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Mini-Review

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Cardiovascular Safety and Sclerostin Inhibition

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Abbreviations: ARCH, ***A***ctive-cont***R***olled fra***C***ture study in postmenopausal women with osteoporosis at ***H***igh risk (NCT01631214); BMD, bone mineral density; BRIDGE, place***B***o-cont***R***olled double-blind study evaluat***I***ng the efficacy an***D*** safety of romosozumab in treatin***G*** m***E***n with osteoporosis (NCT02186171); FRAME, ***FRA***cture study in post***M***enopausal women with ost***E***oporosis (NCT01575834); LRP5, lipoprotein receptor-related protein 5; MACE, myocardial infarction, stroke, and cardiovascular or unexplained death; STRUCTURE, ***ST***udy evaluating effect of ***R***omosoz***U***mab ***C***ompared with ***T***eriparatide in postmenopa***U***sal women with osteoporosis at high risk for fracture p***R***eviously treated with bisphosphonat***E*** therapy (NCT01796301).

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Abstract

Sclerostin, which is primarily produced by the osteocytes, inhibits the canonical Wnt pathway and thereby the osteoblasts and stimulates RANKL release by the osteocytes and thereby osteoclast recruitment. Inhibition of sclerostin therefore causes stimulation of bone formation and inhibition of resorption. In clinical trials, romosozumab, an antibody against sclerostin, increases bone mineral density and reduces the risk of fractures compared with placebo and alendronate.

The cardiovascular safety of romosozumab was adjudicated in 2 large clinical osteoporosis trials in postmenopausal women. Compared with placebo, the incidence of cardiovascular events was similar in the 2 treatment groups. Compared with alendronate, the incidence of serious cardiovascular events was higher in women treated with romosozumab. The incidence of serious cardiovascular adverse events was low and post hoc analyses should therefore be interpreted with caution; however, the relative risk seemed unaffected by preexisting cardiovascular disease or risk factors.

Sclerostin is expressed in the vasculature, predominantly in vascular smooth muscle cells in the media. However, preclinical and genetic studies have not demonstrated any increased cardiovascular risk with continuously low sclerostin levels or inhibition of sclerostin. Furthermore, no potential mechanisms for such an effect have been identified.

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In conclusion, while there is no preclinical or genetic evidence of a harmful effect of sclerostin inhibition on cardiovascular safety, the evidence from the large clinical trials in postmenopausal women is conflicting. Romosozumab should therefore be used for the treatment of postmenopausal women with osteoporosis at high risk of fracture after careful consideration of the cardiovascular risk and the balance between benefits and risks.

Key Words: romosozumab, osteoporosis, sclerostin, cardiovascular safety

Sclerostin is a glycoprotein encoded by the *SOST* gene and primarily, but not exclusively produced by osteocytes (1). Sclerostin inhibits the canonical Wnt pathway by binding to the lipoprotein receptor-related protein 5(LRP5) receptor and thereby inhibiting the LRP5 receptor from binding to its co-receptors Frizzled and Wnt and activating the Wnt pathway. The canonical Wnt pathway is an important pathway for the activation of osteoblasts and stimulation of collagen production by the osteoblasts, a critical step in bone formation (2). Osteoblasts are stimulated by many different factors, including hormones, growth factors, and locally produced signals during bone resorption (3). Osteocytes control bone accrual by releasing sclerostin that subsequently mitigates osteoblast activity and bone formation. Osteocytes also control bone resorption by the release of RANKL, which is stimulated by sclerostin (4).

The importance of sclerostin for the control of bone formation was discovered when it was found that the diseases sclerosteosis and van Buchem disease were caused by loss-of-function mutations in or in relation to the *SOST* gene that encodes sclerostin (5, 6). Patients with these diseases are born with normal bone mass but during childhood and young adulthood they experience unusually large gains in bone mass and skeletal overgrowth which can result in nerve palsy, eg, Bell's palsy. These patients have a very low risk of fracture, since unopposed bone formation translates into higher bone mass and strength. Individuals heterozygous for the mutations have a milder skeletal phenotype, characterized by increased bone mass compared to healthy individuals, low fracture risk, but no skeletal overgrowth or neurological or cardiovascular complications (7).

Postmenopausal osteoporosis is a common condition characterized by low bone mass, deterioration of bone microarchitecture and increased risk of fragility fractures (8). At the cellular level, the condition is characterized by increased activity of osteoclasts and decreased activity of the osteoblasts (9). The clinical findings of increased bone mass, but no skeletal overgrowth and the increased bone formation seen in the heterozygous carriers of the loss-of-function mutations in the *SOST* gene inspired the development of sclerostin antibodies for the treatment of osteoporosis.

