Current Osteoporosis Reports (2021) 19:189–205
https://doi.org/10.1007/s11914-021-00663-1

THERAPEUTICS AND MEDICAL MANAGEMENT (S JAN DE BEUR AND B CLARKE, SECTION EDITORS)

Anabolic Agents for Postmenopausal Osteoporosis: How Do You Choose?

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Accepted: 19 January 2021 / Published online: 26 February 2021

Abstract

Purpose of Review There are now three anabolic agents available for the treatment of postmenopausal women at high risk for fracture. The purpose of this review is to supply a rationale to aid in determining which agent should be used in which clinical settings.

Recent Findings Studies over the last decade have shown that anabolic agents produce faster and larger effects against fracture than antiresorptive agents. Furthermore, trials evaluating anabolic antiresorptive treatment sequences have shown that anabolic first treatment strategies produce the greatest benefits to bone density, particularly in the hip region. However, there are no head-to-head evaluations of the three anabolic therapies with fracture outcomes or bone density, and these studies are not likely to occur. How to decide which agent to use at which time in a woman's life is unknown.

Summary We review the most significant clinical trials of anabolic agents which have assessed fracture, areal or volumetric bone density, microarchitecture, and/or bone strength, as well as information gleaned from histomorphometry studies to provide a rationale for consideration of one agent vs another in various clinical settings. There is no definitive answer to this question; all three agents increase bone strength and reduce fracture risk rapidly. Since the postmenopausal lifespan could be as long as 40–50 years, it is likely that very high-risk women will utilize different anabolic agents at different points in their lives.

Keywords Postmenopausal osteoporosis · Teriparatide · Abaloparatide · Romosozumab · Treatment sequence · Anabolic

Introduction

Recent data from pivotal anabolic trials and comparative studies of anabolic and antiresorptive agents have shown greater and faster antifracture efficacy with anabolic compared with antiresorptive medications and have provided a clear rationale for the initial use of anabolic therapy in patients at high imminent risk for fracture [1–7], including patients with recent or multiple clinical fractures [8–12] and subclinical radiographic vertebral fractures [13, 14]. This evidence is supported by observations indicating that an anabolic first treatment sequence is important in order to attain the highest BMD levels, particularly in the hip [15, 16]; total hip BMD during or after treatment has emerged as a major predictor of future risk of both nonvertebral and vertebral fractures [17–20]. A goal-directed treatment task force concluded that achievement of t score levels above -2.5, is an important target for osteoporosis treatment [21]. For patients who present with BMD levels where there is a low probability that that target t score can be achieved within a 3-year period using antiresorptive medication, anabolic agents should be considered first-line therapy [22].

The existing guidelines, at least from the endocrine community are evolving toward this more proactive view of anabolic

This article is part of the Topical Collection on *Therapeutics and Medical Management*

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therapy [23–25], but certainly do not provide criteria to guide *what* anabolic agent should actually be utilized of the three available in the USA. Aside from the ACTIVE trial which compared abaloparatide and teriparatide directly [3], and a phase 2 study which evaluated the BMD effects of romosozumab with teriparatide [26], there are no other clinical trials which compare anabolic agents in head to head investigations. Therefore, there is little evidence base to guide this decision. Furthermore, it is unlikely that we will ever have this evidence.

In this paper, we review the efficacy and safety data for the three FDA-approved anabolic agents at their FDA-approved doses. We also review the underlying mechanism of action for each of the compounds, including knowledge gleaned from histomorphometric studies. Then we apply the information available to address various clinical scenarios that might help provide a rationale for choosing one medication over another. Much of the discussion is theoretical and cost is not considered.

Mechanism of Action of Anabolic Agents

Molecular Mechanism of Action

All three currently approved osteoanabolic agents work by signaling through the canonical Wnt/beta-catenin pathway. Wnt proteins are secreted proteins that are known to regulate the differentiation, growth, function, and death of cells in many tissues. The involvement of Wnt signaling in bone formation was recognized with the discovery that specific mutations in the Wnt coreceptor low-density lipoprotein receptor–related protein 5 (LRP5) caused high and low bone mass syndromes [27].

Both teriparatide and abaloparatide activate Wnt signaling by binding to the parathyroid hormone receptor type 1 (PTHR1) on osteoblasts and osteocytes. Activation of PTH1R signaling in osteoblasts and osteocytes leads to a cascade of downstream effects with one of the key effects being downregulation of sclerostin expression in osteocytes. Sclerostin acts as a potent inhibitor of Wnt/beta-catenin signaling by preventing binding of Wnt proteins to its coreceptors LRP5 and Frizzled. The Wnt/beta-catenin pathway is therefore activated by removal of this inhibitor. In vitro studies have shown that PTHR1 has two high-affinity conformations: the G protein–independent R0 confirmation and the G protein–dependent RG conformation. Binding to R0 results in prolonged cyclic AMP signaling, which stimulates resorption as well as formation. In contrast, binding to RG results in more transient cyclic AMP signaling responses, which favor bone formation. Abaloparatide apparently binds more selectively to the RG conformation of PTH1R than teriparatide [28].

Romosozumab also activates the Wnt/beta-catenin pathway by lowering sclerostin activity, but not through a receptor-mediated mechanism. Romosozumab is a humanized monoclonal antibody to sclerostin. One of the important differences in activating Wnt/beta-catenin signaling via the receptor-mediated mechanism, in contrast to the sclerostin antibody mechanism, is the effect on bone resorption. Both teriparatide and abaloparatide stimulate resorption by increasing receptor activator of nuclear factor kappa-B ligand (RANKL) and lowering osteoprotogerin (OPG) directly through PTH1R activation, even though sclerostin expression is inhibited. Endogenously produced sclerostin stimulates bone resorption through an autologous effect on osteocyte RANKL production. Since the sole effect of romosozumab is to inhibit sclerostin activity, romosozumab has a suppressive effect on resorption. Thus, abaloparatide and teriparatide can be classified as pro-remodeling osteoanabolic agents, whereas romosozumab is best considered to be a dual-action osteoanabolic agent in that it stimulates formation and, to a lesser extent, inhibits resorption.

Bone Histomorphometry

Osteoanabolic agents can be defined as drugs which increase bone mass by increasing the rate of new bone formation [29]. Their mechanism of action is, therefore, fundamentally different from antiresorptive drugs, which reduce both resorption and formation rates [30]. Of the three currently approved agents in the osteoanabolic class, teriparatide is the most extensively studied by bone histomorphometry.

Teriparatide In the late 1990s, our group conducted paired biopsy studies in eight osteoporotic men treated with teriparatide for 18 months and eight osteoporotic, postmenopausal women treated with teriparatide and concomitant HT for 3 years [31, 32]. The effects of monotherapy with teriparatide on iliac crest bone biopsies were also studied in women who participated in the Fracture Prevention Trial [2, 33–36]. In order to understand the cellular mechanisms underlying teriparatide's early actions on bone, several studies utilized a quadruple tetracycline labeling regimen where patients were double-labeled prior to treatment and then double-labeled again during teriparatide treatment, immediately prior to biopsy [37–39]. This approach permits bone formation parameters to be measured at the same sites before and after treatment within one biopsy. To differentiate the mechanism of action of teriparatide from that of antiresorptive therapies, comparative studies were performed with alendronate, zoledronic acid and denosumab [40–45]. In the first histomorphometric study to investigate the effects of any osteoporosis drug on the human femoral neck, Cosman et al. [46•] investigated the early effects of teriparatide in patients undergoing total hip replacement. Recently, a follow-up study characterized the influence of loading modality and age in the femur neck on the response to teriparatide [47].

Taken together, the histomorphometric studies indicate that the initial response to daily teriparatide treatment, which can

be observed as early as 4 weeks, consists of increased osteoblastic bone formation achieved by an increase in the extent of the bone-forming surface as well as an increase in the linear rate of mineral apposition [37, 48, 49]. Teriparatide initially stimulates bone formation in and adjacent to bone remodeling units that were active before the onset of treatment [37, 43, 44] by stimulating the activity of preexisting osteoblasts, and/or by enhanced recruitment of osteoblasts to preexisting bone-forming sites, and/or by increasing osteoblast longevity [50]. Although most of the new bone formation that is stimulated by teriparatide treatment (~ 70%) occurs over scalloped reversal lines, indicating prior resorption and, therefore, remodeling-based bone formation, there is evidence for formation on previously quiescent surfaces with smooth cement lines, i.e. modeling-based formation [36, 37, 43, 44]. Furthermore, stimulation of both remodeling- and modeling-based formation was observed in the femoral neck of teriparatide-treated subjects after just 6 weeks [51].

Although increased bone formation usually precedes increased remodeling activation with teriparatide, one study showed evidence of increased eroded surface and osteoclast number as early as 28 days [48], although this study used a higher dose than that eventually approved. Increased remodeling indices were also observed following 3 months [38] and 6 months of treatment [39–42, 52], however, they tended to return toward pretreatment values after 12 to 36 months [31, 42, 53]. The temporal pattern of the changes in the morphometric variables of bone remodeling in the iliac crest mirrors that observed with biochemical markers [38, 40, 54–57].

At the structural level, teriparatide-stimulated bone formation leads to an increase in the wall thickness of bone packets on both cancellous and endocortical surfaces, which accounts for the reported increases in cancellous bone volume and cortical thickness [31, 36, 49, 52, 58]. Structural improvement is also confirmed by 3D micro-CT measurements showing increased cancellous bone volume and trabecular connectivity, with a shift toward a more plate-like structure, and increased cortical thickness [31, 34]. Improvements in bone structure following 22 months of teriparatide treatment correlated with the changes in biochemical markers of bone formation at 1 month [33]. Moreover, teriparatide treatment increased the proportion of bone matrix with lower mineralization density, mineral crystallinity, and collagen cross-link ratio, all of which are characteristic of newly formed, younger bone [32, 35]. There is also evidence for an improvement in collagen orientation with teriparatide treatment [59].

While the earlier histomorphometric studies tended to focus exclusively on cancellous bone, later studies also included assessments of endocortical, intracortical, and periosteal compartments and there is now ample evidence that teriparatide stimulates formation on all four bone surfaces [38, 41–44]. Although the concept that teriparatide stimulated formation on the periosteal surface was for some time controversial, quadruple labeling studies provided the most convincing evidence to date that indeed it does [38, 44]. However, the amount of increased formation on the periosteal surface—at least in the iliac crest—is much less than that seen on the other 3 envelopes. Early hopes that this may increase the external diameter of bone in humans and thereby lead to a disproportionate increase in buckling strength were not fulfilled [60, 61]. Nevertheless, one could speculate that any formation on the periosteum may have a salutary effect on bone strength, particularly in focal regions where the cortex is very thin and porous [62]. Smoothing of defects on the periosteal surface could theoretically prevent cracks from developing and propagating.

