REVIEW

THE AMERICAN JOURNAL of MEDICINE®

Western Osteoporosis Alliance Clinical Practice Series: Treat-to-Target for Osteoporosis

E. Michael Lewiecki, MD,[a] David L. Kendler, MD,[b] K. Shawn Davison, PhD,[c] David A. Hanley, MD,[d] Steven T. Harris, MD,[e] Michael R. McClung, MD,[f,g] Paul D. Miller, MD[h]

[a]New Mexico Clinical Research & Osteoporosis Center, Albuquerque, NM; [b]Department of Medicine (Endocrinology), University of British Columbia, Vancouver, Canada; [c]A Priori Medical Sciences, Inc., Victoria, British Columbia, Canada; [d]Departments of Medicine, Community Health Sciences, and Oncology, Cumming School of Medicine and McCaig Institute for Bone and Joint Health Cumming School of Medicine, The University of Calgary, Calgary, Alberta, Canada; [e]University of California, San Francisco, CA; [f]Oregon Osteoporosis Center and Oregon Health & Science University, Portland, OR; [g]Mary MacKillop Institute for Health Research, Australian Catholic University, Melbourne, Victoria, Australia; [h]Colorado Center for Bone Research, Lakewood, CO.

ABSTRACT

Patients often start treatment to reduce fracture risk because of a bone mineral density T-score consistent with osteoporosis (≤ −2.5). Others with a T-score above −2.5 may be treated when there is a history of fragility fracture or when a fracture risk algorithm categorizes them as having a high risk for fracture. It is common to initiate therapy with a generic oral bisphosphonate, unless contraindicated, and continue therapy if the patient is responding as assessed by stability or an increase in bone mineral density. However, some patients may respond well to an oral bisphosphonate, yet remain with an unacceptably high risk for fracture. Recognition of this occurrence has led to the development of an alternative strategy: treat-to-target. This involves identifying a biological marker (treatment target) that represents an acceptable fracture risk and then initiating treatment with an agent likely to reach this target. If the patient is on a path to reaching the target with initial therapy, treatment is continued. If it appears the target will not be reached with initial therapy, treatment is changed to an agent more likely to achieve the goal.

 • The American Journal of Medicine (2019) 132:e771−e777

KEYWORDS: Bone mineral density; Bone turnover markers; Osteoporosis; Goal; Treatment target

INTRODUCTION

Current pharmacologic therapies lower risk of fracture by 20%-70%, depending on fracture site, medication used, and population treated.[1,2] Other helpful interventions include lifestyle modifications, such as preventing falls, good nutrition, ceasing smoking, and avoiding excess alcohol.

It is common clinical practice to initiate treatment with a generic oral bisphosphonate (eg, alendronate, risedronate, or ibandronate), unless contraindicated, in which case

Funding: None.

Conflicts of Interest: EML has received no direct income from potentially conflicting entities in the past year. His employer, New Mexico Clinical Research & Osteoporosis Center, has received research grants from Radius, Amgen, Mereo, Bindex; income for service on scientific advisory boards or consulting for Amgen, Radius, Alexion, Sandoz, Samsung Bioepis; service on speakers' bureaus for Radius, Alexion; project development for University of New Mexico; and royalties from UpToDate for sections on DXA, fracture risk assessment, and prevention of osteoporosis. He is a board member of the National Osteoporosis Foundation, International Society for Clinical Densitometry, and Osteoporosis Foundation of New Mexico. DLK has received institutional grant/research support and speaking honoraria from Amgen, Pfizer, Astrazenica, and Eli Lilly. KSD has received speaking honoraria from Amgen. DAH has received institutional grant/research support and speaking honoraria from Amgen and Eli Lilly. STH has received speaker honoraria from Amgen, Eli Lilly, and Radius Health. MRM has received consulting fees from Amgen and speaking honoraria from Amgen and Radius Health. PDM has received scientific research grants from Amgen, Radius Health, Regeneron, Ultragenyx, National Bone Health Alliance, Immunodiagnostics, and Roche Diagnostics and serves on the Scientific Advisory Boards of Amgen, Radius Health, Ultragenyx, National Bone Health Alliance, and Sandoz.