The Effect of Romosozumab on Bone Mineral Density and Fracture Risk

Romosozumab is a monoclonal, humanized antibody against sclerostin developed for the treatment of osteoporosis (10). It is approved for the treatment of severe osteoporosis in postmenopausal women in many parts of the world, including the United States, Europe, and Japan. The clinical efficacy and safety have been investigated in 4 phase III trials, 3 in postmenopausal women and 1 in men. The FRAME (***FRA***cture study in postmenopausal women with ost***E***oporosis [NCT01575834]) trial included 7180 postmenopausal women with osteoporosis and compared romosozumab 210 mg monthly with placebo for 1 year, followed by denosumab in both groups for another 2 years (11, 12). The study demonstrated large increases in bone mineral density (BMD) and significant reductions in vertebral fractures compared with placebo. The ARCH (***A***ctive-cont***R***olled fra***C***ture study in postmenopausal women with osteoporosis at ***H***igh risk [NCT01631214]) trial included 4093 postmenopausal women with severe osteoporosis and compared romosozumab 210 mg monthly for 1 year followed by alendronate 70 mg weekly with alendronate 70 mg weekly (13). BMD increased significantly more at both the spine and hip in patients treated with romosozumab compared with alendronate during the first year of study and this difference in BMD between the groups was maintained during the following years in which both study groups were treated with alendronate. The ARCH study also demonstrated significant reductions in the risk of vertebral and clinical fractures after 1 year with romosozumab compared with alendronate. The study was event driven and at the time of the primary analysis, the reductions in vertebral, nonvertebral, as well as hip fractures were significantly greater in the women treated with romosozumab followed by alendronate compared with the women who received alendronate throughout the study. The STRUCTURE (***ST***udy evaluating effect of ***R***omosoz***U***mab ***C***ompared with ***T***eriparatide in postmenopa***U***sal women with osteoporosis at high risk for fracture p***R***eviously treated with bisphosphonat***E*** therapy [NCT01796301]) study included 436 postmenopausal women who had been treated with bisphosphonates for

at least 3 years but remained at increased risk of fractures. The women were randomized to romosozumab 210 mg monthly or teriparatide 20 µg daily for 1 year (14). The study demonstrated larger increases with romosozumab in spine, and especially hip BMD. The BRIDGE (placeBocontRolled double-blind study evaluatIng the efficacy anD safety of romosozumab in treatinG mEn with osteoporosis [NCT02186171]) study included 245 men with osteoporosis and compared romosozumab with placebo for 1 year (15). BMD at the spine and hip increased more in the men treated with romosozumab compared with placebo. Neither STRUCTURE nor BRIDGE were powered to evaluate fracture risk reductions. In all 4 studies, the romosozumab was generally well tolerated compared with placebo or alendronate. There were more cases of injection site reactions in the patients receiving romosozumab compared with placebo injections (11, 13).

Cardiovascular Safety With Romosozumab in the Clinical Trials

Based on preclinical evidence (discussed later) demonstrating upregulation of sclerostin in areas of vascular calcification (16) serious cardiovascular events in 3 of the phase III trials (FRAME, ARCH, and BRIDGE) were prospectively adjudicated.

During the first year of the FRAME trial, cardiovascular adverse events and adjudicated serious cardiovascular events were well balanced between the women treated with romosozumab and placebo and remained so during the open-label treatment with denosumab (11). The accumulated incidence of cardiovascular adverse events increased linearly with time, as would be expected based on numerous previous clinical cardiovascular studies investigating cardiovascular events (17-20). Unlike the romosozumab trials, these cardiovascular studies were powered for adverse cardiovascular events and contained 3 to 8 times the number of events compared with that seen in the first year of the FRAME and ARCH studies.

During the first year of the ARCH trial, 50 women treated with romosozumab experienced adjudicated serious cardiovascular events compared with 38 women treated with alendronate (13). The accumulated incidence curve for cardiovascular adverse events in the women treated with romosozumab followed by alendronate increased linearly over time during the entire study period, with no change in the incidence rate seen when treatment in this group was changed from romosozumab to alendronate (21). However, the accumulated incidence curve for women who received alendronate throughout the study period had a nonlinear appearance. The curve was relatively flat, with no events during the first 3 months, followed by a lower incidence rate than in the romosozumab treated women during the next approximately 15 months. Thereafter, with alendronate therapy continuing, the incidence rate increased, and at the end of the study the accumulated incidence was just below the accumulated incidence in the women treated with romosozumab followed by alendronate (22). The number of cases with specific cardiovascular events was small throughout the trial. Numerically, stroke and ischemic heart disease were more common among the women treated with romosozumab whereas cardiac failure was more common among the women treated with alendronate. The imbalance during the first year in ARCH with 12 additional cases of serious adverse cardiovascular events was maintained during the open-label alendronate treatment period but not increased further as 98 and 99 women experienced serious adverse cardiovascular events during the open-label treatment period in the 2 groups, respectively. There were a few more cases of cardiovascular death and death of all causes in women treated with romosozumab during the first 12 months of ARCH; however, this was reversed during the open-label alendronate treatment period so that at the time of primary analysis after a median of 33 months, the incidences of cardiovascular death and death of all causes were comparable in both treatment groups; 67 vs 68 and 101 vs 103, respectively (13).

The hazard ratios for cardiovascular serious adverse events in FRAME and ARCH were 1.00 (0.66-1.50) and 1.32 (0.87-2.01), respectively, and when meta-analyzed the hazard ratio was 1.14 (0.85-1.53). Similarly, the hazard ratios for MACE (myocardial infarction, stroke, and cardiovascular or unexplained death) during the first 12 months in FRAME and ARCH were 1.03 (0.62-1.72) and 1.87 (1.11-3.14), respectively, and when meta-analyzed the hazard ratio was 1.39 (0.97-2.00) (21) (Table 1). The higher overall rate of cardiovascular events in the ARCH trial compared with the FRAME trial reflected that the ARCH trial participants were 3 to 4 years older with higher baseline cardiovascular disease. Hypertension was reported among 60% of the women in ARCH compared with 53% in FRAME, previous cerebrovascular conditions in 8% vs 5%, ischemic heart disease in 13.5% vs 9%, heart failure in 4% vs 2.5%, and atrial fibrillation in 4% vs 2% in women in the ARCH and FRAME trials, respectively. In addition, 62% vs 57% of the women in ARCH and FRAME were treated with cardiovascular medications at baseline, and 28% vs 23% took antithrombotic medications (21). Neither of these pivotal efficacy studies were planned as cardiovascular outcome studies and therefore baseline parameters that would have normally been collected in a cardiovascular outcome study, such as fasting lipid and high sensitivity C-reactive protein levels, were not available. This, together with the lack of validation of cardiovascular risk