Abaloparatide Iliac crest bone biopsies were obtained in a subset of patients ($n = 105$) treated with placebo, abaloparatide, or teriparatide for between 12 and 18 months in the ACTIVE trial [3, 63]. Somewhat unexpectedly, measurement of a standard panel of static, dynamic, and structural histomorphometric indices in 78 evaluable specimens revealed only a few significant differences among the three treatment groups; mineral apposition rate with teriparatide was greater than with placebo, eroded surface was lower with abaloparatide than placebo, and cortical porosity was significantly higher with both abaloparatide and teriparatide compared with placebo (numerically higher with teriparatide compared with abaloparatide). The observation that there were no significant differences in the bone formation rate and activation frequency among the three treatment groups may at first seem surprising, given the osteoanabolic nature of abaloparatide and teriparatide. However, this finding is consistent with those from several previous histomorphometric studies with similar duration of teriparatide [31, 34]. Increases in cancellous bone formation rate with teriparatide treatment have been seen primarily during early treatment [37, 39, 42, 43]. Consistently, treatment with teriparatide for 6 months resulted in a higher activation frequency in cancellous bone than treatment for 18 months [40]. In a more recent, paired biopsy study [42], although the bone formation rate remained constant in cancellous bone between 6 and 24 months, it declined during this interval in the endocortical and intracortical envelopes. Nevertheless, the bone formation rate in endocortical and intracortical bone was still higher, even at 24 months, than it was in cancellous bone, indicating that the majority of bone formed with teriparatide is likely in these envelopes, not in cancellous bone tissue. Unfortunately, analyses of the biopsies performed in ACTIVE considered only cancellous bone, with measurements in cortical bone limited to cortical porosity. The absence of a measurable elevation in cancellous bone formation rate and activation frequency at 12–18 months in the ACTIVE trial is consistent with temporal changes in the biochemical markers in which serum PINP level peaked early and then declined in both the abaloparatide and teriparatide groups [3]. However, the

persistent elevations in PINP at 18 months in ACTIVE (30% elevated above baseline with abaloparatide) are likely due to persistent bone formation stimulation in endocortical, intracortical, and periosteal envelopes. Supporting this concept, Dempster et al. [64] recently reported that a 3-month treatment with abaloparatide induced a marked increase in both remodeling- and modeling-based formation in the iliac crest and the increments in bone formation rate were highly correlated with those in serum PINP. With 3 months of abaloparatide, bone formation was increased on cancellous, endocortical, intracortical, and periosteal envelopes. The magnitude of the increase in periosteal bone formation rate appeared approximately 2-fold greater with abaloparatide than in a study of identical design with teriparatide [38].

One theoretical beneficial effect of pro-remodeling anabolic agents is that they can replace dead or moribund osteocytes with new, healthy osteocytes, which could have an expected life span of decades. Given the fundamental importance of osteocyte viability to bone health and, indeed to extraskeletal mineral metabolism, this effect could be very important. However, data supporting this concept are still lacking.

Romosozumab Bone biopsies were performed in the FRAME study at 2 months (following quadruple labeling) and at 12 months with standard double labeling [65]. The 2-month biopsies showed a significant increase in the bone formation rate in the cancellous and endocortical envelopes in the romosozumab group compared with placebo, but at 12 months, the bone formation rate was lower in the romosozumab group than in placebo. This was consistent with the temporal pattern seen with serum PINP, which peaked early and declined to baseline by 9 months [4, 6]. A trend toward an increase in periosteal bone formation rate was seen at 2 months, but this was not statistically significant. The increments in the bone formation rate in the endocortical envelope were quite similar (≈ 5-fold) with romosozumab, teriparatide, and abaloparatide at similar time points (2–3 months) [38, 64, 65].

At 12 months, when compared with placebo, romosozumab treatment lowered resorption parameters, including eroded surface and osteoclast surface and number, at 2 and 12 months, consistent with the demonstrated early and persistent decline in biochemical markers of resorption [4, 6]. Although cortical porosity was numerically lower with romosozumab vs placebo, the difference was not significant, perhaps due to the modest-moderate potency of the antiresorptive effect. In addition, the baseline level of cortical porosity in older women with osteoporosis is in general much greater than the reduction in cortical porosity that can be measured in bone biopsy specimens, even with the most potent antiresorptive agents. For example, in the FREEDOM trial [66] when compared with placebo, a small, but statistically significant reduction in cortical porosity was seen in the 2-year, but not in the 3-year, biopsies. Microcomputed tomography of bone biopsies after 12 months of romosozumab treatment revealed superior cancellous bone volume and cancellous microstructure (improved trabecular plate structure and prominent increase in trabecular thickness), as well as increased cortical thickness with romosozumab vs placebo [65]. As the early increase in bone formation with romosozumab is accompanied by a decrease in bone resorption, one would anticipate that the bulk of the increased formation would be in the form of modeling-based formation and this has recently been confirmed [67]. However, in contrast to teriparatide and abaloparatide, romosozumab did not increase bone formation in the periosteal surface or intracortical envelopes [65].

As mentioned above, romosozumab is a dual-action anabolic drug and, unlike teriparatide and abaloparatide, does not stimulate remodeling and therefore cannot replace old osteocytes with new. However, romosozumab will still add new osteocytes to the skeleton within the bone that is formed by modeling-based formation. Moreover, a course of romosozumab can still be followed by or preceded by a pro-remodeling anabolic drug to get the maximum, long-term advantages of the two types of anabolic agents currently available. The optimal time interval between discrete courses of anabolic therapy is not known at this time, however, it is probably not advisable to use the anabolic agents sequentially since a common feature to all three osteoanabolic agents is that the anabolic effect declines with time on treatment. Although this is consistent with the concept of a "mechanostat" [68], the mechanisms underlying this effect are not clear. At the cellular level, there is evidence that bone formation declines due to depletion of the osteoblast precursor pool [69, 70]. Alternatively, this could be due to mechanically driven downregulation of Wnt signaling [71]. As a result, sequential use of anabolic agents might result in a suboptimal effect of the second medication.

Summary of Histomorphometric Effects Abaloparatide, Teriparatide, and Romosozumab Cortical porosity increases with both abaloparatide and teriparatide (probably less with abaloparatide than teriparatide) but does not change with romosozumab. Bone formation rate increases on the periosteal surface with abaloparatide and teriparatide (more with abaloparatide vs teriparatide). There is an increase in bone formation rate at an early time point (2–3 months) in both cancellous and cortical bone envelopes with all three medications, but bone formation remains elevated for a longer time with teriparatide (up to 24 months) and presumably abaloparatide (though currently not confirmed). With romosozumab, bone formation rate is below baseline at 12 months (consistent with its antiresorptive effect). Cortical thickness is increased and cancellous microarchitecture is improved with all three medications.

Efficacy and Safety Overview for Anabolic Agents

All three anabolic agents increase biochemical and histomorphometric indices of bone formation, improve spine and hip BMD to varying degrees and reduce vertebral and nonvertebral fracture risk to varying degrees within 12–19 months. In this section, we overview the fracture and BMD data from key studies for each agent, followed by a review of the safety profiles.

Teriparatide Efficacy

In the pivotal teriparatide trial, 1637 women with osteoporosis (mean age 69), all of whom had prevalent vertebral fracture, were randomized to receive either 20 or 40 μg teriparatide or placebo by daily subcutaneous injection [2]. The planned 3-year trial was stopped early after a median treatment time of 19 months due to the increased risk of osteosarcoma seen in rodent toxicology studies [72, 73]. Since the 40 μg teriparatide dose was associated with more hypercalcemia and no greater antifracture efficacy, only the 20-μg dose was FDA approved. Over 19 months, teriparatide 20 μg increased BMD of the spine by 9.7% and total hip by 2.6%. Vertebral fracture risk was reduced 65% with teriparatide, with greater reductions in multiple vertebral fractures and vertebral fractures of moderate and severe degree. Incident nonvertebral fractures were reduced by 35% for all and by 50% for those defined as fragility fractures [2].

Several smaller studies compared teriparatide with bisphosphonates where fracture outcomes were provided (although not the primary outcomes). In 428 patients with glucocorticoid-induced osteoporosis, the incidence of vertebral fractures was 90% lower with teriparatide compared with alendronate over 18 months [74], although there was no group difference in nonvertebral fracture incidence. In 710 patients with back pain related to osteoporotic vertebral fractures [75], the incidence of recurrent vertebral fractures over 1 year was 50% lower with teriparatide vs risedronate, though again there was no difference in nonvertebral fracture incidence. In an older, smaller study of 203 women designed to assess mechanistic differences between alendronate and teriparatide, there was no difference in the small number of clinical fractures but spine x-rays to evaluate vertebral fractures were not performed [55]. In a study of 224 patients who had recently suffered a hip fracture comparing teriparatide with risedronate on fracture healing, incident nonvertebral and hip fracture risks were numerically lower with teriparatide; spine x-rays were not done routinely [76].

The Vertebral Fracture Treatment Comparisons in Osteoporotic Women (VERO) study randomized 1360 women with prevalent vertebral fracture (mean age 73) to receive teriparatide 20 μg daily or risedronate 35 mg weekly for 2 years [5•] and was designed to evaluate the group difference in vertebral fracture incidence as the primary outcome. Compared with risedronate, teriparatide reduced vertebral fracture incidence by 50% within 1 year ($P = .01$) and trended toward reduced nonvertebral fracture incidence ($P = .099$) over 2 years. More women on risedronate had multiple nonvertebral fractures so the number of nonvertebral fractures was 44% lower in women assigned to teriparatide ($P < 0.02$).

Abaloparatide Efficacy

The abaloparatide pivotal trial (Abaloparatide Comparator Trial in Vertebral Endpoints; ACTIVE) enrolled 2463 women with osteoporosis (mean age 69) of whom approximately 25% had prevalent vertebral fracture and 30% had prior nonvertebral fracture. Participants were randomized to receive blinded abaloparatide 80 μg or matching placebo, or open-label teriparatide 20 μg daily subcutaneously for 18 months [3]. At 18 months, spine BMD increments were 11.2% with abaloparatide and 10.5% with teriparatide (no group difference). At the total hip and femoral neck, BMD increments were larger with abaloparatide vs teriparatide from 6 months onward; at 18 months, total hip BMD had increased 4.2% with abaloparatide and 3.3% with teriparatide ($P < 0.01$ treatment group difference). New vertebral fracture incidence was 86% lower for abaloparatide and 80% lower for teriparatide compared with the placebo group (both $P < .001$ vs. placebo). Over 18 months, nonvertebral fracture risk reductions were 43% with abaloparatide ($P < 0.05$ vs placebo) and 28% with teriparatide ($P = 0.22$ vs placebo), though there was no significant difference in nonvertebral fracture incidence between abaloparatide and teriparatide groups.

In a post hoc analysis of the ACTIVE and ACTIVE Extension trials [7], vertebral fracture rate was 2.5 new vertebral fractures per 100 patient-years with placebo and 0.5 per 100 patient-years with abaloparatide. After the placebo group transitioned to alendronate in the extension study [77, 78], alendronate reduced the rate of new vertebral fracture to 1.7 vertebral fractures per 100 patient-years. Although both abaloparatide and alendronate reduced vertebral fractures compared with placebo, abaloparatide reduced new vertebral fractures by 71% compared with alendronate. There was also a trend toward lower incident nonvertebral fracture with abaloparatide versus alendronate (rate 45% lower with abaloparatide; $P = 0.11$).

Teriparatide and Abaloparatide Safety

Rodents who received high-dose long-term treatment with either teriparatide or abaloparatide had an increased risk of osteosarcoma [72, 73, 79]; however, no increased osteosarcoma risk with teriparatide has been seen in primates [80] or in long-term surveillance of patients [81–83]. Nevertheless,

these agents are not recommended for individuals who are at underlying elevated risk for osteosarcoma, including those with a personal or family history of osteosarcoma, those who have had radiation involving the skeleton and patients with Paget's disease. Furthermore, because these PTH receptor type 1 (PTHR1) agonists stimulate bone remodeling, they are not appropriate for individuals who have a primary tumor which has metastasized to bone. For 18 years, the US Food and Drug Administration (FDA) guidance suggested clinical use of PTHR1 agonists be limited to a total cumulative period of no more than 2 years. In November of 2020, the boxed warning concerning the potential risk for osteosarcoma was removed from the branded teriparatide label and the 24-month cumulative use restriction was lifted. There has been no change to the abaloparatide label (as of January 2021). Both teriparatide and abaloparatide have potential to increase serum calcium levels and should not be used in hypercalcemic states such as primary hyperparathyroidism. Potential side effects include symptoms associated with mild vasodilation and mild orthostatic hypotension, such as dizziness, palpitations, nausea, and headache. A modest increase in urinary calcium can be seen, and patients with recent or multiple renal calculi should be assessed prior to starting either of these agents.

