosphonate therapy is supported by findings from an analysis of two large (> 47,000 participants), long-term, prospective databases in the USA, which demonstrated no statistical difference in the long-term rates of MI or death [86]. Interestingly, in this study, the patients who underwent coronary angiography were investigated as a high-risk subgroup and, again, no benefit of bisphosphonate therapy was observed [86].

The possible cardioprotective effects of bisphosphonates remain under scrutiny, and there is certainly not sufficiently robust, cohesive data to support a recommendation for this class of medications to be used to treat cardiovascular disease, or even to recommend using them to treat osteoporosis in those at high risk of MI or stroke. A recent meta-analysis reported that mortality was not altered by bisphosphonate treatment [87].

The connection between bisphosphonates and arrhythmia has an equally mixed picture. Early analysis of the safety data from the HORIZON trial demonstrated a significantly higher incidence of arrhythmia in the zoledronate arm (6.9% vs 5.3% in the placebo arm, $p = 0.003$) and that within this group 'serious atrial fibrillation' (atrial fibrillation that resulted in a serious adverse event) was significantly more common (1.3% vs 0.5% in the placebo arm, $p < 0.001$) [82]. A similar trend had been previously observed in the Fracture Intervention Trial (of alendronate) [88], but although the cumulative incidence of serious atrial fibrillation had numerically increased with alendronate, the rise had not been statistically significant.

Further studies sought to investigate this association, with conflicting findings. A case–controlled study from a healthcare database in the USA found that a greater number of atrial fibrillation case patients than controls had ever used alendronate (6.5% vs 4.1%, $p = 0.03$) and that when comparing ever-users (of bisphosphonates) to never-users, the ever-users had a higher risk of incident atrial fibrillation (OR 1.86, 95% CI 1.09–3.15) [89]. However, a European population-based, case–control study (comparing ~ 13,500 patients with atrial fibrillation or flutter to ~ 68,000 controls) found no evidence of increased risk of arrhythmia with bisphosphonates [90]. This finding was supported by another European case–control, register-based cohort study, which found that the highest risk of atrial fibrillation was in the subgroup of patients who only received the bisphosphonates once and the longer the patient was adherent to bisphosphonates, the lower the risk of atrial fibrillation [91].

An interesting hypothesis from the latter study was that fracture patients were inherently more likely to experience atrial fibrillation (compared to non-fracture controls) and more likely to receive bisphosphonates, thus confounding the association [91]. This theory was supported in the aforementioned study of two large prospective databases, which found that patients on bisphosphonates were inherently older with a greater cardiovascular disease burden, thus increasing their risk of atrial fibrillation.

Considering that the majority of the signal is for an increased risk of atrial fibrillation with bisphosphonate therapy came from the HORIZON trial and zoledronic acid, it should be acknowledged that in the Recurrent HORIZON trial (consisting of a more elderly, infirm, post-hip fracture population), there was no significant increase in serious atrial fibrillation [83]. Neither was atrial fibrillation increased in those on zoledronate in the PREVENTION study (a 6-year randomised, placebo-controlled trial of 2000 women) [84].

Therefore, in conclusion, there is no substantial signal for the development of atrial fibrillation with bisphosphonates at present, though further studies examining and powered to answer this exact question are warranted.

8 Denosumab

Denosumab (60 mg, every 6 months) is a fully human monoclonal antibody and inhibitor of receptor activator of nuclear factor-κB (RANK) ligand, which prevents the maturation and activity of osteoclasts and therefore acts to reduce bone resorption. There is a potential, though tenuous, link with cardiovascular health via RANK-ligand, RANK and osteoprotegerin (OPG). OPG is found in calcifications in the aorta and renal arteries, and transgenic overexpression of OPG leads to inhibition of these calcified vascular lesions. Indeed, when an atherogenic mouse model was treated with OPG, there was a significant reduction in calcified lesions. RANK-ligand itself is known to induce calcification of vascular smooth muscle, and the development of vascular calcifications depends on RANK-ligand–mediated expression of bone morphogenetic protein-2 (BMP-2) and matrix Gla protein. Thus OPG could potentially inhibit the formation of vascular calcifications by blocking RANK-ligand and there is thus a plausible biological mechanism for some prevention of cardiovascular pathology when treated with denosumab. This is, however, not borne out by the evidence from randomised controlled trials.

The Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) study was a phase 3, multicentre, double-blind, placebo-controlled trial of denosumab over 3 years [92]. It included a total of 7868 women (with 31.7% of these ≥ 75 years), and throughout this initial trial period, there was no significant difference in cardiovascular events, stroke, coronary heart disease, peripheral vascular disease or atrial fibrillation [92]. Despite the fact that FREEDOM was not powered to investigate mortality, there was a non-significant trend towards reduced mortality in the denosumab group (1.8% participants in denosumab group vs 2.3% participants in the control group, $p = 0.08$) [92].

In 2014, there was a further analysis of a subset of 2363 women (1142 placebo, 1221 denosumab) from the FREEDOM trial who were at high risk of cardiovascular disease (as defined by the RUTH criteria) [93]. In this study, aortic calcification and progression was assessed using a semi-quantitative method from lateral spine radiographs. There was no significant difference in aortic calcification progression over the 3 years of the trial between the placebo (22%) and denosumab (22%) groups and no difference in cardiovascular risk across the two groups (in the high cardiovascular risk population) [93].

In conclusion, although a plausible biological connection exists between denosumab and cardiovascular disease, there is no evidence from human trials to support a positive or negative effect on cardiovascular risk, at least at the dose used in osteoporosis therapy.

9 Parathyroid Hormone Analogues

It has long been known, initially from animal studies, that PTH has chronotropic effects via receptors in cardiac myocytes and transient dilatory effects on the peripheral vasculature, leading to an increase in heart rate and reduction in blood pressure, respectively [94]. These effects may have manifested as adverse events in the trials for the two PTH analogues that are currently used in osteoporosis clinical practice: teriparatide and abaloparatide.

The Summary of Product Characteristics for teriparatide lists nausea, headache and dizziness as potential adverse effects, which could potentially be related to the cardiovascular mechanisms described above from animal studies. Indeed in the VERtebral Fracture Treatment Comparisons in Osteoporotic Women (VERO) trial comparing teriparatide to risedronate, there was a significantly higher incidence of dizziness (teriparatide 30 [4.4%], risedronate 12 [1.8%], $p = 0.007$) in those taking teriparatide, but there was no excess incidence of cardiovascular adverse events [95]. Even in post-marketing surveillance, there was no perceptible signal of increased risk of cardiovascular adverse events, as demonstrated by a Japanese, prospective, observational study [96].

A similar story was observed in the Abaloparatide Comparator Trial in Vertebral Endpoints (ACTIVE) [97], which included teriparatide and placebo arms. In the abaloparatide arm, discontinuation of the study drug was most commonly due to nausea (1.6%), dizziness (1.2%), headache (1.0%) and palpitations (0.9%). Dizziness had a higher incidence in the abaloparatide group (10.0%) than in the teriparatide group (7.3%) or placebo group (6.1%). However, 'dizziness' is a symptom with both potential cardiovascular and neurological aetiology, and it is therefore interesting that the more cardiovascular endpoint of orthostatic hypotension was defined as an adverse event of special interest and was very similar across all three arms (17.1% in the teriparatide arm, 16.4% in the placebo arm and 15.5% in the teriparatide arm) suggesting a lack of association. Palpitations were most common with abaloparatide (5.1%), with a lower incidence with teriparatide (1.6%), and placebo being the lowest (0.4%). There was no excess risk of MI, falls or syncope.

In conclusion, animal models have demonstrated potential effects of PTH on the cardiovascular system [94], and these may lead to increased rates of dizziness [95] with PTH analogues. However, whether this increased risk is manifested via the cardiovascular system is not clear, and there is certainly no current evidence to suggest an increased risk of atherosclerotic or thromboembolic cardiac disease with this group of interventions.

10 Romosozumab

Romosozumab is a humanised monoclonal antibody, approved by the Food and Drug Administration (FDA) [98] and European Medicines Agency (EMA) [99], which inhibits sclerostin. Sclerostin is an effective antagonist of Wnt signalling, and thus romosozumab acts as an anabolic agent for bone formation and as an inhibitor of bone resorption. Controversy exists regarding the cardiovascular safety of this drug from the point of biological plausibility, the outcomes of randomised controlled trials [100–102] and the output of meta-analyses [103]. Current guidance (in some regions) advocates against use in those with a history of MI and ischaemic stroke and recommends a judicious approach in those with a high baseline risk of cardiovascular disease [99, 104].

The arguments for the biological plausibility of adverse cardiovascular effects of romosozumab centre on a potential role in arterial calcification. Sclerostin is the product of the *SOST* gene and is primarily secreted by osteocytes. It plays an important role in bone turnover by upregulating bone formation and downregulating bone resorption [101, 105]. Beyond the skeleton, increased sclerostin expression has been observed in smooth muscle tissue in areas of vascular calcification [106]. At these sites, sclerostin may act to limit the formation of calcified plaques [107] and confer a degree of cardiovascular benefit.