Table 1. Adjudicated major adverse cardiovascular events (MACE), cardiovascular serious adverse events and cardiovascular deaths (21)

	FRAME			ARCH			Meta-analysis FRAME and ARCH	BRIDGE	
	Postmenopausal women			Postmenopausal women			Postmenopausal women	Men	
	Romosozumab	Placebo	HR	Romosozumab	Alendronate	HR	HR	Romosozumab	Placebo
N, safety analysis	3581	3576		2040	2014			163	81
MACE, n (%)	30 (0.8)	29 (0.8)	1.03 (0.62–1.72)	41 (2.0)	22 (1.1)	1.87 (1.11–3.14)	1.39 (0.97–2.00)		
CV deaths, n (%)	17 (0.5)	15 (0.4)	1.13 (0.56–2.26)	17 (0.8)	12 (0.6)	1.42 (0.68–2.97)		2 (1.2)	1 (1.2)
Myocardial infarction, n (%)	9 (0.3)	8 (0.2)	1.12 (0.43–2.91)	16 (0.8)	5 (0.2)	3.21 (1.18–8.77)			
Stroke, n (%)	8 (0.2)	10 (0.3)	0.80 (0.32–2.02)	13 (0.6)	7 (0.3)	1.86 (0.74–4.67)			
Any CV SAE, n (%)	46 (1.3)	46 (1.3)	1.00 (0.66–1.50)	50 (2.5)	38 (1.9)	1.32 (0.87–2.01)	1.14 (0.85–1.53)	8 (4.9)	2 (2.5)
Cardiac ischemic event, n (%)	16 (0.4)	16 (0.4)	1.00 (0.50–2.00)	16 (0.8)	6 (0.3)	2.68 (1.50–6.84)		3 (1.8)	0 (0.0)
Heart failure, n (%)	7 (0.2)	5 (0.1)	1.40 (0.44–4.40)	4 (0.2)	8 (0.4)	0.50 (0.15–1.66)		1 (0.6)	0 (0.0)
Non-coronary revascularization, n (%)	1 (<0.01)	2 (<0.01)	0.50 (0.05–5.49)	3 (0.1)	5 (0.2)	0.60 (0.14–2.52)			
Cerebrovascular event, n (%)	10 (0.3)	11 (0.3)	0.91 (0.39–2.14)	16 (0.8)	7 (0.3)	2.30 (0.94–5.58)		3 (1.8)	1 (1.2)

Abbreviations: ARCH, Active-cont*R*olled fraCture study in postmenopausal women with osteoporosis at *H*igh risk (NCT01631214); BRIDGE: place*Bo*-cont*R*olled double-blind study evaluat*I*ng the efficacy an*D* safety of romosozumab in treatin*G* m*E*n with osteoporosis (NCT02186171); CV, cardiovascular; FRAME, *FRA*cture study in post*M*enopausal women with ost*E*oporosis (NCT01575834); HR, hazard ratio; MACE, myocardial infarction, stroke, and cardiovascular or unexplained death; SAE, serious adverse event.

calculators in the ARCH and FRAME subject age groups, limited the direct comparison of baseline risk between the studies and between study arms. However, a post hoc analysis of the ARCH study at the end of the double-blind study period investigated the relationship between cardiovascular risk factors, such as diabetes, hypertension, and previous myocardial infarction and adverse cardiovascular events. Absolute cardiovascular risk was higher in women with one or more of these risk factors but the relatively increased risk or hazard ratio in women treated with romosozumab compared to women treated with alendronate were similar across a range of cardiovascular risk factors (21). Cardiovascular adverse events were not adjudicated in the smaller STRUCTURE study. Atrial fibrillation was reported in 2 patients treated with romosozumab. Two patients died, 1 in each group (14).

Adjudicated serious cardiovascular adverse events occurred in 8 of 163 (4.9%) men treated with romosozumab and 2 of 81 (2.5%) placebo treated men in the BRIDGE study. Two (1.2%) and 1 (1.2%) men, respectively, in the 2 treatment groups died (15).

None of the phase I to III clinical trials investigating romosozumab found any effect of romosozumab on blood pressure, heart rate, electrocardiography, or biochemical markers of or established risk factors of cardiovascular disease (21).

Cardiovascular Safety With Other Sclerostin Antibodies in Clinical Development

Two additional sclerostin antibodies have been investigated in clinical trials. Blosozumab has been investigated for the treatment of osteoporosis. A phase II clinical trial randomized 120 postmenopausal women with osteoporosis to 3 different blosozumab regimens or placebo for 52 weeks. The treatment response with respect to BMD and bone turnover markers for the highest dose was comparable to the treatment response seen with romosozumab 210 mg monthly. Injection site reactions were seen in up to 40% of the women, but only few cases of major adverse cardiovascular events were seen in the study without imbalance between women treated with blosozumab and placebo (23). Further development of blosozumab was stopped.