Romosozumab Efficacy

The Fracture Study in Postmenopausal Women with Osteoporosis (FRAME) randomized 7180 women with osteoporosis (mean age 74), 20% of whom had prevalent vertebral or history of nonvertebral fracture, to receive blinded romosozumab 210 mg once monthly subcutaneously versus placebo for 1 year followed by open-label denosumab for the second year of the trial [4]. With romosozumab, BMD increments at 1 year averaged 13.3% in the spine and 6.8% in the total hip. Romosozumab reduced new vertebral fractures by 73% compared with placebo at 12 months ($P < 0.001$) and by 75% over 24 months in women who received romosozumab first compared with placebo for 1 year followed by denosumab from 12 to 24 months ($P < 0.001$). At 12 months, there was a trend ($P = 0.096$) toward reduced nonvertebral fractures with romosozumab compared with placebo. In prespecified subgroup analyses, a significant geographical region-by-treatment effect was seen in the Latin American cohort [84] with a very low placebo group nonvertebral fracture rate and no nonvertebral fracture risk reduction with romosozumab. In the rest of the world FRAME population, which was grouped post hoc, romosozumab reduced nonvertebral fracture risk by 42% ($P = 0.012$).

In the Active Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk (ARCH) study [6•], 4093 women with prevalent vertebral fracture or recent hip fracture (mean age 74) were randomized to receive blinded romosozumab 210 mg once monthly or alendronate 70 mg once weekly for 1 year. All women then received alendronate for the remainder of the event-driven trial (median treatment 33 months). Fracture risk reductions with romosozumab versus alendronate were already apparent at 12 months: new vertebral fracture incidence was reduced by 37% ($P = 0.003$) and nonvertebral fracture incidence reduced by 26% ($P = 0.06$). At the primary endpoint of 24 months, new vertebral fracture risk was reduced by 48% ($P < .001$) in patients treated with romosozumab followed by alendronate versus alendronate alone. Similarly, at the end of the study (another primary analysis endpoint), nonvertebral fractures were reduced by 19% ($P < 0.04$) and hip fractures reduced by 38% ($P < 0.02$) in patients who received romosozumab first followed by alendronate, compared with those who received only alendronate.

Romosozumab Safety

In the ARCH study, the risk of all serious cardiovascular events did not differ significantly with romosozumab vs alendronate (incidence 2.5% vs 1.9%), however major adverse cardiac events (MACE; the composite of myocardial infarction, cerebrovascular accident, and cardiac death) were more common with romosozumab than with alendronate over 12 months (2% vs 1.1%). In contrast, there was no imbalance in the larger FRAME trial, where romosozumab was compared with placebo. Given the difference in cardiovascular findings from the two pivotal studies and the pattern of the events, it is very possible that the MACE imbalance was due to chance [85•]. This is consistent with the lack of preclinical evidence for an impact of sclerostin inhibition on cardiovascular function, calcification or atheroprogression [86], although in a study of genetic variants which model pharmacologic sclerostin inhibition, cardiovascular disease risk was increased [87]. Currently, FDA guidance suggests that romosozumab not be administered to patients who have had a heart attack or stroke within the preceding year. Treatment with romosozumab can be associated with hypocalcemia and hypersensitivity reactions, particularly of the skin. Mild injection site reactions have been observed.

Determining Which Anabolic to Use

Clearly, individual patient considerations, such as comfort with daily injections at home, vs monthly visits to a medical facility, must be considered when choosing which anabolic agent to utilize. Cost and insurance coverage are also key factors that affect this decision-making; those factors will not be considered here. In this section, we use the data available to help determine which patient types would be better candidates for one anabolic agent vs another based on efficacy and safety outcomes. The patient types considered here are

defined by information routinely ascertained during the clinical evaluation of almost any high-risk patient with osteoporosis. Patient types considered include women with:

- underlying comorbidities
- advanced age
- prevalent vertebral fracture, very low spine BMD, and/or degraded trabecular bone score (TBS)
- prior nonvertebral or hip fracture and/or very low hip BMD
- on bisphosphonate or denosumab treatment
- low baseline biochemical turnover marker levels or high FRAX scores.

To address each of these patient types, we considered data from the main fracture trials, DXA BMD, and information from other imaging techniques, including TBS, both central and high-resolution peripheral quantitative computed tomography (QCT) and finite element analyses of bone strength. Where applicable, we also considered the potential theoretical benefits of each agent with respect to mechanism of action and dynamic and structural indices assessed histomorphometrically.

Patients with Underlying Comorbidities

Due to the rodent osteosarcoma findings with PTH1R agonists, women who have an elevated risk for osteosarcoma should not be treated with teriparatide or abaloparatide. Because romosozumab has not been shown to increase rodent osteosarcoma risk, it can be given to patients at elevated risk for osteosarcoma.

Since teriparatide and abaloparatide increase risk of hypercalcemia, patients with baseline hypercalcemia are better treated with romosozumab. Women who have had a recent heart attack or stroke (or unstable ischemic angina or transient ischemic attack) should not be treated with romosozumab; however, these patients can receive teriparatide or abaloparatide [2, 5, 88]. Women who have drug related adverse reactions to teriparatide may be able to tolerate abaloparatide or can be offered romosozumab and women who have adverse reactions to romosozumab can be treated with teriparatide or abaloparatide. Hypersensitivity to romosozumab is not predictive of hypersensitivity to teriparatide or abaloparatide.

The presence of underlying chronic kidney disease does not provide a rationale for choosing one agent over another. In the ACTIVE study, vertebral fracture risk reduction and BMD gain at spine and hip were robust with abaloparatide, without meaningful differences in efficacy or safety as a function of baseline renal function [89]. Similarly, with romosozumab in ARCH, the magnitude of vertebral fracture risk reduction and BMD gain between romosozumab and alendronate groups did not differ by baseline GFR, though the population with low GFR was limited by inclusion criteria (>35 ml/min) [90]. In FRAME, BMD gain and vertebral fracture risk reductions were robust across GFR categories, though there was a significant interaction reported for spine and total hip BMD [91].

Abaloparatide and teriparatide effects were assessed in the diabetic cohort of the ACTIVE trial, which included 198 women divided among the three treatment arms [92]. BMD gains at spine and total hip were similar in the diabetic cohort to those seen in the full ACTIVE population and there were significant TBS improvements at 18 months with both abaloparatide and teriparatide (numerically greater with abaloparatide). Fracture numbers were overall low, but consistently numerically lower with abaloparatide and teriparatide vs placebo. No data have yet been published exploring the efficacy of romosozumab in patients with diabetes.

Although ACTIVE, FRAME, and ARCH excluded patients on glucocorticoids at the time of enrollment, the VERO trial included about 10% of patients on glucocorticoids at study enrollment [5, 93]. There was no difference in relative benefit of teriparatide vs risedronate in the subgroup of women on glucocorticoids compared with those not treated with glucocorticoids.

Conclusion Aside from specific contraindications for each anabolic medication, other underlying chronic diseases do not provide a rationale for choosing one medication over another, however, a comprehensive assessment of efficacy and safety in the diabetic population has not yet been completed for romosozumab.

Advanced Age

The pivotal trials enrolled postmenopausal women with broad age ranges: 42–86 years for teriparatide, 49–86 years for abaloparatide and 55–90 years of age for romosozumab. In a subgroup analysis from the teriparatide trial, comparing women < 65, 65–75, and > 75 years of age, there was no interaction between age and fracture risk reduction or BMD gain [94]. The VERO study enrolled postmenopausal women above the age of 45, including about 30% below age 69 and 30% above 77 years of age. In prospectively designed subgroup analyses, there was no difference in the relative efficacy of teriparatide vs risedronate on fracture reduction in those with advanced age vs younger women [93]. In the prespecified subgroup analysis from the ACTIVE trial, which included 20% of patients ≥ 75 years and almost 20% below age 65 years, there were no significant interactions between treatment and age category (below 65, 65–75, and > 75 years) for fracture protection or BMD gain [95]. In another investigation of abaloparatide in advanced age from the ACTIVE study, in the 94 participants who were aged 80 years and older, BMD increments with abaloparatide vs placebo were similar to those seen in the full population [96].

In the FRAME trial, 31% of patients were above the age of 75 and about 20% below the age of 65; prespecified subgroup analyses indicated no interactions between age and treatment effects [4].

Therefore, the clinical trial data do not seem to support the view that one agent should be chosen over another on the basis of greater or lesser effectiveness at older or younger age. However, it could be argued that given the association between incidence and prevalence of fractures with advancing age [97], the most potent agent, should be used in older individuals. One skeletal contribution to hip fracture risk in aged women, beyond BMD, is cortical architecture, including width, thickness, and porosity. All three anabolic agents increase cortical width and thickness to a similar degree [31, 34, 63, 65]; however, teriparatide also increases cortical porosity. This latter effect is primarily on the inner aspect of the cortex, however, which has a minimal effect on bone strength. Nevertheless, it is possible that teriparatide's impact on cortical porosity might reduce the early impact of teriparatide on cortical strength and delay its effect against hip and other nonvertebral fractures. Since abaloparatide stimulates remodeling less than teriparatide, it might have a superior effect on cortical microstructure, although (as noted above) there was no difference in cortical porosity in iliac crest biopsies comparing the drugs in the ACTIVE trial [63]. Even with romosozumab, which has a moderate antiresorptive effect, there were no significant differences in cortical porosity on biopsies obtained from women on romosozumab compared with placebo [65]. This could be related to the short time frame for assessment (1 year) or the potency of the antiresorptive effect. However, as mentioned above, differences in cortical porosity are difficult to demonstrate even with the most potent antiresorptive agents, such as denosumab [66].

On the other hand, since older individuals on average have older bone and older osteocytes with microcracks and other age-associated microdamage [98], there could be a theoretical advantage of a pro-remodeling agent to replace this older tissue with new bone. If this thesis is true, teriparatide might have the greatest potential benefit since it stimulates bone remodeling to the largest extent, with abaloparatide as the close second agent. Romosozumab would have the least effect on replacing old bone with new due to its intrinsic antiresorptive properties. How much of an influence on bone strength could be expected through this mechanism, in contrast to the known impact of bone mass and density is unknown. Furthermore, even a temporary increase in bone remodeling associated with cortical porosity as remodeling is stimulated, might be disadvantageous, particularly to older women at high imminent risk of fracture.

Conclusion It is possible that romosozumab might have some advantage over teriparatide and perhaps even abaloparatide in very aged women, particularly in those with more severe cortical bone abnormalities. The best scenario might be treatment of these women at an earlier age with abaloparatide (or teriparatide) to renew and replace some of the older bone tissue and older osteocytes, followed by later use of romosozumab to add more new bone on top of the already "renewed" bone associated with abaloparatide (or teriparatide).