Authorship: All authors had access to the data and a role in writing this manuscript.

Requests for reprints should be addressed to E. Michael Lewiecki, MD, Director, New Mexico Clinical Research & Osteoporosis Center, Director, Bone Health TeleECHO, UNM Health Sciences Center, 300 Oak St. NE, Albuquerque, NM 87106.

E-mail address: mlewiecki@gmail.com

0002-9343/
https://doi.org/10.1016/j.amjmed.2019.04.044

parenteral antiresorptive agents (eg, zoledronic acid or denosumab) may be offered (Table 1).[3] Antiresorptive agents increase bone mineral density, improve bone strength, and reduce risk of fracture by decreasing the rate of bone remodeling, initially decreasing bone resorption more than formation. Patients at very high risk of fracture, such as those with a recent fragility fracture, multiple fragility fractures, or very low bone mineral density, may be treated initially with an osteo-anabolic agent (eg, teriparatide or abaloparatide). Osteo-anabolic medications increase bone mineral density and reduce risk of fracture by increasing the rate of bone remodeling and modeling and increasing bone formation more than resorption, resulting in improvements in bone structure and an increase in bone mineral density.[4] Because the sequence of therapy (antiresorptive followed by osteo-anabolic vs osteo-anabolic followed by antiresorptive) may be clinically relevant,[5] careful therapy selection is required. Head-to-head clinical trials have demonstrated osteo-anabolic agents are superior to antiresorptive agents for reducing risk of fracture in patients in a high-risk categorgy.[6–8]

Except for teriparatide and abaloparatide, limited by the US Food and Drug Administration (FDA) to no more than 24 months of cumulative lifetime use, there is little evidence-based guidance regarding duration of treatment and when to continue, change, or stop medication. Patients are typically monitored with bone mineral density testing by dual-energy X-ray absorptiometry (DXA) 1 to 2 years after starting therapy. Stability or an increase in bone mineral density and the absence of fractures is generally assumed to be good response to treatment, leading to continuation of the same medication.[9] However, there may be circumstances in which a patient responds well to therapy, yet continues to have an unacceptably high risk for fractures. Response to therapy alone is not the desired treatment outcome for other chronic diseases (eg, hypertension, diabetes mellitus), and should not be for osteoporosis. Response to therapy is necessary, but it is not always sufficient to achieve an acceptable level of fracture risk. This is the fundamental principle behind the concept of treat-to-target for osteoporosis.

CLINICAL SIGNIFICANCE

- When initiating therapy because of a T-score ≤ -2.5, a reasonable target T-score is > -2.0.
- Osteo-anabolic therapy has been demonstrated to reduce fracture risk more than antiresorptive therapy in patients at high risk.
- Bone mineral density should be monitored for response to therapy and progress toward the treatment target.
- If there is unacceptable progress toward the treatment target, reevaluate and consider changing treatment.

TREAT-TO-TARGET

Treat-to-target is used to manage a variety of different chronic diseases, including rheumatoid arthritis,[10] hypertension,[11] and diabetes mellitus.[12] The treatment targets in these diseases are imperfect, but they provide frameworks for clinical decisions with opportunities for improving, harmonizing, and simplifying disease management and still allowing individualized treatment decisions.

Table 1 Comparison of Two Strategies for Managing Patients with Osteoporosis

Treatment Step	Current Paradigm	Treat-to-Target
Decision to treat	Determined by baseline level of fracture risk, typically according to T-score, prior to fragility fracture, or fracture-risk algorithm (ie, FRAX)	Same
Evaluation for secondary causes of osteoporosis	Yes	Yes
Goal of treatment	Response to treatment	Achievement of an acceptable level of fracture risk; treatment target is identified before treatment is started
Selection of initial treatment	Usually a generic oral bisphosphonate unless a contraindication is present	Treatment most likely to be successful in reaching the treatment target is selected
Monitor for treatment effect	Yes, usually BMD measurement by DXA, sometimes bone turnover marker	Same
Treatment success	Stability or increase in BMD	Attainment of treatment target
Markers of treatment failure	Significant decrease in BMD, lack of expected change in bone turnover marker, fracture(s) on therapy	Failure to reach treatment target or be on a pathway toward the target
Managing treatment failure	Change to treatment more likely to elicit a response	Change to treatment more likely to reach the treatment target

BMD = bone mineral density; DXA = dual-energy X-ray absorptiometry; FRAX = Fracture Risk Assessment Tool.
From *Curr Osteoporos Rep*. 2017 Apr;15(2):103-109. doi: 10.1007/s11914-017-0350-7.[33]
Osteoporosis: Treat-to-Target. Lewiecki EM (with permission from Springer Nature).