Setruzumab or BPS804 has been investigated in small clinical trials of short duration including few patients with osteogenesis imperfecta (24) and hypophosphatasia (25). No cardiovascular adverse events were reported in these studies. A larger study in adult patients with osteogenesis imperfecta (NCT03118570) is monitoring cardiovascular safety along with the relevant clinical outcomes. The study is completed, but the results have not yet been published.

Preclinical Evidence for the Effect of Sclerostin and Sclerostin Inhibition on Cardiovascular Outcomes

The SOST mRNA encoding sclerostin and the sclerostin glycoprotein are widely expressed and not limited to anatomical sites of osteocytes, ie, the bone. Thus, tissues with consistent low abundant expression of SOST mRNA include the heart, aorta, kidney and liver, and the sclerostin protein has been detected in the aorta (6, 26). Under pathological conditions of vascular and valvular calcification, a process that resembles heterotopic ossification, sclerostin expression was focally upregulated (16, 27-29). Interestingly, sclerostin has not been detected in the fibrous cap of atherosclerotic plaques or endothelium (30) and the function of sclerostin in the vasculature and in vascular pathogenesis is unknown. Sclerostin expression in calcified vessels and valves may represent an epiphenomenon, representing the ossification process, in which vascular smooth muscle cells transdifferentiate toward an osteoblastic/osteocytic phenotype during the calcification process (31). In support of this hypothesis, Zhu et al demonstrated that sclerostin and other osteocyte markers are expressed during calcification of vascular smooth muscle cells in vitro and in an ex vivo mouse model of the Enpp-deficient mouse, a model of severe medial calcification (16). Claes et al investigated the prevalence of aortic calcifications in a cohort of patients with chronic kidney disease and found that patients with aortic calcifications had higher serum levels of sclerostin, but these patients were older and had more reduced kidney function and multivariate analysis demonstrated that lower serum levels of sclerostin was associated with vascular calcifications (32). As a caveat, circulating sclerostin levels reflect sclerostin produced by many different cell types and may therefore not fully represent local expression patterns. Alternatively, sclerostin upregulation could serve as a potential safeguard and negative regulator of vascular calcification and inhibition of sclerostin could therefore theoretically promote vascular calcification. However, in contrast to the latter hypothesis, several preclinical studies investigating long-term effects of sclerostin inhibition in rats (33) and monkeys (34) have consistently demonstrated no histological or radiographic evidence of vascular pathology or calcification. Sclerostin inhibition in ZDF rats with type 2 diabetes mellitus, a known risk factor for vascular disease, did not accelerate vascular disease or calcification, while markedly increasing bone strength and repair (35). In addition, sclerostin inhibition did not affect inflammation, apoptosis, neutrophil recruitment, oxidative stress pathways, or platelet activation in ApoE-deficient, ovariectomized mice (36), an experimental model of concurrent premature vascular disease and osteoporosis.

Other agonists and antagonists of the Wnt pathway have been associated with elements of the atherosclerotic process without establishing a causal relationship (37).

Genetic Evidence for the Effect of Sclerostin on Cardiovascular Outcomes

Patients with sclerosteosis and van Buchem disease have no increased risk of cardiovascular disease. Similarly, increased risk of cardiovascular disease has not been reported in individuals heterozygous for the loss-of-function mutations associated with sclerosteosis and van Buchem (38). As a caveat, these populations are small and individuals are, on average, younger compared with women with postmenopausal osteoporosis.

A mouse model of sclerosteosis, the *SOST* gene knockout mouse was investigated by Li et al (39). Comprehensive characterization of the mouse model replicated the bone phenotype seen in humans with sclerosteosis but did not demonstrate increased vascular calcification.

A third approach to investigate the genetic evidence for an effect of sclerostin on the cardiovascular system is based on commonly occurring variants in the *SOST* and other Wnt pathway genes. The rs2741856 variant in the *SOST* gene is the variant most significantly associated with BMD. The more common C allele is associated with increased BMD, reduced fracture risk, and reduced sclerostin expression in aorta and tibial artery (40, 41). A search through available genome-wide association study databases, including the Gene Atlas and Rapid GWAS and the Global Biobank Engine databases found no detectable effect of this variant on the risk of myocardial infarction or stroke (21). Two other variants in the *SOST* gene; rs7209826, allele frequency 40% and rs188810925, allele frequency 8% in the UK Biobank are associated with increased bone mass and reduced fracture risk (42). Expression of SOST mRNA was lower in different human tissues from individuals carrying these variants (43). These variants have not directly been associated with cardiovascular phenotypes; however, a recent publication using modeling of genetic effects suggested that they may increase the risk of cardiovascular disease (43).

Inactivating mutations in LRP5/6 have been associated with cardiovascular disease or clinical risk factors associated with cardiovascular risk. A G611C mutation in the *LRP6* gene was identified in an Iranian family with early-onset coronary heart disease and osteoporosis. The variant was found to impair Wnt signaling in vitro (44). Thirteen patients, homozygous or heterozygous for inactivating mutations in *LRP5* were found to have low bone mass and

fragility fractures and half of the patients had impaired glucose tolerance test due to impaired beta-cell function, which is a known risk factor for cardiovascular disease (45).

Discussion

The phase III trials in the clinical development program for romosozumab showed consistent results with respect to the effect of romosozumab on bone phenotypes: increased bone formation, suppressed bone resorption, large increases in bone mass, and significant reductions in fracture risk (11, 13-15). Similar findings have been seen with other anti-sclerostin antibodies (23). Romosozumab is generally well tolerated but there is a risk of injection site reactions (11, 13-15).