In a murine model of increased cardiovascular risk, apolipoprotein E (apoE)-null mice (prone to aortic aneurysm and atherosclerosis) were provided with an infusion of angiotensin II [108]. They were then subjected to sclerostin from either transgenic overexpression or exogenous recombinant murine sclerostin. Increased sclerostin, from either source, was found to be protective against aortic aneurysm formation and atherosclerosis. This was further supported by data from experiments in which a murine model of glucocorticoid-induced osteopenia was crossed with a Sost-deficient (and therefore sclerostin-deficient) mouse [109], with resultant sudden death in ~ 10% of mice. On post-mortem, histopathological evidence of peracute haemopericardium and cardiac tamponade was observed. These murine data support the theory of a cardiovascular protective effect of sclerostin.

This has resulted in the hypothesis that romosozumab-induced sclerostin inhibition could modulate Wnt-β-catenin signalling [110] via a compensatory increase in expression of Dickkopf Wnt signalling pathway inhibitor 1 (DKK1) [111] to result in vascular calcification and destabilisation of atherosclerotic plaques [112].

However, this effect of romosozumab has not been clearly demonstrated in animal models. Indeed, the administration of romosozumab did not significantly alter DKK1 levels in a rat model of progressive renal osteodystrophy [113] or ovariectomised cynomolgus monkeys in response to romosozumab [114].

In human conditions associated with reduced activity of sclerostin, neither van Buchem's disease nor sclerosteosis demonstrate cardiovascular disease manifestations [115, 116], although it should be noted that a substantial proportion of homozygous individuals die in early adulthood (mean age of death 33 years) due to complications of increased intracranial pressure [117], and the effect of sclerostin inhibition in an older age-group may be different.

As described above, although there are potential hypotheses, there is not a robust demonstration of a biological basis for cardiovascular disease related to romosozumab.

The FRActure study in postmenopausal woMEn with osteoporosis (FRAME) was a randomised controlled trial comparing romosozumab to placebo, before transitioning onto denosumab [100, 101]. In this trial, there were no observed associations between romosozumab and cardiovascular adverse events, including major adverse cardiac events (MACE) (a composite of non-fatal MI, non-fatal stroke and cardiovascular death), with an HR of 1.1 (95% CI 0.7–1.7). In the FRAME extension study, the percentage of positively adjudicated adverse cardiac events did not differ significantly, with 3.6% for romosozumab and 3.5% for placebo [118]. However, it should be noted that the participant population included women with a broad range of osteoporosis severity, rather than being focused only on those with severe disease.

The Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk (ARCH) [102] compared romosozumab to alendronate, before transitioning onto long-term alendronate therapy. Unlike FRAME, ARCH did focus on individuals with severe osteoporosis, and therefore the participant group was older and had a higher baseline prevalence of cardiovascular disease and risk.

Although ARCH was designed and powered to assess efficacy in the treatment of osteoporosis, the primary cardiac safety endpoint was serious cardiovascular adverse events (composed of MACE outcomes [non-fatal MI, non-fatal stroke and cardiovascular death] plus heart failure and non-coronary heart disease), and this did not differ significantly between treatment groups (2.5% romosozumab and 1.9% alendronate; HR 1.32, 95% CI 0.87–2.01, $p = 0.2$) [102]. In post hoc analyses of MACE, the incidence was 2.0% in the romosozumab group and 1.1% in the alendronate group, indicating a significant preponderance for cardiovascular disease with romosozumab (HR 1.7, 95% CI 1.1–2.6) [99].

Examining the constituent parts of MACE separately, an increased risk of cardiovascular ischaemia was observed in the romosozumab group ($n = 2040$) compared to the alendronate group ($n = 2014$) (OR 2.65, 95% CI 1.03–6.77) [102]. However, there was no increased risk of cerebrovascular disease (OR 2.27, 95% CI 0.93–5.22) or cardiovascular

mortality (OR 1.42, 95% CI 0.68–2.97) when analysed in isolation, rather than being included with cardiovascular ischaemia in the MACE composite endpoint [102]. It is important to note that, in ARCH, any undisclosed cause of death was recorded as a cardiovascular death, which may have led to overestimation [99]. Interestingly, the incidence of heart failure, non-coronary revascularisation and peripheral vascular ischaemic events not requiring revascularisation was lower in the romosozumab arm [102].