Treat-to-target strategies aim to reduce end-organ damage and improve clinical outcomes.[13] A useful target is achievable with current therapies, intuitive for health care providers, and easily applied. Treat-to-target strategies set a biomarker value associated with a sufficiently reduced level of risk for the consequences of the disorder being treated. The therapy that has the highest probability of reaching that target in a reasonable time frame is then selected. Progress toward the target is reassessed periodically, facilitating decisions to stop, continue, or change therapy (Table 2).

POTENTIAL TARGETS FOR OSTEOPOROSIS TREATMENT

The goal of osteoporosis treatment should be a fracture risk below the risk threshold for initiating therapy. Because there is no direct way to measure bone strength or fracture risk in individuals, surrogates are used. Candidate surrogates include bone turnover markers, estimates of fracture risk using a validated fracture risk algorithm, and bone mineral density (expressed as T-score, the standard deviation [SD] difference between the patient's bone mineral density and the bone mineral density of a young-adult reference population; Table 2).

Bone Turnover Markers

Bone turnover markers (eg, C-telopeptide, a marker of bone resorption; N-terminal propeptide of type 1 collagen, a marker of bone formation) are biological by-products of bone remodeling that change rapidly with treatment, allowing for assessment of treatment response within weeks to months of starting or changing therapy.[14] In a meta-analysis, a 70% decrease in bone turnover markers was associated with an approximate 40% lower risk of fracture with bisphosphonate therapy taken for a year.[15] A suggested target for antiresorptive therapies has been the reduction of bone turnover markers below the mean premenopausal level.[16] Although the changes in bone turnover markers may be useful to monitor therapy, there are many limitations, including preanalytical and analytical variability, limited availability and affordability, lack of consensus on reference ranges, inadequate definition of the least significant change, and debate about the preferred marker for different medications.[17] In numerous phase III trials where anti-fracture therapies were assessed, there were substantial overlaps in the changes of bone turnover markers between placebo and treatment arms,[18] casting doubt on the use of bone turnover markers as a target in individual patients. In clinical trials, there was also a large overlap of bone turnover marker levels between those who go on to develop fractures and those who do not.[17] Given these uncertainties, a bone turnover marker is currently not an appropriate sole target in a treat-to-target strategy.

Fracture-Risk Algorithms

Fracture-risk tools such as the Fracture Risk Assessment Tool (FRAX) combine information from bone mineral density and selected clinical risk factors to provide an estimate of the risk of fracture in untreated individuals. However, the fracture-risk assessment tools currently in use do not appear to capture the reduction in risk associated with osteoporosis treatments.[19] A fracture-risk algorithm for patients being treated would need to incorporate bone mineral density change during therapy, the impact of fracture during therapy, and recency of fracture. Such a tool has not yet been developed and validated, and therefore, none can be used as a treatment target.

Bone Mineral Density

Bone mineral density is the leading candidate for a treatment target. It is used for the diagnosis of osteoporosis and is strongly correlated with risk of fracture in patients left untreated, with an approximate doubling of risk for fracture for each SD decrease (approximately equal to 1 T-score unit) in bone mineral density.[20]

There is usually an increase in bone mineral density with osteoporosis therapies. Because greater treatment-related increases in bone mineral density are associated with greater decreases in the risk of fracture,[15,21–26] the bone mineral density attained with therapy is a logical target, while acknowledging that improvement in bone mineral