Cardiovascular safety was investigated in 3 of the 4 phase III trials as preclinical studies had demonstrated expression of sclerostin in the vasculature (16), albeit the expression predominantly was found in the media within vascular smooth muscle cells rather than in the intima. At this location, any potential adverse clinical effect would be expected to be delayed rather than early after treatment initiation, as was seen in the ARCH trial. The adjudication process of the cardiovascular events in the phase III romosozumab studies seems thorough and the outcome was consistent in 2 independent evaluations. The initial adjudication of all death and serious adverse events that by the investigators were evaluated to be of potential cardiovascular origin or etiology were performed by the Duke Clinical Research Institute. When the cardiovascular safety signal was discovered, all adverse event data was assessed by the Thrombolysis and Myocardial Infarction (TIMI) study group. All death and serious adverse events were re-adjudicated, blinded to the prior adjudication by the Duke Clinical Research Institute. The 2 adjudications yielded very similar results. It is therefore unlikely that the findings are incorrect. The interpretation of the results is difficult, however, because of the discrepancy between the findings of the individual trials; an increased risk of cardiovascular events in women treated with romosozumab in ARCH compared to women treated with alendronate (13), whereas the same risk of cardiovascular events was found in women treated with romosozumab and placebo in FRAME (11).

There are 2 important differences between FRAME and ARCH. First, the women in ARCH were older and as such had more comorbidities and concomitant medical treatment, including cardiovascular diseases and treatments at baseline, compared with the women in FRAME (11, 13). This could potentially make the women in ARCH more susceptible to any harmful effect of romosozumab on the cardiovascular system. As expected, the absolute risk of experiencing a cardiovascular adverse event was higher in women with preexisting cardiovascular risk factors or a history of previous cardiovascular events; however, the hazard ratios of cardiovascular adverse events seen in the women treated with romosozumab compared with alendronate were not clearly related to existing cardiovascular risk factors, such as previous myocardial infarction, hypertension, diabetes, and age (21). If the increased incidence of cardiovascular risk seen with romosozumab in ARCH was based on biology, some interaction with these preexisting risk factors for cardiovascular disease might have been expected.

The second important difference between FRAME and ARCH is the comparator; alendronate in ARCH and placebo in FRAME. Another theoretical explanation for the discrepant findings could therefore be that alendronate protects against adverse cardiovascular events. This has previously been suggested in a clinical trial and a retrospective cohort study investigating alendronate (46, 47) and has also been demonstrated in a study investigating the effects of zoledronate, another bisphosphonate. In this latter study including 2000 postmenopausal women with low bone mass who were treated for 6 years with zoledronate, the risk of myocardial infarction was reduced (48). In addition, a network meta-analysis found reduced risk of cardiovascular events in patients treated with bisphosphonate compared with patients treated with denosumab, whereas the risk in patients treated with denosumab was comparable to the risk in patients treated with placebo (49). As part of the assessment of the cardiovascular safety with romosozumab, the Food and Drug Administration (FDA) performed a network meta-analysis of ARCH and FRAME and when comparing the hazard of MACE in the alendronate arm from ARCH with the placebo arm from FRAME, the hazard ratio was 0.55 (0.27-1.14), suggesting a 45% reduction of the risk of MACE in the women treated with alendronate (21). However, other extensive meta-analyses found no evidence that bisphosphonates reduce the risk of cardiovascular events (50, 51) or death (52) compared with placebo. The fact that the incidence rate did not decrease in the women who changed treatment from romosozumab to alendronate after 1 year and that the incidence rate for those continuing on alendronate after the double-blind phase tended to rise toward that of the romosozumab arm in the ARCH study also suggests that a cardioprotective effect of alendronate is an unlikely explanation of the differences in MACE in the ARCH study.

There are pitfalls in overinterpreting imbalances in event rates in clinical trials where event rates are low, event numbers are small, and trials are not powered for safety endpoints. Premature evaluation of the ISIS-2 trial of aspirin in acute myocardial infarction from the 1980s illustrated the danger (53). However, given that the ARCH

findings were seen within the confines of a well-designed clinical trial, cautions in the product information were appropriate. The FDA addressed the issue through a boxed warning not to use romosozumab in patients suffering myocardial infarction or stroke in the preceding year whereas the European Medicines Agency (EMA) has contraindicated the drug in patients with a history of either event regardless of time of onset.

Bovijn et al recently investigated the effect of genetic variants in the *SOST* gene on bone mass, expression of sclerostin and cardiovascular phenotypes. They choose 2 genetic variants in the *SOST* locus, where the minor allele was associated with increased BMD (43). The same variants were associated with lower expression of sclerostin in various human tissue including artery. The authors then calculated a scaling factor in order to make the effect of the genetic variants on heel BMD comparable to the effect of treatment with romosozumab for 1 year and then made 2 assumptions. First, that an effect on BMD of the genetic variant developed over many years including childhood, adolescence, and adult years are comparable to a change obtained during treatment for 1 year. Second, that the scaling factor is the same for all phenotypes of interest, including bone and cardiovascular phenotypes. Using this approach, the authors found that carriers of the variants in the *SOST* gene had a 10% to 18% higher risk of adverse cardiovascular events and a higher risk of having higher systolic blood pressure, higher body mass index, and type 2 diabetes mellitus. The authors suggest that the increased risk of cardiovascular disease in the carriers of these variants were at least in part caused by the increased blood pressure, body mass index, and prevalence of type 2 diabetes; however, none of these phenotypes were affected by treatment with romosozumab in any of the clinical trials. The approach by Bovijn et al, trying to combine genetic, preclinical, and clinical evidence is interesting, but it also carries large risks of misinterpretations due to the many assumptions made. It is surprising why they did not include the rs2741856 variant in the *SOST* gene in the analyses as this is the variant with the most prominent effect on BMD and fracture risk in populations (40, 41). Using this variant would have eliminated the need for a scaling of the effects on other phenotypes as the effect of the variant is of a similar magnitude to what is seen after treatment with romosozumab for one year. No associations have been found between this variant and cardiovascular phenotypes.