Patients with Prevalent Vertebral Fracture, Very Low Spine BMD, and/or Highly Degraded TBS

For teriparatide, fracture and BMD outcomes did not differ in subgroups defined by number or severity of prior vertebral fractures in the pivotal study [94] or in the VERO trial [5, 93]. In ACTIVE, where approximately 25% of women had prevalent vertebral fracture at study baseline, prespecified evaluations of treatment effects on both incident fracture and BMD revealed no significant treatment subgroup interactions based on presence (vs absence) of baseline fracture [95]. In FRAME, about 20% of the population had prevalent vertebral fracture at baseline and treatment effect did not differ by presence of fracture in pre-planned subgroup analysis [4]. In ARCH, 96% of the patients had prevalent vertebral fracture; no subgroup analyses have been published evaluating any potential treatment interaction based on number or severity. The same studies also suggest that fracture outcomes for all three agents did not differ based on baseline spine BMD [4, 5, 93–96].

Even though all three agents work to reduce the risk of subsequent radiographic vertebral fracture regardless of the presence or absence of vertebral fracture at study baseline, the subsequent absolute risk of vertebral fracture is much higher in women with prevalent fracture [13]. When comparing across pivotal trials, the magnitude of the relative risk reduction in radiographic vertebral fracture (in the ACTIVE trial) appears slightly larger with abaloparatide and teriparatide vs placebo, in comparison with the relative reduction seen with romosozumab vs placebo [3, 4]. If that is true, it might be logical in patients who are at particularly high risk for subsequent vertebral fracture (including those with prevalent vertebral fractures that are recent, multiple, or more severe) to be offered treatment with abaloparatide or teriparatide. Abaloparatide and teriparatide appear quite similar to each other with respect to reducing vertebral fractures (relative risk reductions for vertebral fracture in ACTIVE are very similar at 80–86% [3]).

In general, treatment outcomes are also similar when considering clinically diagnosed vertebral fractures compared with radiographically diagnosed vertebral fractures, although clinical fractures are much less common (often no more than 20% of the total number of vertebral fractures) [13]. Over 12 months in the FRAME trial [4], there were 59 (1.8%) radiographic vertebral fractures in the placebo group and 16 (0.5%) in the romosozumab group. Over the same time

period, there were 119 instances of back pain thought possibly related to vertebral fracture; radiographs confirmed a vertebral fracture in 20 of the cases of which 17 were in the placebo group and only 3 in the romosozumab group; relative risk reduction for clinical vertebral fracture was 83% [99]. In the ACTIVE trial, there were 9 clinical vertebral fractures in the placebo group (incidence 1.1%), 1 in the abaloparatide group (0.1%), and 3 in the teriparatide (0.4%) group [3], consistent with a 90% reduction in the incidence of clinical vertebral fractures with abaloparatide.

Spine BMD does increase substantially with all three agents, but even more with romosozumab than abaloparatide or teriparatide. Although this might suggest that romosozumab might be a better choice in the setting of prevalent vertebral fracture or very low spine BMD, the fracture data reviewed above are not supportive of a superior benefit of romosozumab. This might be because spine strength, assessed using finite element analyses of QCT data, have shown that spine strength improvement with teriparatide appears to be greater than the improvement in BMD alone [100]. In a subset of women ($n = 53$) from a study comparing teriparatide with alendronate, there were teriparatide-induced increments in the strength to density ratio with teriparatide, in part related to a re-distribution of density within the vertebra [101].

In a subset of women from the phase 2 study comparing romosozumab with teriparatide and placebo [26], 82 had baseline and 12-month vertebral QCT [101], including 24 women on romosozumab, 27 on placebo, and 31 on teriparatide. Vertebral strength increased dramatically with romosozumab (27%) and with teriparatide (19%) and declined with placebo (− 4%). Although the increase in strength with romosozumab was significantly higher than that with teriparatide, the magnitude of the difference between anabolic agents was low compared with the increments with both agents vs placebo. Furthermore, the time frame for assessment was 1 year, the treatment period for romosozumab, although the treatment period for teriparatide is longer (18–24 months). As noted, stimulation of bone formation continue during 12–24 months of teriparatide treatment [42, 102] and additional strengthening effects can occur during this later period. Moreover, there may be material changes with teriparatide or abaloparatide, as discussed above, that are not considered in the strength determinations. Lastly, the difference in vertebral strength has not been compared between abaloparatide and romosozumab; that difference is likely to be minimized further vs the difference between teriparatide and romosozumab.

Of course, we must exercise substantial caution when comparing fracture effects across studies, but even if relative vertebral fracture risk reduction is similar for romosozumab, abaloparatide and teriparatide, there is some inconsistency between the magnitude of the effect and spine BMD gain. BMD increases more with romosozumab vs teriparatide over 1 year [26], yet certainly, the vertebral fracture risk reduction does not appear to be superior with romosozumab compared with teriparatide (as seen in ACTIVE). Also, the effect with abaloparatide might be minimally greater than with teriparatide. Consistent with this thesis, in a phase 2 study in 138 women with evaluable TBS measurements at 6 months, TBS increased with both abaloparatide and teriparatide, but the increment was significantly greater with abaloparatide vs teriparatide (4.2% vs 2.2%) [103]. In the diabetic cohort of the ACTIVE trial, the increment in TBS was also numerically higher with abaloparatide vs teriparatide at both 6 and 18 months; at the 18-month time point, TBS increased 3.7% with abaloparatide and 2.4% with teriparatide. The magnitude of this increment in TBS with teriparatide was similar to that seen after 2 years of teriparatide monotherapy (2.7%) in another study [104]. Although TBS changes have not yet been assessed with romosozumab, iliac crest biopsy data show that both teriparatide and romosozumab improve cancellous and cortical microarchitecture (see above).

Conclusion In patients at very high risk for vertebral fracture based on prevalent vertebral fracture (especially multiple, severe, and/or recent events), or very low spine BMD and/or degraded trabecular architecture (assessed via TBS), abaloparatide might be considered the ideal first anabolic agent, followed closely by teriparatide and then romosozumab.

Patients with Prevalent Nonvertebral or Hip Fracture or Very Low Hip BMD

Nonvertebral Fracture Effects As noted above, all three anabolic agents reduce the occurrence of nonvertebral fracture in their pivotal trials. In FRAME, romosozumab just missed statistical significance for the full population at 1 year, but reduced nonvertebral fracture risk by 42% in the Rest of the World subgroup [84]. Furthermore, the ARCH study confirms the efficacy of romosozumab against the alendronate comparator group, with a 19% further reduction in nonvertebral fracture occurrence compared with alendronate. In the ACTIVE trial, the effect of abaloparatide against nonvertebral fracture appeared more rapidly than that of teriparatide, and was statistically significant at 18 months, whereas the effect of teriparatide appeared to be of lower magnitude and not significant vs placebo. Still, the nonvertebral fracture reduction did not differ between the abaloparatide and teriparatide groups and certainly the teriparatide pivotal trial confirms the efficacy of teriparatide against nonvertebral fracture. Differences in the apparent efficacy of teriparatide against nonvertebral fracture between the ACTIVE study [3] and the teriparatide pivotal trial [2] are likely due to the greater osteoporosis severity in the latter study. Consistent with this thesis, incident vertebral fracture rates in the teriparatide pivotal trial placebo group

were 14%, compared with only 4.2% in the ACTIVE placebo group and nonvertebral fragility fracture rates in the respective placebo groups were 6% and 4.7%. Within the ACTIVE trial, possible differences between teriparatide and abaloparatide potency and significance against nonvertebral fracture might be related to differential binding affinity for the different conformations of the PTH1 receptor, as discussed above [28].

Abaloparatide-induced reductions in vertebral and nonvertebral fracture risk were independent of baseline hip BMD and prior nonvertebral fracture history [95]. Similarly, teriparatide treatment effects in VERO were independent of lowest baseline BMD (hip or spine) or prevalent nonvertebral fracture at baseline. With romosozumab also, effects against vertebral and nonvertebral fractures were independent of baseline hip BMD and fracture history [84].

Hip Fracture Effects Of the three anabolic agents, only romosozumab has proven efficacy against hip fracture, but this is likely a function of study sample size, not lack of efficacy. Medications that reduce risk of nonvertebral fracture would be expected to also reduce risk of hip fracture (obviously included in the composite) if enough people were studied, since osteoporosis is the underlying cause of almost all adulthood hip fractures. Studies of radionuclide bone scan and positron emission tomography also show that teriparatide stimulates uptake in the hip and femur by 20–50% [105, 106]. In addition, teriparatide stimulates bone formation in the femoral neck within 6 weeks of administration, similar to its effect on the iliac crest [46•]. Teriparatide increases hip BMD by DXA and QCT and improves hip strength by FEA (see below).

In FRAME, the number of hip fractures was reduced by 50% with romosozumab vs placebo (7 vs 13, though the group difference was not significant [4]. In ARCH, romosozumab reduced hip fracture occurrence by 38% over a median treatment period of 33 months [6•], compared with the alendronate arm (which itself reduces hip fracture risk by about 50%) [107]. In the pivotal teriparatide trial, there were only 4 hip fractures in the placebo group and 2 in the teriparatide group [2]. In a study of 224 recent hip fracture patients randomized to teriparatide vs risedronate (designed to evaluate effects on fracture healing), there were 7 recurrent hip fractures in the risedronate group and 2 in the teriparatide group [76]. A meta-analysis of teriparatide 20 mcg trials, where many of the control groups were antiresorptive agents (65% of the control group population as a whole), indicated that teriparatide reduced hip fracture risk by 56% (10 hip fractures with teriparatide, 24 with control), though there was no significant difference in upper extremity fractures [108]. In another meta-analysis comparing teriparatide and other non-bisphosphonate medications (but did not include abaloparatide), teriparatide had the greatest efficacy against hip fracture, followed closely by the romosozumab/alendronate treatment sequence [109]. Consistent with the teriparatide findings, during the 18 months of the ACTIVE trial, there were two hip fractures in the placebo group and zero in each of the teriparatide and abaloparatide groups [3].

Hip BMD Effects With teriparatide treatment, areal BMD of the total hip increased by 3–4% in the total hip and femoral neck over 18–24 months [2, 55, 102]. Abaloparatide increased both total hip and femoral neck BMD significantly more than teriparatide in the ACTIVE trial over 18 months (total hip BMD increase 4.2% with abaloparatide, 3.3% with teriparatide). In the phase 2 study, romosozumab increased total hip and femoral neck at 12 months substantially more than teriparatide [26]. In the FRAME and ARCH studies, romosozumab produced large gains in both total hip (6.2–6.8%) and femoral neck BMD (4.9–5.2%) at 12 months [4, 6].

Three-dimensional modeling of hip DXA data from a large subset of patients in the ACTIVE trial (250 patients from each arm of the study) [110] indicated that both abaloparatide and teriparatide increased trabecular volumetric BMD (9%) and cortical thickness (1.5%) significantly at 18 months (vs baseline). However, abaloparatide increased cortical volumetric BMD by 1.3%, significantly more than teriparatide (0.4% increase). This could be due to greater cortical remodeling and porosity associated with teriparatide vs abaloparatide administration and might explain the more rapid and greater effect against nonvertebral fracture with abaloparatide [110].

QCT/FEA Studies In a comparative study of teriparatide and alendronate, in the subgroup of women who had QCT data at baseline and at 18 months ($n = 48$), teriparatide increased volumetric BMD (significantly more than seen with alendronate), decreased peripheral BMD, and did not change integral BMD [55, 111]. Hip strength increased by 5.4% ($P = 0.06$) and the strength to density ratio was significantly higher for teriparatide compared with alendronate, consistent with the possibility that some of the strengthening benefits with teriparatide exceeds its effect on BMD alone.