Table 2 Considerations in the Use of Treatment Targets for Osteoporosis

Indication for Treatment*	Treatment Target	Comments
T-score ≤ -2.5	T-score > -2.0	Supported by evidence from post hoc analyses of clinical trials with bisphosphonates and denosumab. Very low baseline T-score and very high risk for fractures suggest the need for aggressive treatment most likely to reach the target, often osteo-anabolic followed by antiresorptive therapy.
High risk for fracture (eg, FRAX, CAROC)	Fracture risk below the treatment threshold	Largely aspirational because a validated fracture-risk algorithm that captures the reduction in fracture risk with treatment does not yet exist.
Fragility fracture (independent of T-score and fracture risk algorithm)	T-score > -2.0 or appropriate response of bone turnover marker	Rapid-acting highly-effective therapy may be desirable because of a high risk of another fracture in the first 1-2 years after a fracture

CAROC = Canadian Association of Radiologists and Osteoporosis Canada; FRAX = Fracture Risk Assessment Tool.

*The treatment target must vary according to the indication for treatment. The best validated target is T-score.

density alone does not capture the full benefit of therapy. With alendronate, etidronate, calcitonin, and raloxifene, larger changes in bone mineral density are associated with greater reductions in risk for vertebral fractures,[24] and with denosumab and zoledronic acid, the relationship between increases in bone mineral density and reduction in risk for fractures are especially strong with correlations of more than 0.8.[22,23]

There are limitations to the use of bone mineral density as a target. With most medications, the rate of change in bone mineral density is slow. Because intervals between bone mineral density tests may be 1 year or longer, it could take years to assess attainment of the treatment target. Bone mineral density alone does not adequately stratify risk, as many patients with T-score values > -2.5 (cutoff for densitometric diagnosis of osteoporosis by DXA) will fracture,[27] owing to a variety of other skeletal and nonskeletal factors.[28] There is no consensus on a bone mineral density or a T-score value that represents an acceptably low risk for fracture, whether there needs to be adjustment for age or clinical risk factors and which skeletal site is optimal to assess. Notwithstanding these limitations, the power of bone mineral density to predict fracture is similar to the power of blood pressure to predict stroke and superior to serum cholesterol for the prediction cardiovascular disease end points.[20]

BONE MINERAL DENSITY T-SCORE AS A TARGET FOR OSTEOPOROSIS THERAPY

The target bone mineral density T-score of > -2.5 is consistent with reports from the Western Osteoporosis Alliance and the American Society of Bone and Mineral Research, which suggest that a bisphosphonate "holiday" be considered when hip T-score is > -2.5 after at least 5 years of an oral bisphosphonate or 3 years of an intravenous bisphosphonate.[29,30] Given that the least significant change (smallest statistically significant change with a 95% level of confidence) for bone mineral density measurement is generally about 3%-5%,[31] attaining a T-score of > -2.0 provides a high degree of confidence that the T-score is truly > -2.5.

There are several clinical benefits of having a T-score treatment target. Bone mineral density testing by DXA is widely available and already used by clinicians to establish a baseline before treatment and to monitor treatment effect. Selection of initial treatment can be guided according to the likelihood of reaching the T-score target, and treatment modification can be guided according to progress, or lack of it, in reaching the T-score target. The T-score can be used to determine when a bisphosphonate holiday should be considered and T-score or fracture-risk assessment can be used to determine when the holiday should end.

Table 2 presents considerations for treatment targets for the 3 categories of treatment indications.

EVIDENCE SUPPORTING A T-SCORE TARGET

The evidence supporting a T-score treatment target has been reviewed elsewhere in detail.[32,33] Briefly, there are accumulating data showing that greater bone mineral density increases are associated with larger reductions in the risk of fracture, at both vertebral and nonvertebral sites.[24–26]

There may be little benefit to continuing bisphosphonate treatment in patients who have attained a T-score > -2.5 to > -2.0.[34,35] The Fracture Intervention Trial Long-term Extension (FLEX) and the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) trials demonstrated that patients with a T-score of < -2.5 after 3-5 years of therapy (and patients with T-score < -2.0 and a vertebral fracture) may benefit from continued therapy.[31,36,37]

With denosumab in the Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) Extension, patients attaining femoral neck or total hip T-score > -2.5 after 3 years of therapy had no further reductions in nonvertebral fracture risk with continued therapy, whereas those with T-score < -2.5 did benefit.[38] However, because discontinuation of long-term denosumab may be followed by a rapid rise in bone remodeling, decrease of bone mineral density, and return of fracture risk to baseline,[39] a drug holiday is not appropriate with denosumab as it may be with bisphosphonates. Rather, treatment should be continued or transitioned to another antiresorptive medication.