At present, there is no biologically plausible explanation from preclinical in vivo studies to suggest that sclerostin is generally vasculoprotective and that inhibition of sclerostin may confer a cardiovascular risk. Across a variety of animal studies, mainly in rats, mice, and monkeys and "experiments of nature" with a small number of patients with (sclerosteosis and van Buchem), reduction of sclerostin bioavailability (due to inhibition or reduced production) did not initiate or propagate vascular disease (21). The rodent models used to test sclerostin inhibition are generally less susceptible to vascular disease unless challenged by diet or when combined with genetic models that increase cardiovascular vulnerability and they are therefore not fully comparable with the risk pattern and biology of postmenopausal women with osteoporosis, a condition shown to be associated with an increased risk of vascular calcifications and adverse cardiovascular events (31, 54).

Romosozumab is approved for treatment of postmenopausal women with severe osteoporosis and is being prescribed for this indication in many countries around the world. Observational studies investigating the clinical efficacy and safety are therefore to be expected. In addition, pharmacovigilance studies agreed on between the authorities and the manufacturer of romosozumab as part of the approval process, with the aim of investigating if the contraindication or precautions are being followed when clinicians are prescribing romosozumab in the clinic and if there is an increased risk of cardiovascular events in women treated with romosozumab, are being conducted or planned in many countries. While waiting for more information about the cardiovascular adverse events potentially associated with the use of romosozumab, clinicians should follow the guidance provided by contraindications and warnings given in the label and carefully evaluate benefits and risks associated with romosozumab treatment in postmenopausal women with severe osteoporosis. This is central to prescribing across all diseases and for the individual patient requires careful evaluation and discussion with the patient about potential morbidity and mortality of major fractures balanced against potential risk of an adverse cardiovascular event. Cardiologists and neurologists may be helpful in evaluating uncertain histories or detailing possible structural abnormalities in heart or brain but cross-referral should be needed in only a minority where real uncertainties persist or where cardiovascular issues dominate the clinical picture. There is some clinical reassurance that throughout the FRAME and ARCH trials in the target population with severe osteoporosis, the reduction in fracture rate exceeded the risk of an adverse cardiovascular event at all time points and this difference widened over time.

There is still a large treatment gap in osteoporosis. This is primarily caused by patients not being diagnosed with osteoporosis or not being offered treatment despite being diagnosed. A considerable part of the gap is caused by patients and physicians refusing treatment because of concerns of adverse events. It is hoped that the recommendations in the recently published American Society for Bone and Mineral

Research–led consensus on prevention on secondary fractures (55) and the labels concerning romosozumab from both FDA and EMA stating that the benefits and risks associated with treatment of osteoporosis should be discussed with the patient before making a treatment decision will help physicians to find the optimal treatment for the individual patient and will reduce the number of patients who decline any treatment.

In conclusion, while there is no preclinical or genetic evidence of a harmful effect of sclerostin inhibition on cardiovascular safety, the evidence from the large clinical trials in postmenopausal women is conflicting. Romosozumab should therefore be used for the treatment of postmenopausal women with osteoporosis at high risk of fracture after appropriate consideration of the cardiovascular risk and the balance between benefits and risks.

Additional Information

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Data Availability: Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