A numerical preponderance towards cardiac adverse events was observed (as a non-primary outcome) in placeBo-contRolled study evaluatIng the efficacy anD safety of romosozumab in treatinG mEn with osteoporosis (BRIDGE) (which examined the bone health of 170 males) [119]. Only ten participants experienced positively adjudicated serious cardiovascular adverse events, 4.9% with romosozumab and 2.5% in the placebo group.

Therefore, the bulk of evidence against the cardiac safety of romosozumab comes from the ARCH trial [102]. This has been the subject of commentaries defining the possible explanations for the increased risk of MACE with romosozumab shown in this study as being due to increased cardiac risk of romosozumab, or the decreased cardiac risk with alendronate or the result of a chance finding [120].

Previously in this paper, we examined the potential cardiovascular protective effect of bisphosphonates and concluded that there was no robust evidence to support this supposition (particularly over the short, 12-month study period of ARCH). Indeed, there is evidence against either drug effect, as once participants were switched to alendronate, there was no change in cardiovascular disease risk [99]. Additionally, there was no apparent inflection of the slope of the cumulative incidence plot of time to first occurrence of MACE as participants switched from romosozumab to alendronate [99], suggesting that there was either no change in the risk of MACE or that the risk of MACE accrued by romosozumab was constant after the 12 months of treatment.

The ARCH population had significantly greater cardiovascular risk factors and a greater history of previous cardiovascular events than the FRAME population, which may have implications for the safety of the drug in an older population. In addition, when all the data were considered together, there were more deaths in patients aged over 75 years given the medicine [121]. However, subgroup analyses from ARCH demonstrated no difference in the cardiovascular risk between high- and low-risk subgroups (including those aged < 75 or ≥ 75, ever or never smokers and use of cardiovascular disease medications at baseline) [99].

When all these results were meta-analysed for the association between romosozumab and cardiovascular disease, the associations were non-significant for MACE (1.39, 95% CI 0.97–2.00) and serious adverse cardiovascular events (1.14, 95% CI 0.85–1.53). In support, a recent meta-analysis of six trials found a 39% increased risk of 4-point MACE (including death, MI, stroke and cardiac failure) with romosozumab, which was statistically significant [103]. When examining the cardiovascular adverse event profile of each arm in these trials, it is important to remember that the primary outcomes were efficacy rather than safety related. It is also important to note that the results of this meta-analysis are driven by the results of ARCH and that the marked differences in study populations and design make meta-analysis an ineffective approach for ARCH and FRAME [99].

The delay in the decision regarding the benefit–risk balance of romosozumab when considering cardiovascular safety is understandable. The studies undertaken in patients with a relatively mild deficit in bone mineral density (the best example of which is FRAME) suggest no increase in the risk of a major cardiovascular events, but appear to have equivocal benefits on non-spine fractures [100, 101]. However, those studies focussing on older, frail patients with more severe osteoporosis and previous fracture demonstrate marked effectiveness against recurrent fracture but an increased risk of MACE and cardiovascular ischaemia with romosozumab [102].

Debate may continue as to the extent to which the imbalance in cardiovascular events and mortality represents a protective effect of bisphosphonates on IHD compared to an adverse increase in risk attributable to romosozumab or whether it is a simply a chance effect [120].

For this reason, the EMA have reasonably concluded that romosozumab can be used for postmenopausal women with severe osteoporosis who are at a high risk of fracture, but not in those with a history of MI or stroke [121]. In those individuals with a high baseline cardiovascular risk, a robust risk–benefit assessment should be performed [99]. We now have to wait for data from pharmacovigilance studies that have been instigated worldwide to assess this benefit–risk balance in larger populations when drug use can be evaluated on a more routine clinical basis.

11 Conclusions

In conclusion, despite past studies demonstrating an association with coronary heart disease, there are no consistent data to suggest an association between calcium and coronary artery disease, and vitamin D supplementation does not appear to be associated with increased cardiac risk. There is a window of opportunity until 10 years after the menopause in which to use MHT without apparent detriment regarding cardiovascular disease. SERMs are associated with a significantly increased risk of VTE and may be associated with fatal stroke. Bisphosphonates cannot be recommended

for cardiac benefit, and associations with atrial fibrillation are inconsistent. There is no evidence of adverse cardiac effects with denosumab or PTH analogues. The signal on cardiovascular disease adverse events with romosozumab needs post-marketing surveillance, which will be crucial in confirming cardiovascular safety.

Compliance with Ethical Standards

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