CLINICAL APPLICATIONS FOR A T-SCORE TARGET

The National Osteoporosis Foundation Clinician's Guide to Prevention and Treatment of Osteoporosis[40] recommends treatment to reduce risk of fracture for a postmenopausal woman or man age 50 years or older when the T-score measured by DXA is ≤ -2.5 at the lumbar spine, total hip, or femoral neck. The guidelines, however, do not clearly specify how to select a specific drug for starting treatment, how long to give it, and when, if ever, treatment should be changed. Some examples of applying the concept of treat-to-target in clinical practice follow.

TREAT-TO-TARGET CASE STUDIES

Patient 1

Consider a 65-year-old woman with L1-L4 T-score of -2.5 and no known fracture. Treatment could be initiated with alendronate, a generic oral bisphosphonate that is inexpensive and generally well tolerated. This decision is concordant with treat-to-target principles, with a target T-score > -2.5 and ideally > -2.0 expected to be achievable. In the Fracture Intervention Trial,[41] postmenopausal women with osteoporosis treated with alendronate were observed to have a 4-year bone mineral density increase of 8.3% at the lumbar spine and 3.4% at the total hip compared with baseline, with a significant decrease in vertebral fracture risk.

This patient would achieve target on alendronate and may then qualify for a drug holiday after 3-5 years of treatment.

Patient 2

Consider another patient with much higher fracture risk: a 78-year-old woman with total hip T-score of −3.4 and a recent severe (Grade 3) low-trauma T9 vertebral fracture. The very low T-score and recent severe vertebral fracture suggest that the risk of future fracture is very high. Treatment with alendronate would be unlikely to reach a target T-score > −2.5 or −2.0 and unlikely to achieve an acceptable level of risk of fracture. A more promising plan might be to start treatment with an osteo-anabolic agent (eg, teriparatide, abaloparatide) for 2 years, followed by a potent antiresorptive agent, such as denosumab, to consolidate and enhance the benefits of anabolic therapy.[5] A recent study enrolling postmenopausal women with vertebral fractures, most of whom had had prior bisphosphonate, showed a 60% reduction in clinical fractures with transition to teriparatide for 2 years as compared to continuing risedronate antiresorber for 2 years.[6]

Treat-to-target can also influence clinical decisions after treatment is started. As an example, if patient 2 had been initially treated with alendronate and a DXA study 2 years later showed a bone mineral density increase of 3% at the lumbar spine and 2% at the total hip, it would be reasonable to conclude that she was responding to therapy and the risk of fracture was reduced. However, it would also be likely that risk for fracture remains very high. Other risks may also supervene. If this patient were to have a new T10 vertebral fracture, the likelihood of future fractures becomes even higher than previously estimated, despite improvement in bone mineral density. Treat-to-target would suggest a change in therapy to an anabolic drug or more potent antiresorptive agent. Switching to denosumab increases bone mineral density more than continuing alendronate or switching to ibandronate, risedronate, or zoledronic acid.[41–45]

CONTROVERSIES

There is evidence that switching from a bisphosphonate to denosumab results in additional gains in bone mineral density.[42–45] Although there are robust data showing that bigger increases in bone mineral density with treatment are associated with greater reductions in risk for fracture, there is no direct evidence that switching from a bisphosphonate to denosumab results in a further reduction in risk for fracture. For some patients with very low bone mineral density (eg, baseline T-score < −3.5), it may not be possible to achieve the treatment target with current medications. There is no consensus as to what is an acceptably low risk of fracture and how this should be expressed. It would be ideal to have a fracture-risk algorithm that fully captures the reduction in risk for fracture with treatment. Once the target has been attained, there is little to guide the subsequent course of action, although it seems reasonable to consider a bisphosphonate holiday for a patient who has been treated with a bisphosphonate for at least 3-5 years,[30] to continue denosumab for at least 10 years, switch from denosumab to a bisphosphonate, or switch to an antiresorptive agent for a patients who has completed a course of therapy with teriparatide or abaloparatide. Bisphosphonate or denosumab after teriparatide is likely to maintain or further increase bone mineral density.[5] Bisphosphonate after denosumab may, in some but not all cases, maintain bone mineral density.[46] It must be recognized that osteoporosis is a lifelong disease that requires lifelong attention, including in patients who have achieved the treatment target.