References

1. Ke HZ, Richards WG, Li X, Ominsky MS. Sclerostin and Dickkopf-1 as therapeutic targets in bone diseases. *Endocr Rev*. 2012;**33**(5):747-783.
2. Baron R, Kneissel M. WNT signaling in bone homeostasis and disease: from human mutations to treatments. *Nat Med*. 2013;**19**(2):179-192.
3. Marie PJ, Kassem M. Osteoblasts in osteoporosis: past, emerging, and future anabolic targets. *Eur J Endocrinol*. 2011;**165**(1):1-10.
4. Wijenayaka AR, Kogawa M, Lim HP, Bonewald LF, Findlay DM, Atkins GJ. Sclerostin stimulates osteocyte support of osteoclast activity by a RANKL-dependent pathway. *Plos One*. 2011;**6**(10):e25900.
5. Balemans W, Ebeling M, Patel N, et al. Increased bone density in sclerosteosis is due to the deficiency of a novel secreted protein (SOST). *Hum Mol Genet*. 2001;**10**(5):537-543.
6. Brunkow ME, Gardner JC, Van Ness J, et al. Bone dysplasia sclerosteosis results from loss of the SOST gene product, a novel cystine knot-containing protein. *Am J Hum Genet*. 2001;**68**(3):577-589.
7. Gardner JC, van Bezooijen RL, Mervis B, et al. Bone mineral density in sclerosteosis; affected individuals and gene carriers. *J Clin Endocrinol Metab*. 2005;**90**(12):6392-6395.
8. Consensus development conference: diagnosis, prophylaxis, and treatment of osteoporosis. *Am J Med*. 1993;**94**(6):646-650.
9. Eriksen EF, Hodgson SF, Eastell R, Cedel SL, O'Fallon WM, Riggs BL. Cancellous bone remodeling in type I (postmenopausal) osteoporosis: quantitative assessment of rates of formation, resorption, and bone loss at tissue and cellular levels [see comments]. *J Bone Miner Res*. 1990;**5**(4):311-319.
10. Padhi D, Jang G, Stouch B, Fang L, Posvar E. Single-dose, placebo-controlled, randomized study of AMG 785, a sclerostin monoclonal antibody. *J Bone Miner Res*. 2011;**26**(1):19-26.
11. Cosman F, Crittenden DB, Adachi JD, et al. Romosozumab treatment in postmenopausal women with osteoporosis. *N Engl J Med*. 2016;**375**(16):1532-1543.
12. Lewiecki EM, Dinavahi RV, Lazaretti-Castro M, et al. One Year of romosozumab followed by two years of denosumab maintains fracture risk reductions: results of the FRAME extension study. *J Bone Miner Res*. 2019;**34**(3):419-428.
13. Saag KG, Petersen J, Brandi ML, et al. Romosozumab or Alendronate for Fracture Prevention in Women with Osteoporosis. *N Engl J Med*. 2017;**377**(15):1417-1427.
14. Langdahl BL, Libanati C, Crittenden DB, et al. Romosozumab (sclerostin monoclonal antibody) versus teriparatide in postmenopausal women with osteoporosis transitioning from oral bisphosphonate therapy: a randomised, open-label, phase 3 trial. *Lancet*. 2017;**390**(10102):1585-1594.
15. Lewiecki EM, Blicharski T, Goemaere S, et al. A phase III randomized placebo-controlled trial to evaluate efficacy and safety of romosozumab in men with osteoporosis. *J Clin Endocrinol Metab*. 2018;**103**(9):3183-3193.
16. Zhu D, Mackenzie NC, Millán JL, Farquharson C, MacRae VE. The appearance and modulation of osteocyte marker expression during calcification of vascular smooth muscle cells. *Plos One*. 2011;**6**(5):e19595.
17. Wiviott SD, Raz I, Bonaca MP, et al.; DECLARE–TIMI 58 Investigators. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2019;**380**(4):347-357.
18. Bohula EA, Wiviott SD, McGuire DK, et al.; CAMELLIA–TIMI 61 Steering Committee and Investigators. Cardiovascular safety of lorcaserin in overweight or obese patients. *N Engl J Med*. 2018;**379**(12):1107-1117.
19. Bonaca MP, Bhatt DL, Cohen M, et al.; PEGASUS-TIMI 54 Steering Committee and Investigators. Long-term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med*. 2015;**372**(19):1791-1800.
20. Scirica BM, Bhatt DL, Braunwald E, et al.; SAVOR-TIMI 53 Steering Committee and Investigators. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med*. 2013;**369**(14):1317-1326.
21. Food and Drug Administration. 2019. FDA Briefing Document: Meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee, BLA 761062 Romosozumab, Amgen, Inc. January 16, 2019. https://www.fda,gov/media/121257/download. Accessed October 2, 2020.
22. Cummings SR, McCulloch C. Explanations for the difference in rates of cardiovascular events in a trial of alendronate and romosozumab. *Osteoporos Int*. 2020;**31**(6):1019-1021.
23. Recker RR, Benson CT, Matsumoto T, et al. A randomized, double-blind phase 2 clinical trial of blosozumab, a sclerostin