In a subset of women from the phase 2 study comparing romosozumab with teriparatide and placebo [26], 46 had baseline and 12-month femoral QCT [101]. Femoral strength increased 3.6% with romosozumab but did not increase with placebo and actually declined − 0.7% with teriparatide ($P = 0.03$ group difference).

In a small study of 20 postmenopausal women where central QCT and peripheral HRpQCT measurements were performed after 2 years of teriparatide [112], although all spine parameters improved, there was no change in total proximal femur volumetric BMD.

Wrist and Tibia Effects In the teriparatide trial, there were 7 wrist fractures in teriparatide-treated women compared with 13 on placebo; for wrist fractures considered due to fragility, there were 2 with teriparatide and 7 with placebo [2]. A recent

large meta-analysis of randomized teriparatide trials of at least 6 months duration did not show any reduction in wrist or upper limb fracture overall [108], but 65% of the control group sample was on active anti-osteoporosis therapy which might minimize the apparent teriparatide effect.

In the ACTIVE trial, the incidence of wrist fracture with placebo was 1.8%, with teriparatide 2.1%, and with abaloparatide 0.8% ($P = 0.052$ vs teriparatide) [113]. Consistent with the wrist fracture data, at 18 months, ultradistal radial BMD increased with abaloparatide, but decreased with both placebo and teriparatide ($P < .01$ abaloparatide vs. both other groups). In the 1/3 radius site, BMD declined slightly with both abaloparatide and placebo (NS $P > .05$) but declined significantly more with teriparatide ($P < .01$ vs. both placebo and abaloparatide). No significant changes were seen with either teriparatide or romosozumab at 12 months at the 1/3 radius by DXA [26].

In the study of 20 women with HRpQCT measurements before and after 2 years of teriparatide, radius and tibia cortical volumetric BMD declined by about 3% and cortical porosity increased by 21% and 10% in radius and tibia, respectively [112]. In the DATA trial, HRpQCT measurements of the tibia and radius at both 1 and 2 years also showed mild reductions in total volumetric BMD, with significant decrements in cortical volumetric BMD and increments in cortical porosity at both sites. Estimates of bone strength did not decrease, however [114, 115].

Bone Structure Histomorphometric assessments indicate that teriparatide increases cortical porosity, but also increases cortical thickness in the iliac crest, perhaps through stimulation of bone formation on both periosteal and endocortical surfaces, though the latter effect is of much greater magnitude [38]. Teriparatide also stimulates bone formation in the femoral neck very rapidly [46•], and this increased bone formation appears to be due to stimulation of remodeling- and overflow remodeling-based formation with some stimulation of modeling-based formation as well [51].

It is not yet clear how different abaloparatide is from teriparatide with regard to cortical porosity. In the bone biopsy sub-study of ACTIVE, cortical porosity was higher than placebo in both the abaloparatide and teriparatide groups (placebo, 4.7%; abaloparatide, 5.8%; teriparatide, 6.1%) [63]. The bone biopsies comparing the two agents were done between 12 and 18 months; differences that occur earlier have not been assessed.

As stated above, it appears that abaloparatide might stimulate periosteal bone deposition to a greater extent than teriparatide [38, 44, 64]. There is no confirmation that romosozumab stimulates bone formation on the periosteal surface. Even if bone diameter is not expanded as a function of a modest increase in periosteal bone formation, if deposited in cortical regions with critical weakness, strength and fracture resistance could be improved [62, 110].

Conclusion The large gains in hip BMD combined with the microstructural improvements in cortical bone and strength assessed by FEA suggest that for patients at very high risk for nonvertebral fractures, especially those who have had hip or other major nonvertebral fractures and/or have very low hip BMD, romosozumab might be the ideal initial therapy and abaloparatide would be a close second choice. Teriparatide would be the third option in this scenario.

Patients on Bisphosphonate or Denosumab Therapy

Switching from bisphosphonates to teriparatide produces an increase in spine BMD, but a decline in hip BMD [12, 116]. The same is true upon switching from denosumab to teriparatide [102], but the hip BMD decline is much more dramatic. No studies have yet been performed evaluating the BMD effects of a switch from either a bisphosphonate or denosumab to abaloparatide.

In the STRUCTURE study, women who had been on an oral bisphosphonate for at least 3 years (of which the last year had to be alendronate) were switched to either romosozumab ($n = 218$) or teriparatide ($n = 218$) with DXA and QCT outcomes assessed at 1 year [116]. Both agents increased volumetric BMD of the spine, though the increment was larger with romosozumab. Over 12 months, mean areal BMD of the total hip decreased by 0.6% with teriparatide and increased 2.6% with romosozumab. Volumetric BMD of the hip declined modestly with teriparatide, largely due to the substantial decline in cortical (peripheral) volumetric BMD (− 3.6% at 12 months), whereas it increased significantly (1.1%) with romosozumab. At 12 months, hip strength by FEA decreased by 0.7% with teriparatide and increased 2.5% with romosozumab.

In women on prior denosumab treatment, there have been no head to head studies of the effect of switching to different anabolic agents. In one study, after 2 years of treatment with denosumab, upon switching to teriparatide, hip BMD declined from the on-denosumab baseline and remained below baseline for the entire 2 years of teriparatide treatment (though spine BMD increased significantly) [102]. In one of the extensions to the phase 2 romosozumab study, in women who received placebo for 2 years, followed by denosumab for 1 year, after switching to romosozumab treatment for 1 year, spine BMD increased 5.3% and hip BMD increased 0.9% [117].

Conclusion Romosozumab would be preferred to teriparatide in women on prior bisphosphonates and in women on prior denosumab (though the optimal strategy for this latter group is still unknown). It is likely that abaloparatide would be superior to teriparatide because of the lesser pro-remodeling effect of abaloparatide, but there are no confirmatory data. Another approach to patients on bisphosphonates to maximize the effect on hip BMD is to add teriparatide [118, 119] or abaloparatide.

This strategy might be effective for women already on denosumab, but again, data are lacking.

Other Criteria

Patients with Low Baseline Bone Turnover It was logical to hypothesize that anabolic agents would be particularly suited to patients with low bone turnover at baseline, however, for teriparatide, spine and hip BMD gains were larger in patients with higher baseline bone turnover marker levels in the teriparatide pivotal trial [120]. Additional analyses indicated that absolute fracture risk was higher in patients who had higher baseline bone turnover and therefore absolute fracture risk reduction was highest in these women; however relative risk reduction with treatment was independent of baseline marker levels [121]. In an observational study of untreated and bisphosphonate-treated women, baseline serum PINP level was weakly correlated with BMD increment in both spine and hip with teriparatide [122]. No data have been published evaluating the effect of either abaloparatide or romosozumab as a function of baseline biochemical marker level. With romosozumab, since most of the bone formation occurs through stimulation of modeling rather than remodeling, it may be less affected by baseline bone turnover.

Patients with Higher FRAX Scores In the ACTIVE trial, the effect of abaloparatide against vertebral and nonvertebral fracture risk was independent of baseline fracture probability, as assessed by FRAX [123], including women estimated to be at high risk [124]. In contrast, with romosozumab in the FRAME study, significant interactions were observed between antifracture efficacy and baseline FRAX probability for composite outcomes of clinical fractures, major osteoporotic fractures, and nonvertebral fractures, but not vertebral fractures [125]. Efficacy of romosozumab was significantly greater in patients at high baseline fracture risk.

Conclusion The concept that anabolic agents might be particularly effective in patients with low bone turnover might not be true, particularly for teriparatide and abaloparatide, where BMD effects are correlated with baseline bone turnover marker levels. Whether romosozumab might be better in patients with baseline low baseline bone turnover due to its predominant modeling-based formation effect is unclear based on available data. High-risk patients will have a good response to any of the anabolic agents.

Overall Conclusions

Women with osteoporosis at high risk for fracture are optimally treated with anabolic agents that reduce fracture risk and improve BMD faster and to a greater extent than antiresorptive treatment [1]. The differences between anabolic and antiresorptive agents are greater than the differences among the anabolic agents themselves.

We have tried to provide a rationale for choosing one or other anabolic agent in different clinical circumstances based on available data, but it must be acknowledged that there are major limitations to this approach. Namely, there are no studies which compare all three anabolic agents in head to head trials for any outcomes, including fracture, BMD, strength, or other surrogate imaging endpoints.

Over 40–50 years with osteoporosis, it is likely that multiple anabolic agents could and should be used in high-risk patients. Women who have received teriparatide or abaloparatide in the past can be treated with romosozumab in the future. In addition, there have been no animal models showing an increased risk of osteosarcoma with romosozumab and the label does not preclude administration of multiple courses of this medication. The recent change in the branded teriparatide label also allows for repeat courses of teriparatide to be administered in patients who remain or return to a high risk for fracture.

Declarations

Conflict of Interest *Felicia Cosman, MD*: Amgen Inc., Grants and medication supply for research, Advisory Board and Consulting Fees, Honoraria for promotional speaking. Radius Health: Grants and medication supply for research, Advisory Board and Consulting Fees, Honoraria for promotional speaking. *David W. Dempster, PhD*: Amgen Inc., Grants and medication supply for research, Advisory Board and Consulting Fees, Honoraria for promotional speaking. Radius Health: Grants and medication supply for research, Advisory Board and Consulting Fees, Honoraria for promotional speaking.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Cosman F. Anabolic therapy and optimal treatment sequences for patients with osteoporosis at high risk for fracture. Endocr Pract. 2020;26:777–86.
2. Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med. 2001;344:1434–41.
3. Miller PD, Hattersley G, Riis BJ, Williams GC, Lau E, Russo LA, et al. Effect of abaloparatide vs placebo on new vertebral fractures in postmenopausal women with osteoporosis: a randomized clinical trial. JAMA. 2016;316:722–33.
4. Cosman F, Crittenden DB, Adachi JD, Binkley N, Czerwinski E, Ferrari S, et al. Romosozumab treatment in postmenopausal women with osteoporosis. N Engl J Med. 2016;375:1532–43.

5.• Kendler DL, Marin F, Zerbini CAF, et al. Effects of teriparatide and risedronate on new fractures in post-menopausal women with severe osteoporosis (VERO): a multicentre, double-blind, double-dummy, randomised controlled trial. *Lancet*. 2018;391:230–40 **This landmark study in 1360 women with prevalent vertebral fracture, at very high risk for subsequent fracture, compared teriparatide and risedronate head-to-head over 2 years. Compared with risedronate, teriparatide reduced vertebral fractures by 50% and reduced the number of nonvertebral fractures by 44%.**

6.• Saag KG, Petersen J, Brandi ML, et al. Romosozumab or alendronate for fracture prevention in women with osteoporosis. *N Engl J Med*. 2017;377:1417–27 **This landmark study of 4093 women with prevalent vertebral fracture or recent hip fracture, at very high risk for subsequent fracture, compared romosozumab followed by alendronate for 1 year followed by alendronate in all women thereafter. Over the first year, vertebral fracture incidence was reduced by 37% and nonvertebral fracture incidence reduced by 26% in women on romosozumab compared with alendronate.**

7. Leder BZ, Mitlak B, Hu MY, Hattersley G, Bockman RS. Effect of abaloparatide vs alendronate on fracture risk reduction in postmenopausal women with osteoporosis. J Clin Endocrinol Metab. 2020;105(3):938–43.