RESEARCH AGENDA

We recognize the need for further study to develop and validate treatment targets for all patients who are treated to reduce risk of fractures. There are some critical questions that need to be addressed to better implement a treat-to-target strategy for all patients, whether they are treated because of baseline T-score ≤ −2.5 or with baseline T-score > −2.5 and previous fragility fracture or high-risk of fracture. First, a fracture-risk assessment tool that is validated to capture the reduction in risk of fracture associated with all therapies is needed. These data could then be linked to various potential targets, such as T-score at various skeletal sites and perhaps bone turnover markers. The probabilities of reaching the T-score target based on different therapies need to be elucidated. More study is needed on the long-term anti-fracture efficacy of switching therapies to better inform clinicians of the benefits of switching therapy (eg, from a weak antiresorptive agent to one more potent or from an antiresorptive agent to an osteo-anabolic) in patients who are not reaching their target.

SUMMARY

Some patients who respond to osteoporosis therapy still have an unacceptably high risk of fracture. With a treat-to-target approach, a target is established before treatment is started. This can guide selection of initial therapy with a medication or combination of medications most likely to reach that target. Decisions to stop, continue, or change therapy can be made according to progress toward that target over time. For patients started on treatment because of T-score ≤ −2.5, the most feasible treatment target is T-score > −2.0. We suggest that initial treatment be with a medication that has a greater than 50% probability of reaching a T-score > −2.0 within 3 years. The choice of therapy should be determined by factors that include comorbidities, cost, access to therapy, and patient preference. Patient preference may be influenced by the length of clinical experience with the therapy, the route of administration (oral vs subcutaneous injection vs intravenous infusion), the frequency of administration, the out-of-pocket expense, and the perceived risks of therapy. For patients at very high risk of fracture, especially those with a recent fragility fracture, multiple fragility fractures, or very low bone mineral

density (eg, T-score <−3.5), more aggressive treatment with an anabolic agent (eg, teriparatide, abaloparatide) should be considered, with consideration of patient preference and cost. For a patient with baseline T-score > 2.5 who is started on treatment because of the presence of a fracture or high probability of fracture, a treatment target at this time is indeterminate (largely aspirational), although it would be reasonable to try to achieve a T-score that is significantly better than the baseline.