antibody, in postmenopausal women with low bone mineral density. *J Bone Miner Res*. 2015;**30**(2):216-224.
24. Glorieux FH, Devogelaer JP, Durigova M, et al. BPS804 anti-sclerostin antibody in adults with moderate osteogenesis imperfecta: results of a randomized phase 2a trial. *J Bone Miner Res*. 2017;**32**(7):1496-1504.
25. Seefried L, Baumann J, Hemsley S, et al. Efficacy of anti-sclerostin monoclonal antibody BPS804 in adult patients with hypophosphatasia. *J Clin Invest*. 2017;**127**(6):2148-2158.
26. Didangelos A, Yin X, Mandal K, Baumert M, Jahangiri M, Mayr M. Proteomics characterization of extracellular space components in the human aorta. *Mol Cell Proteomics*. 2010;**9**(9):2048-2062.
27. Brandenburg VM, Kramann R, Koos R, et al. Relationship between sclerostin and cardiovascular calcification in hemodialysis patients: a cross-sectional study. *BMC Nephrol*. 2013;**14**:219.
28. Kramann R, Kunter U, Brandenburg VM, et al. Osteogenesis of heterotopically transplanted mesenchymal stromal cells in rat models of chronic kidney disease. *J Bone Miner Res*. 2013;**28**(12):2523-2534.
29. Rukov JL, Gravesen E, Mace ML, et al. Effect of chronic uremia on the transcriptional profile of the calcified aorta analyzed by RNA sequencing. *Am J Physiol Renal Physiol*. 2016;**310**(6):F477-F491.
30. Holdsworth G, Hall P, van Koeverden L, et al. Sclerostin expression is down-regulated in advanced atherosclerotic plaques and is not associaed with coronary artery disease or peripheral artery disease prior to, or major cardiovascular events in the 3-year period following, surgical endarterectomy. *J Bone Min Res*. 2019;**34**(supplementary 1):Abstract 1086.
31. Hofbauer LC, Brueck CC, Shanahan CM, Schoppet M, Dobnig H. Vascular calcification and osteoporosis–from clinical observation towards molecular understanding. *Osteoporos Int*. 2007;**18**(3):251-259.
32. Claes KJ, Viaene L, Heye S, Meijers B, d'Haese P, Evenepoel P. Sclerostin: Another vascular calcification inhibitor? *J Clin Endocrinol Metab*. 2013;**98**(8):3221-3228.
33. Chouinard L, Felx M, Mellal N, et al. Carcinogenicity risk assessment of romosozumab: A review of scientific weight-of-evidence and findings in a rat lifetime pharmacology study. *Regul Toxicol Pharmacol*. 2016;**81**:212-222.
34. Ominsky MS, Boyd SK, Varela A, et al. Romosozumab improves bone mass and strength while maintaining bone quality in ovariectomized cynomolgus monkeys. *J Bone Miner Res*. 2017;**32**(4):788-801.
35. Hamann C, Rauner M, Höhna Y, et al. Sclerostin antibody treatment improves bone mass, bone strength, and bone defect regeneration in rats with type 2 diabetes mellitus. *J Bone Miner Res*. 2013;**28**(3):627-638.
36. Turk JR, Deaton AM, Yin J, et al. Nonclinical cardiovascular safety evaluation of romosozumab, an inhibitor of sclerostin for the treatment of osteoporosis in postmenopausal women at high risk of fracture. *Regul Toxicol Pharmacol*. 2020;**115**:104697.
37. Catalano A, Bellone F, Morabito N, Corica F. Sclerostin and vascular pathophysiology. *Int J Mol Sci*. 2020;**21**(13):4779.
38. van Lierop AH, Appelman-Dijkstra NM, Papapoulos SE. Sclerostin deficiency in humans. *Bone*. 2017;**96**:51-62.
39. Li X, Ominsky MS, Niu QT, et al. Targeted deletion of the sclerostin gene in mice results in increased bone formation and bone strength. *J Bone Miner Res*. 2008;**23**(6):860-869.
40. Medina-Gomez C, Kemp JP, Trajanoska K, et al. Life-course genome-wide association study meta-analysis of total body BMD and assessment of age-specific effects. *Am J Hum Genet*. 2018;**102**(1):88-102.
41. MacArthur J, Bowler E, Cerezo M, et al. The new NHGRI-EBI catalog of published genome-wide association studies (GWAS Catalog). *Nucleic Acids Res*. 2017;**45**(D1):D896-D901.
42. Kemp JP, Morris JA, Medina-Gomez C, et al. Identification of 153 new loci associated with heel bone mineral density and functional involvement of GPC6 in osteoporosis. *Nat Genet*. 2017;**49**(10):1468-1475.
43. Bovijn J, Krebs K, Chen CY, et al. Evaluating the cardiovascular safety of sclerostin inhibition using evidence from meta-analysis of clinical trials and human genetics. *Sci Transl Med*. 2020;**12**(549):eaay6570.
44. Mani A, Radhakrishnan J, Wang H, et al. LRP6 mutation in a family with early coronary disease and metabolic risk factors. *Science*. 2007;**315**(5816):1278-1282.
45. Saarinen A, Saukkonen T, Kivelä T, et al. Low density lipoprotein receptor-related protein 5 (LRP5) mutations and osteoporosis, impaired glucose metabolism and hypercholesterolaemia. *Clin Endocrinol (Oxf)*. 2010;**72**(4):481-488.
46. Kang JH, Keller JJ, Lin HC. Bisphosphonates reduced the risk of acute myocardial infarction: a 2-year follow-up study. *Osteoporos Int*. 2013;**24**(1):271-277.
47. Sing CW, Wong AY, Kiel DP, et al. Association of alendronate and risk of cardiovascular events in patients with hip fracture. *J Bone Miner Res*. 2018;**33**(8):1422-1434.
48. Reid IR, Horne AM, Mihov B, et al. Fracture prevention with zoledronate in older women with osteopenia. *N Engl J Med*. 2018;**379**(25):2407-2416.
49. Seeto AH, Abrahamsen B, Ebeling PR, Rodriguez AJ. Cardiovascular safety of denosumab across multiple indications: a systematic review and meta-analysis of randomized trials. *J Bone Miner Res*. 2021;36(1):24-40.
50. Kim DH, Rogers JR, Fulchino LA, Kim CA, Solomon DH, Kim SC. Bisphosphonates and risk of cardiovascular events: a meta-analysis. *Plos One*. 2015;**10**(4):e0122646.
51. Kranenburg G, Bartstra JW, Weijmans M, et al. Bisphosphonates for cardiovascular risk reduction: a systematic review and meta-analysis. *Atherosclerosis*. 2016;**252**:106-115.
52. Cummings SR, Lui LY, Eastell R, Allen IE. Association between drug treatments for patients with osteoporosis and overall mortality rates: a meta-analysis. *JAMA Intern Med*. 2019;179(11):1491-1500.
53. Peto R. Current misconception 3: that subgroup-specific trial mortality results often provide a good basis for individualising patient care. *Br J Cancer*. 2011;**104**(7):1057-1058.
54. Tankó LB, Christiansen C, Cox DA, Geiger MJ, McNabb MA, Cummings SR. Relationship between osteoporosis and cardiovascular disease in postmenopausal women. *J Bone Miner Res*. 2005;**20**(11):1912-1920.
55. Conley RB, Adib G, Adler RA, et al. Secondary fracture prevention: consensus clinical recommendations from a multistakeholder coalition. *J Bone Miner Res*. 2020;**35**(1):36-52.