8.•• Balasubramanian A, Zhang J, Chen L, et al. Risk of subsequent fracture after prior fracture among older women. *Osteoporos Int*. 2019;30:79–92 **This very large Medicare database study in 377,561 evaluated recurrent fracture risk in women 65 years of age with a first fracture. Overall clinical fracture risk after the first fracture event was 10% in 1 year and 18% in 2 years. The data suggest that potent osteoporosis therapy should be initiated as soon as possible after a sentinel fracture event to prevent additional fractures.**

9. Kanis JA, Johansson H, Odén A, Harvey NC, Gudnason V, Sanders KM, et al. Characteristics of recurrent fractures. Osteoporos Int. 2018;29:1747–57.

10. Roux C, Briot K. Imminent fracture risk. Osteoporos Int. 2017;28:1765–9.

11. Gehlbach S, Saag KG, Adachi JD, Hooven FH, Flahive J, Boonen S, et al. Previous fractures at multiple sites increase the risk for subsequent fractures: the global longitudinal study of osteoporosis in women. J Bone Miner Res. 2012;27:645–53.

12. van Helden S, Cals J, Kessels F, Brink P, Dinant GJ, Geusens P. Risk of new clinical fractures within 2 years following a fracture. Osteoporos Int. 2006;17:348–54.

13. Lindsay R, Silverman SL, Cooper C, Hanley DA, Barton I, Broy SB, et al. Risk of new vertebral fracture in the year following a fracture. JAMA. 2001;285:320–3.

14. Delmas PD, Genant HK, Crans GG, Stock JL, Wong M, Siris E, et al. Severity of prevalent vertebral fractures and the risk of subsequent vertebral and nonvertebral fractures: results from the MORE trial. Bone. 2003;33:522–32.

15.•• Cosman F, Nieves JW, Dempster DW. Treatment sequence matters: anabolic and antiresorptive therapy for osteoporosis. *J Bone Miner Res*. 2017;32:198–202 **This paper was the first to highlight the consistent observation that hip BMD declines for 12–24 months in women switched from bisphosphonates or denosumab to teriparatide. The paper concludes that treatment with teriparatide as first-line therapy produces a greater hip BMD gain and likely superior strength, particularly against nonvertebral fracture, compared with the inverse sequence.**

16. Cosman F, Kendler D, Langdahl B, et al. Treatment Sequences with Romosozumab Before or After Antiresorptive Medication. J Bone Miner Res 2020; 35 (Suppl 1), Available at https://www.asbmr.org/ItineraryBuilder/PresentationDetail.aspx?pid=ea239907-6383-4bce-bfb1-1fde067749bf&ptag=SessionsList, Accessed [October 27, 2020].

17. Ferrari S, Libanati C, Lin CJF, Brown JP, Cosman F, Czerwiński E, et al. Relationship between bone mineral density T-score and nonvertebral fracture risk over 10 years of denosumab treatment. J Bone Miner Res. 2019;34:1033–40.

18.• Cosman F, Lewiecki EM, Ebeling P, et al. T-score as an indicator of fracture risk on therapy: evidence from romosozumab vs alendronate treatment in the ARCH trial. *J Bone Miner Res*. 2020;35:1333–42 **This study highlights the importance of the total hip BMD level in patients on osteoporosis medication. It showed that the total hip *T* score achieved at 1 year on therapy with either romosozumab or alendronate is a major predictor of the subsequent risk of both vertebral and nonvertebral fractures. Consisent with the Ferrari paper (reference 17), in patients on denosumab, this study suggests that attaining a total hip *T* score above osteoporosis range should be one of our treatment goals in the management of osteoporosis.**

19. Black DM, Schwartz AV, Ensrud KE, Cauley JA, Levis S, Quandt SA, et al. Effects of continuing or stopping alendronate after 5 years of treatment: the fracture intervention trial long-term extension (FLEX): a randomized trial. JAMA. 2006;296:2927–38.

20. Cosman F, Cauley JA, Eastell R, Boonen S, Palermo L, Reid IR, et al. Reassessment of fracture risk in women after 3 years of treatment with zoledronic acid: when is it reasonable to discontinue treatment? J Clin Endocrinol Metab. 2014;99:4546–54.

21. Cummings SR, Cosman F, Leweicki EM, et al. Goal-directed treatment for osteoporosis: a progress report from the ASBMR-NOF working group on goal-directed treatment for osteoporosis. J Bone Miner Res. 2017;32:3–10.

22. Cummings S, Libanati C, Hamilton C, et al. Probability of achieving T-scores goals above -2.5 with alendronate or romosozumab followed by alendronate or denosumab. J Bone Miner Res 2020; 35 (Suppl 1), Available at https://www.asbmr.org/ItineraryBuilder/PresentationDetail.aspx?pid=d8739d53-2c84-4db2-9d99-816babb42b20&ptag=WebItinerarySearch, Accessed [October 27, 2020].

23.• Camacho PM, Petak SM, Binkley N, et al. American Association of Clinical Endocrinologists/American College of Endocrinology clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis – 2020 Update. *Endocr Pract*. 2020;26(Suppl 1):1–44 **The revised AACE guidelines are very important because they define the very high-risk patient and recommend first-line treatment with anabolic therapy for these patients. Very high-risk patients include those with recent fractures and multiple fractures, as well as those who start with a *T* score of − 3 or below. The authors suggest that these patients should be considered for treatment with abaloparatide, romosozumab, or teriparatide as initial therapy.**

24. Eastell R, Rosen CJ, Black DM, Cheung AM, Murad MH, Shoback D. Pharmacological management of osteoporosis in postmenopausal women: an Endocrine Society* clinical practice guideline. J Clin Endocrinol Metab. 2019;104:1595–622.

25. Shoback D, Rosen CJ, Black DM, Cheung AM, Murad MH, Eastell R. Pharmacological management of osteoporosis in postmenopausal women: an Endocrine Society guideline update. J Clin Endocrinol Metab. 2020;105:587–94.

26. McClung MR, Grauer A, Boonen S, et al. Romosozumab in postmenopausal women with low bone density. N Engl J Med. 2014;370:412–20.

27. Gori F, Baron R. WNT signaling in skeletal homeostasis and disease. In: Dempster DW, Cauley JA, Bouxsein ML, Cosman F, editors. *Marcus and Feldman's osteoporosis*. 5th Edition (Two-Volume set) ed. San Diego: Academic Press/Elsevier Inc.; 2021. p. 257–79.

28. Hattersley G, Dean T, Corbin BA, Bahar H, Gardella TJ. Binding selectivity of abaloparatide for PTH-type-1-receptor conformations and effects on downstream signaling. Endocrinology. 2016;157(1):141–9.
29. Recker RR, Kimmel DB, Dempster D, Weinstein RS, Wronski TJ, Burr DB. Issues in modern bone histomorphometry. Bone. 2011;49(5):955–64.
30. Zhou H, Dempster DW. Lessons from bone histomorphometry on the mechanism of action of osteoporosis drugs. In: Dempster DW, Cauley JA, Bouxsein ML, Cosman F, editors. *Marcus and Feldman's Osteoporosis*. 5th Edition (Two-Volume set) ed. San Diego: Academic Press/Elsevier Inc.; 2021. p. 1835–63.
31. Dempster DW, Cosman F, Kurland ES, Zhou H, Nieves J, Woelfert L, et al. Effects of daily treatment with parathyroid hormone on bone microarchitecture and turnover in patients with osteoporosis: a paired biopsy study. J Bone Miner Res. 2001;16(10):1846–53.
32. Misof BM, Roschger P, Cosman F, Kurland ES, Tesch W, Messmer P, et al. Effects of intermittent parathyroid hormone administration on bone mineralization density in iliac crest biopsies from patients with osteoporosis: a paired study before and after treatment. J Clin Endocrinol Metab. 2003;88(3):1150–6.
33. Dobnig H, Sipos A, Jiang Y, Fahrleitner-Pammer A, Ste-Marie LG, Gallagher JC, et al. Early changes in biochemical markers of bone formation correlate with improvements in bone structure during teriparatide therapy. J Clin Endocrinol Metab. 2005;90(7):3970–7.
34. Jiang Y, Zhao JJ, Mitlak BH, Wang O, Genant HK, Eriksen EF. Recombinant human parathyroid hormone (1-34) [teriparatide] improves both cortical and cancellous bone structure. J Bone Miner Res. 2003;18(11):1932–41.
35. Paschalis EP, Glass EV, Donley DW, Eriksen EF. Bone mineral and collagen quality in iliac crest biopsies of patients given teriparatide: new results from the fracture prevention trial. J Clin Endocrinol Metab. 2005;90(8):4644–9.
36. Ma YL, Zeng Q, Donley DW, Ste-Marie LG, Gallagher JC, Dalsky GP, et al. Teriparatide increases bone formation in modeling and remodeling osteons and enhances IGF-II immunoreactivity in postmenopausal women with osteoporosis. J Bone Miner Res. 2006;21:855–64.
37. Lindsay R, Cosman F, Zhou H, Bostrom MP, Shen VW, Cruz JD, et al. A novel tetracycline labeling schedule for longitudinal evaluation of the short-term effects of anabolic therapy with a single iliac crest bone biopsy: early actions of teriparatide. J Bone Miner Res. 2006;21(3):366–73.
38. Dempster DW, Zhou H, Recker RR, Brown JP, Recknor CP, Lewiecki EM, et al. Differential effects of teriparatide and denosumab on intact PTH and bone formation indices: AVA osteoporosis study. J Clin Endocrinol Metab. 2016;101:1353–63.
39. Dempster DW, Cosman F, Zhou H, Nieves J, Bostrom M, Lindsay R. Effects of daily or cyclic teriparatide on bone formation in the iliac crest in women on no prior therapy and in women on alendronate. J Bone Miner Res. 2016;31:1518–26.
40. Arlot M, Meunier PJ, Boivin G, Haddock L, Tamayo J, Correa-Rotter R, et al. Differential effects of teriparatide and alendronate on bone remodeling in postmenopausal women assessed by histomorphometric parameters. J Bone Miner Res. 2005;20(7):1244–53.
41. Dempster DW, Zhou H, Recker RR, Brown JP, Bolognese MA, Recknor C, et al. Skeletal histomorphometry in subjects on teriparatide or zoledronic acid therapy (SHOTZ) study: a randomized controlled trial. J Clin Endocrinol Metab. 2012;97:2799–808.
42. Dempster DW, Zhou H, Recker RR, Brown JP, Bolognese MA, Recknor CP, et al. A longitudinal study of skeletal histomorphometry at 6 and 24 months across four bone envelopes in postmenopausal women with osteoporosis receiving teriparatide or zoledronic acid in the SHOTZ trial. J Bone Miner Res. 2016;31:1429–39.
43. Dempster DW, Zhou H, Ruff VA, Melby TE, Alam J, Taylor KA. Longitudinal effects of teriparatide or zoledronic acid on bone modeling- and remodeling-based formation in the SHOTZ study. J Bone Miner Res. 2018;33(4):627–33.
44. Dempster DW, Zhou H, Recker RR, Brown JP, Recknor CP, Lewiecki EM, et al. Remodeling- and modeling-based bone formation with teriparatide versus denosumab: a longitudinal analysis from baseline to 3 months in the AVA study. J Bone Miner Res. 2018;33(2):298–306.
45. Dempster DW, Roschger P, Misof BM, Zhou H, Paschalis EP, Alam J, et al. Differential effects of teriparatide and zoledronic acid on bone mineralization density distribution at 6 and 24 months in the SHOTZ study. J Bone Miner Res. 2016;31(8):1527–35.
46.• Cosman F, Dempster DW, Nieves JW, Zhou H, Zion M, Roimisher C, et al. Effect of teriparatide on bone formation in the human femoral neck. J Clin Endocrinol Metab. 2016;101(4):1498–505 **This novel study was the first to show that teriparatide could stimulate bone formation in the proximal femur after just 4–6 weeks of administration similarly to what had previously been demonstrated in the iliac crest. Analyses of extent and location of bone formation in the femoral neck provide additional evidence for the ability of teriparatide to strengthen bone of the hip and reduce the likelihood of hip fracture.**
47. Rooney AM, Bostrom MPG, Dempster DW, Nieves JW, Zhou H, Cosman F. Loading modality and age influence teriparatide-induced bone formation in the human femoral neck. Bone. 2020;136:115373.
48. Hodsman AB, Fraher LJ, Ostbye T, Adachi JD, Steer BM. An evaluation of several biochemical markers for bone formation and resorption in a protocol utilizing cyclical parathyroid hormone and calcitonin therapy for osteoporosis. J Clin Invest. 1993;91(3):1138–48.
49. Hodsman AB, Kisiel M, Adachi JD, Fraher LJ, Watson PH. Histomorphometric evidence for increased bone turnover without change in cortical thickness or porosity after 2 years of cyclical hPTH(1-34) therapy in women with severe osteoporosis. Bone. 2000;27(2):311–8.
50. Jilka RL, Weinstein RS, Bellido T, Roberson P, Parfitt AM, Manolagas SC. Increased bone formation by prevention of osteoblast apoptosis with parathyroid hormone. J Clin Invest. 1999;104(4):439–46.
51. Dempster DW, Nieves J, Zhou H, Bostrom M, Cosman F. Effects of teriparatide on modeling-based and remodeling-based bone formation in the human femoral neck. J Bone Miner Res 2020; 35 (Suppl 1), Available at: https://www.asbmr.org/ItineraryBuilder/PresentationDetail.aspx?pid=edf24b66-aee3-4fa5-b88b-06ac23975f04&ptag=WebItinerarySearch, Accessed [October 27, 2020].
52. Reeve J, Meunier PJ, Parsons JA, Bernat M, Bijvoet OL, Courpron P, et al. Anabolic effect of human parathyroid hormone fragment on trabecular bone in involutional osteoporosis: a multicentre trial. Br Med J. 1980;280(6228):1340–4.
53. Reeve J, Bradbeer JN, Arlot M, Davies UM, Green JR, Hampton L, et al. hPTH 1-34 1991 treatment of osteoporosis with added hormone replacement therapy: biochemical, kinetic and histological responses. Osteoporos Int. 1991;1(3):162–70.
54. Lindsay R, Nieves J, Formica C, Henneman E, Woelfert L, Shen V, et al. Randomised controlled study of effect of parathyroid hormone on vertebral-bone mass and fracture incidence among postmenopausal women on oestrogen with osteoporosis. Lancet. 1997;350(9077):550–5.