References

1. MacLean C, Newberry S, Maglione M, et al. Systematic review: comparative effectiveness of treatments to prevent fractures in men and women with low bone density or osteoporosis. *Ann Intern Med.* 2008;148(3):197–213.
2. Cummings SR, McClung MR, Christiansen C, et al. A phase III study of the effects of denosumab on vertebral, nonvertebral, and hip fracture in women with osteoporosis: results from the FREEDOM trial. *J Bone Miner Res.* 2008;23(suppl 1):S80.
3. Camacho PM, Petak SM, Binkley N, et al. American Association of Clinical Endocrinologists and American College of Endocrinology clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis - 2016 - executive summary. *Endocr Pract.* 2016;22(9):1111–8.
4. Dempster DW, Zhou H, Recker RR, et al. Skeletal histomorphometry in subjects on teriparatide or zoledronic acid therapy (SHOTZ) study: a randomized controlled trial. *J Clin Endocrinol Metab.* 2012;97(8):2799–808.
5. Cosman F, Nieves JW, Dempster DW. Treatment Sequence matters: anabolic and antiresorptive therapy for osteoporosis. *J Bone Miner Res.* 2017;32(2):198–202.
6. 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(10117):230–40.
7. Saag KG, Petersen J, Brandi ML, et al. Romosozumab or alendronate for fracture prevention in women with osteoporosis. *N Engl J Med.* 2017;377(15):1417–27.
8. Saag KG, Shane E, Boonen S, et al. Teriparatide or alendronate in glucocorticoid-induced osteoporosis. *N Engl J Med.* 2007;357(20):2028–39.
9. Lewiecki EM, Watts NB. Assessing response to osteoporosis therapy. *Osteoporos Int.* 2008;19(10):1363–8.
10. Singh JA, Saag KG, Bridges SL Jr., et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Rheumatol.* 2016;68(1):1−26.
11. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014;311(5):507–20.
12. Chamberlain JJ, Rhinehart AS, Shaefer C.F. Jr., Neuman A. Diagnosis and management of diabetes: synopsis of the 2016 American Diabetes Association standards of medical care in diabetes. *Ann Intern Med.* 2016;164(8):542–52.
13. Lewiecki EM, Cummings SR, Cosman F. Treat-to-target for osteoporosis: is now the time? *J Clin Endocrinol Metab.* 2013;98(3):946–53.
14. Lee J, Vasikaran S. Current recommendations for laboratory testing and use of bone turnover markers in management of osteoporosis. *Ann Lab Med.* 2012;32(2):105–12.
15. Hochberg MC, Greenspan S, Wasnich RD, Miller P, Thompson DE, Ross PD. Changes in bone density and turnover explain the reductions in incidence of nonvertebral fractures that occur during treatment with antiresorptive agents. *J Clin Endocrinol Metab.* 2002;87(4):1586–92.
16. Bauer DC, Black DM, Bouxsein ML, et al. Treatment-Related changes in bone turnover and fracture risk reduction in clinical trials of anti-resorptive drugs: a meta-regression. *J Bone Miner Res.* 2018;33(4):634–42.
17. Vasikaran S, Eastell R, Bruyere O, et al. Markers of bone turnover for the prediction of fracture risk and monitoring of osteoporosis treatment: a need for international reference standards. *OsteoporosInt.* 2011;22(2):391–420.
18. Reginster JY, Sarkar S, Zegels B, et al. Reduction in PINP, a marker of bone metabolism, with raloxifene treatment and its relationship with vertebral fracture risk. *Bone.* 2004;34(2):344–51.
19. Leslie WD, Lix LM, Johansson H, Oden A, McCloskey E, Kanis JA. Does osteoporosis therapy invalidate FRAX for fracture prediction? *J Bone Miner Res.* 2012;27(6):1243–51.
20. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. BMJ. 1996;312(7041):1254–9.
21. Hochberg MC, Ross PD, Black D, et al. Larger increases in bone mineral density during alendronate therapy are associated with a lower risk of new vertebral fractures in women with postmenopausal osteoporosis. *Arthritis Rheum.* 1999;42(6):1246–54.
22. Jacques RM, Boonen S, Cosman F, et al. Relationship of changes in total hip bone mineral density to vertebral and nonvertebral fracture risk in women with postmenopausal osteoporosis treated with once-yearly zoledronic acid 5 mg: the HORIZON-Pivotal Fracture Trial (PFT). *J Bone Miner Res.* 2012;27(8):1627–34.
23. Austin M, Yang YC, Vittinghoff E, et al. Relationship between bone mineral density changes with denosumab treatment and risk reduction for vertebral and nonvertebral fractures. *J Bone Miner Res.* 2012;27(3):687–93.
24. Wasnich RD, Miller PD. Antifracture efficacy of antiresorptive agents are related to changes in bone density. *J Clin Endocrinol Metab.* 2000;85(1):231–6.
25. Black DM, Vittinghoff E, Eastell R, et al. Hip BMD by DXA Can reliably estimate reduction in hip risk in osteoporosis trials: a meta-regression. *J Bone Miner Res.* 2015;30(S1):S49.
26. Bouxsein ML, Eastell R, Lui LY, et al. Change in bone density and reduction in fracture risk: a meta-regression of published trials. *J Bone Miner Res.* 2019;34:632–42.
27. Kanis JA, Johnell O, Oden A, Jonsson B, Dawson A, Dere W. Risk of hip fracture derived from relative risks: an analysis applied to the population of Sweden. *Osteoporos Int.* 2000;11(2):120–7.
28. Kanis JA, on behalf of the World Health Organization Scientific Group. *Assessment of Osteoporosis at the Primary Health-Care Level.* Technical Report. World Health Organization Collaborating Centre for Metabolic Bone Diseases. University of Sheffield. In: *UK: University of Sheffield*; 2007.
29. Adler RA, El-Hajj Fuleihan G, Bauer DC, et al. Managing osteoporosis in patients on long-term bisphosphonate treatment: report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res.* 2016;31(1):16–35.
30. McClung M, Harris ST, Miller PD, et al. Bisphosphonate therapy for osteoporosis: benefits, risks, and drug holiday. *Am J Med.* 2013;126(1):13–20.
31. Cosman F, Cauley JA, Eastell R, 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(12):4546–54.
32. Cummings SR, Cosman F, Lewiecki 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(1):3–10.
33. Lewiecki EM. Osteoporosis: treat-to-target. *Curr Osteoporos Rep.* 2017;15(2):103–9.
34. Schwartz AV, Bauer DC, Cummings SR, et al. Efficacy of continued alendronate for fractures in women with and without prevalent vertebral fracture: the FLEX trial. *J Bone Miner Res.* 2010;25(5):976–82.
35. Black DM, Bauer DC, Schwartz AV, Cummings SR, Rosen CJ. Continuing bisphosphonate treatment for osteoporosis—for whom and for how long? *N Engl J Med.* 2012;366(22):2051–3.