55. McClung MR, San Martin J, Miller PD, et al. Opposite bone remodeling effects of teriparatide and alendronate in increasing bone mass. Arch Intern Med. 2005;165:1762–8.
56. Kurland ES, Cosman F, McMahon DJ, Rosen CJ, Lindsay R, Bilezikian JP. Parathyroid hormone as a therapy for idiopathic osteoporosis in men: effects on bone mineral density and bone markers. J Clin Endocrinol Metab. 2000;85:3069–76.
57. Cosman F, Nieves J, Woelfert L, Formica C, Gordon S, Shen V, et al. Parathyroid hormone added to established hormone therapy: effects on vertebral fracture and maintenance of bone mass after parathyroid hormone withdrawal. J Bone Miner Res. 2001;16: 925–31.
58. Bradbeer JN, Arlot ME, Meunier PJ, Reeve J. Treatment of osteoporosis with parathyroid peptide (hPTH 1-34) and oestrogen: increase in volumetric density of iliac cancellous bone may depend on reduced trabecular spacing as well as increased thickness of packets of newly formed bone. Clin Endocrinol. 1992;37(3): 282–9.
59. Ascenzi MG, Liao VP, Lee BM, Billi F, Zhou H, Lindsay R, et al. Parathyroid hormone treatment improves the cortical bone microstructure by improving the distribution of type I collagen in postmenopausal women with osteoporosis. J Bone Miner Res. 2012;27(3):702–12.
60. Zanchetta JR, Bogado CE, Ferretti JL, Wang O, Wilson MG, Sato M, et al. Effects of teriparatide [recombinant human parathyroid hormone (1-34)] on cortical bone in postmenopausal women with osteoporosis. J Bone Miner Res. 2003;18:539–43.
61. Uusi-Rasi K, Semanick LM, Zanchetta JR, Bogado CE, Eriksen EF, Sato M, et al. Effects of teriparatide [rhPTH (1-34)] treatment on structural geometry of the proximal femur in elderly osteoporotic women. Bone. 2005;36:948–58.
62. Whitmarsh T, Treece GM, Gee AH, Poole KE. Mapping bone changes at the proximal femoral cortex of postmenopausal women in response to alendronate and teriparatide alone, combined or sequentially. J Bone Miner Res. 2015;30(7):1309–18.
63. Moreira CA, Fitzpatrick LA, Wang Y, Recker RR. Effects of abaloparatide-SC (BA058) on bone histology and histomorphometry: the ACTIVE phase 3 trial. Bone. 2017;97: 314–9.
64. Dempster DW, Zhou H, Rao SD, Recknor C, Miller PD, Leder BZ, et al. Early effects of abaloparatide on bone formation and resorption indices in postmenopausal women with osteoporosis. J Bone Miner Res. 2021. https://doi.org/10.1002/jbmr.4243.
65. Chavassieux P, Chapurlat R, Portero-Muzy N, Roux JP, Garcia P, Brown JP, et al. Bone-forming and antiresorptive effects of romosozumab in postmenopausal women with osteoporosis: bone histomorphometry and microcomputed tomography analysis after 2 and 12 months of treatment. J Bone Miner Res. 2019;34(9): 1597–608.
66. Reid IR, Miller PD, Brown JP, Kendler DL, Fahrleitner-Pammer A, Valter I, et al. Denosumab phase 3 bone histology study group. Effects of denosumab on bone histomorphometry: the FREEDOM and STAND studies. J Bone Miner Res. 2010;25(10):2256–65.
67. Eriksen EF, Chapurlat R, Boyce R, Brown JP, Horlait S, Libanati C, Shi Y, Wagman RB, Chavassieux P. Extensive modeling-based bone formation after 2 months of romosozumab treatment: results from the FRAME clinical trial. J Bone Miner Res 2019;35 (Suppl 1). Available at https://www.asbmr.org/meetings/annualmeeting/AbstractDetail?aid=d112527c-6efe-46cd-96af-04ce66040dcd. Accessed [July 28, 2020].
68. Frost HM. Bone's mechanostat: A 2003 Update. Anat Rec Part A. 2003;275A:1081–101.
69. Rubin MR, Manavalan JS, Dempster DW, Shah J, Cremers S, Kousteni S, et al. Parathyroid hormone stimulates circulating osteogenic cells in hypoparathyroidism. J Clin Endocrinol Metab. 2011;96(1):176–86. https://doi.org/10.1210/jc.2009-2682.
70. Ominsky MS, Brown DL, Van G, Cordover D, Pacheco E, Frazier E, et al. Differential temporal effects of sclerostin antibody and parathyroid hormone on cancellous and cortical bone and quantitative differences in effects on the osteoblast lineage in young intact rats. Bone. 2015;81:380–91.
71. Gerbaix M, Amman P, Ferrari S. Mechanically driven counter-regulation of cortical bone formation in response to sclerostin-neutralizing antibodies. J Bone Miner Res. 2020. https://doi.org/10.1002/jbmr.4193.
72. Vahle JL, Long GG, Sandusky G, Westmore M, Ma YL, Sato M. Bone neoplasms in F344 rats given teriparatide [rhPTH(1-34)] are dependent on duration of treatment and dose. Toxicol Pathol. 2004;32:426–38.
73. Vahle JL, Sato M, Long GG, Young JK, Francis PC, Engelhardt JA, et al. Skeletal changes in rats given daily subcutaneous injections of recombinant human parathyroid hormone (1-34) for 2 years and relevance to human safety. Toxicol Pathol. 2002;30: 312–21.
74. Saag KG, Shane E, Boonen S, Marín F, Donley DW, Taylor KA, et al. Teriparatide or alendronate in glucocorticoid-induced osteoporosis. N Engl J Med. 2007;357(20):2028–39.
75. Hadji P, Zanchetta JR, Russo L, Recknor CP, Saag KG, McKiernan FE, et al. The effect of teriparatide compared with risedronate on reduction of back pain in postmenopausal women with osteoporotic vertebral fractures. Osteoporos Int. 2012;23: 2141–50.
76. Malouf-Sierra J, Tarantino U, Garcia-Hernandez A, Corradini C, et al. Effect of teriparatide or risedronate in elderly patients with a recent pertrochanteric hip fracture: final results of a 78-week randomized clinical trial. J Bone Miner Res. 2017;32:1040–51.
77. Cosman F, Miller PD, Williams GC, Hattersley G, Hu MY, Valter I, et al. Eighteen months of treatment with subcutaneous abaloparatide followed by 6 months of treatment with alendronate in postmenopausal women with osteoporosis: results of the ACTIVExtend trial. Mayo Clin Proc. 2017;92:200–10.
78. Bone HG, Cosman F, Miller PD, Williams GC, Hattersley G, Hu MY, et al. ACTIVExtend: 24 months of alendronate after 18 months of abaloparatide or placebo for postmenopausal osteoporosis. J Clin Endocrinol Metab. 2018;103:2949–57.
79. Jolette J, Attalla B, Varela A, Long GG, Mellal N, Trimm S, et al. Comparing the incidence of bone tumors in rats chronically exposed to the selective PTH type 1 receptor agonist abaloparatide or PTH(1-34). Regul Toxicol Pharmacol. 2017;86:356–65.
80. Vahle JL, Zuehlke U, Schmidt A, Westmore M, Chen P, Sato M. Lack of bone neoplasms and persistence of bone efficacy in cynomolgus macaques after long-term treatment with teriparatide [rhPTH(1-34)]. J Bone Miner Res. 2008;23:2033–9.
81. Andrews EB, Gilsenan AW, Midkiff K, Sherrill B, Wu Y, Mann BH, et al. The US postmarketing surveillance study of adult osteosarcoma and teriparatide: study design and findings from the first 7 years. J Bone Miner Res. 2012;27:2429–37.
82. Von Scheele B, Martin RD, Gilsenan AW, et al. The European postmarketing adult osteosarcoma surveillance study: characteristics of patients, a preliminary report. Acta Orthop. 2009;80:67–74.
83. Gilsenan A, Harding A, Kellier-Steele N, Harris D, Midkiff K, Andrews E. The Forteo patient registry linkage to multiple state cancer registries: study design and results from the first 8 years. Osteoporos Int. 2018;29:2335–43.
84. Cosman F, Crittenden DB, Ferrari S, Lewiecki EM, Jaller-Raad J, Zerbini C, et al. Romosozumab FRAME study: a post hoc analysis of the role of regional background fracture risk on nonvertebral fracture outcome. J Bone Miner Res. 2018;33(8):1407–16.
85.• Cummings S, McCullogh C. Explanations for the difference in rates of cardiovascular events in a trial of alendronate and

romosozumab. *Osteoporos Int*. 2020;31:1019–21 **This important editorial analyzes the incidence and pattern of major adverse cardiovascular events from the FRAME and ARCH trials and suggests that the imbalance of events seen with romosozumab in ARCH but not in FRAME is likely due to chance.**

86. Turk JR, Deaton AM, Yin J, Stolina M, Felx M, Boyd G, 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.
87. Bovijn J, Krebs K, Chen C-Y, 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: eaay6570.
88.• Cosman F, Peterson LR, Towler DA, Mitlak B, Wang Y, Cummings SR. Cardiovascular Safety of Abaloparatide in Postmenopausal Women With Osteoporosis: Analysis From the ACTIVE Phase 3 Trial. J Clin Endocrinol Metab. 2020;105(11): dgaa450. https://doi.org/10.1210/clinem/dgaa450 **This paper analyzed major cardiac events with abaloparatide and teriparatide compared with placebo from the ACTIVE trial in 2463 women. It shows that there was no increased risk of serious cardiovascular events by either agent and, in fact, time to first major event (heart attack, stroke, heart failure, and cardiovascular death) appeared significantly longer with both agents compared with placebo.**
89. Bilezikian J, Hattersley G, Mitlak BH, et al. Abaloparatide in patients with mild or moderate renal impairment: results from the ACTIVE phase 3 trial. Curr Med Res Opin. 2019;35:2097–102.
90. Miller PD, Cheung AM, Reid I, Rojeski M, Vanderkelen M, Ruiz Santiago N, et al. Efficacy and safety of romosozumab vs alendronate is similar across different levels of renal function among postmenopausal women with osteoporosis. *J Endocr Soc*. 2020;4(Issue Supplement_1):MON-378. https://doi.org/10.1210/jendso/bvaa046.050.
91. Miller PD, Chines A, Albergaria B-H, Gielen E, Langdahl B, Miyauchi A, Vanderkelen M, Milmont CE, Maddox J, Adachi J. Efficacy and safety of romosozumab vs placebo among patients with mild-to-moderate chronic kidney disease (CKD). J Bone Miner Res 202932 (Suppl 1)Available at https://www.asbmr.org/meetings/annualmeeting/AbstractDetail?aid=929df174-0beb-4b05-8b9c-594e553b9929 Accessed [October 27, 2020}.
92. Dhaliwal R, Hans D, Hattersley G, et al. Abaloparatide in postmenopausal women with osteoporosis and type 2 diabetes: a post hoc analysis of the ACTIVE study. JBMR Plus 2020; 4(4).
93. Geusens P, Marin F, Kendler DL, Russo LA, Zerbini CA, Minisola S, et al. Effects of teriparatide compared with risedronate on the risk of fractures in subgroups of postmenopausal women with severe osteoporosis: the VERO trial. J Bone Miner Res. 2018;33(5):783–94.
94. Marcus R, Wang O, Satterwhite J, Mitlak B. The skeletal response to teriparatide is largely independent of age, initial bone mineral density, and prevalent vertebral fractures in postmenopausal women with osteoporosis. J Bone Miner Res. 2003;18:18–23.
95. Cosman F, Hattersley G, Hu MY, Williams GC, Fitzpatrick LA, Black DM. Effects of abaloparatide-SC on fractures and bone mineral density in subgroups of postmenopausal women with osteoporosis and varying baseline risk factors. J Bone Miner Res. 2017;32:17–23.
96. McClung MR, Harvey NC, Fitzpatrick LA, et al. Effects of abaloparatide on bone mineral density and risk of fracture in postmenopausal women aged 80 years or older with osteoporosis. Menopause. 2018;25:767–71.
97. Kanis JA, Borgstrom F, De Laet C, Johansson H, Johnell O, Jonsson B, et al. Assessment of fracture risk. Osteoporos Int. 2005;16(6):581–9.
98. Manolagas SC, Parfitt AM. What old means to bone. Trends Endocrinol Metab. 2010;21(6):369–74.
99. Geusens P, Oates M, Miyauchi A, Adachi JD, Lazaretti-Castro M, Ebeling PR, et al. The effect of 1 year of romosozumab on the incidence of clinical vertebral fractures in postmenopausal women with osteoporosis: results from the FRAME study. JBMR Plus. 2019;3:e10211.
100. Keaveny TM, Donley DW, Hoffmann PF, Mitlak BH, Glass EV, San Martin JA. Effects of teriparatide and alendronate on vertebral strength as assessed by finite element modeling of QCT scans in women with osteoporosis. J Bone Miner Res. 2007;22(1):149–57.
101. Keaveny TM, Crittenden DB, Bolognese MA, Genant HK, Engelke K, Oliveri B, et al. Greater gains in spine and hip strength for romosozumab compared with teriparatide in postmenopausal women with low bone mass. J Bone Miner Res. 2017;32(9): 1956–62.
102. Leder BZ, Tsai JN, Uihlein AV, Wallace PM, Lee H, Neer RM, et al. Denosumab and teriparatide transitions in postmenopausal osteoporosis (the DATA-Switch study): extension of a randomised controlled trial. Lancet. 2015;386(9999):1147–55.
103. Bilezikian JP, Hattersley G, Fitzpatrick LA, Harris AG, Shevroja E, Banks K, et al. Abaloparatide-SC improves trabecular microarchitecture as assessed by trabecular bone score (TBS): a 24-week randomized clinical trial. Osteoporos Int. 2018;29(2): 323–8.
104. Tsai JN, Jiang LA, Lee H, Hans D, Leder BZ. Effects of teriparatide, denosumab, or both on spine trabecular microarchitecture in DATA-Switch: a randomized controlled trial. J Clin Densitom. 2017;20(4):507–12.
105. Eriksen EF, Keaveny TM, Gallagher ER, Krege JH. Literature review: the effects of teriparatide therapy at the hip in patients with osteoporosis. Bone. 2014;67:246–56.
106. Frost ML, Siddique M, Blake GM, Moore AE, Schleyer PJ, Dunn JT, et al. Differential effects of teriparatide on regional bone formation using (18)F-fluoride positron emission tomography. J Bone Miner Res. 2011;26(5):1002–11. https://doi.org/10.1002/jbmr.305.
107. Black DM, Thompson DE, Bauer DC, Ensrud K, Musliner T, Hochberg MC, et al. Cummings SR; fracture intervention trial. Fracture risk reduction with alendronate in women with osteoporosis: the Fracture Intervention Trial. FIT Research Group. J Clin Endocrinol Metab. 2000;85(11):4118–24.
108. Díez-Pérez A, Marin F, Eriksen EF, Kendler DL, et al. Effects of teriparatide on hip and upper limb fractures in patients with osteoporosis: a systematic review and meta-analysis. Bone. 2019;120: 1–8.
109. Simpson EL, Martyn-St James M, Hamilton J, Wong R, Gittoes N, Selby P, et al. Clinical effectiveness of denosumab, raloxifene, romosozumab, and teriparatide for the prevention of osteoporotic fragility fractures: a systematic review and network meta-analysis. Bone. 2020;130:115081.
110. Winzenrieth R, Ominsky MS, Wang Y, Humbert L, Weiss RJ. Differential effects of abaloparatide and teriparatide on hip cortical volumetric BMD by DXA-based 3d modeling. Endocrine Society Abstract SUN-385. J Endocrine Soc 2020; A129; https://doi.org/10.1210/jendso/bvaa046
111. Keaveny TM, McClung MR, Wan X, Kopperdahl DL, Mitlak BH, Krohn K. Femoral strength in osteoporotic women treated with teriparatide or alendronate. Bone. 2012;50(1):165–70.
112. Paggiosi MA, Yang L, Blackwell D, Walsh JS, McCloskey E, Peel N, et al. Teriparatide treatment exerts differential effects on the central and peripheral skeleton: results from the MOAT study. Osteoporos Int. 2018;29(6):1367–78.

113. Watts N, Hattersley G, Fitzpatrick L, et al. Abaloparatide effect on forearm bone mineral density and wrist fracture risk in postmenopausal women with osteoporosis. Osteoporos Int. 2019;30:1187–94.
114. Tsai JN, Uihlein AV, Burnett-Bowie SA, Neer RM, Zhu Y, Derrico N, et al. Comparative effects of teriparatide, denosumab, and combination therapy on peripheral compartmental bone density, microarchitecture, and estimated strength: the DATA-HRpQCT study. J Bone Miner Res. 2015;30(1):39–45.
115. Tsai JN, Nishiyama KK, Lin D, Yuan A, Lee H, Bouxsein ML, et al. Effects of denosumab and teriparatide transitions on bone microarchitecture and estimated strength: the DATA-Switch HR-pQCT study. J Bone Miner Res. 2017;32(10):2001–9.
116. Langdahl BL, Libanati C, Crittenden DB, Bolognese MA, Brown JP, Daizadeh NS, 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):1585–94.
117. McClung M, Bolognese MA, Brown JP, Reginster J-Y, Langdahl BL, Ruiz-Santiago N, Shi Y, Rojeski M, Timoshanko J, Libanati C, Kassahun H, Oates M. Romosozumab after denosumab improves lumbar spine and maintains total hip bone mineral density in postmenopausal women with low bone mass J Bone Miner Res 2019;35 (Suppl 1). Available at https://www.asbmr.org/ItineraryBuilder/PresentationDetail.aspx?pid=4e8cf911-5a4d-46b1-88fd-b4f2a1022414&ptag=WebItinerarySearch. Accessed [October 27,2020].
118. Cosman F, Keaveny TM, Kopperdahl D, Wermers RA, Wan X, Krohn KD, et al. Hip and spine strength effects of adding versus switching to teriparatide in postmenopausal women with osteoporosis treated with prior alendronate or raloxifene. J Bone Miner Res. 2013;28(6):1328–36.
119. Cosman F, Wermers RA, Recknor C, Mauck KF, Xie L, Glass EV, et al. Effects of teriparatide in postmenopausal women with osteoporosis on prior alendronate or raloxifene: differences between stopping and continuing the antiresorptive agent. J Clin Endocrinol Metab. 2009;94(10):3772–80.
120. Chen P, Satterwhite JH, Licata AA, Lewiecki EM, Sipos AA, Misurski DM, et al. Early changes in biochemical markers of bone formation predict BMD response to teriparatide in postmenopausal women with osteoporosis. J Bone Miner Res. 2005;20(6):962–70.
121. Delmas PD, Licata AA, Reginster JY, Crans GG, Chen P, Misurski DA, et al. Fracture risk reduction during treatment with teriparatide is independent of pretreatment bone turnover. Bone. 2006;39(2):237–43.
122. Blumsohn A, Marin F, Nickelsen T, Brixen K, Sigurdsson G, de la Vera González J, et al. Early changes in biochemical markers of bone turnover and their relationship with bone mineral density changes after 24 months of treatment with teriparatide. Osteoporos Int. 2011;22(6):1935–46.
123. McCloskey EV, Johansson H, Oden A, Harvey NC, Jiang H, Modin S, et al. The effect of abaloparatide-SC on fracture risk is independent of baseline FRAX fracture probability: a post hoc analysis of the ACTIVE study. J Bone Miner Res. 2017;32:1625–31.
124. McCloskey EV, Fitzpatrick LA, Hu MY, Williams G, Kanis JA. Effect of abaloparatide on vertebral, nonvertebral, major osteoporotic, and clinical fractures in a subset of postmenopausal women at increased risk of fracture by FRAX probability. Arch Osteoporos. 2019;14:15.
125. McCloskey EV, Helena Johansson H, Harvey NC, Lorentzon M, Shi Y, Kanis JA. Romosozumab efficacy on fracture outcomes is greater in patients at high baseline risk: a post-hoc analysis of the first year of the FRAME study. Osteoporos Int. 2021. https://doi.org/10.1007/s00198-020-05815-0.