36. Black DM, Schwartz AV, Ensrud KE, 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(24):2927–38.
37. Black DM, Reid IR, Boonen S, et al. The effect of 3 versus 6 years of zoledronic acid treatment of osteoporosis: a randomized extension to the HORIZON-Pivotal Fracture Trial (PFT). *J Bone Miner Res.* 2012;27(2):243–54.
38. Ferrari S, Adachi JD, Lippuner K, et al. Further reductions in nonvertebral fracture rate with long-term denosumab treatment in the FREEDOM open-label extension and influence of hip bone mineral density after 3 years. *Osteoporos Int.* 2015;26(12):2763–71.
39. Cummings SR, Ferrari S, Eastell R, et al. Vertebral Fractures after discontinuation of denosumab: a post hoc analysis of the randomized placebo-controlled FREEDOM Trial and its extension. *J Bone Miner Res.* 2018;33(2):190–8.
40. Cosman F, de Beur SJ, LeBoff MS, et al. Clinician's guide to prevention and treatment of osteoporosis. *Osteoporos Int.* 2014;25(10):2359–81.
41. Cummings SR, Black DM, Thompson DE, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. *JAMA.* 1998;280(24):2077–82.
42. Kendler DL, Roux C, Benhamou CL, et al. Effects of denosumab on bone mineral density and bone turnover in postmenopausal women transitioning from alendronate therapy. *J Bone Miner Res.* 2010;25(1):72–81.
43. Roux C, Hofbauer LC, Ho PR, et al. Denosumab compared with risedronate in postmenopausal women suboptimally adherent to alendronate therapy: efficacy and safety results from a randomized open-label study. *Bone.* 2014;58:48–54. https://doi.org/10.1016/j.bone.2013.10.006.
44. Recknor C, Czerwinski E, Bone HG, et al. Denosumab compared with ibandronate in postmenopausal women previously treated with bisphosphonate therapy: a randomized open-label trial. *Obstet Gynecol.* 2013;121(6):1291–9.
45. Miller PD, Pannacciulli N, Brown JP, et al. Denosumab or zoledronic acid in postmenopausal women with osteoporosis previously treated with oral bisphosphonates. *J Clin Endocrinol Metab.* 2016;101(8):3163–70.
46. Freemantle N, Satram-Hoang S, Tang ET, et al. Final results of the DAPS (denosumab adherence preference satisfaction) study: a 24-month, randomized, crossover comparison with alendronate in postmenopausal women. *Osteoporos Int.* 2012;23(1):317–26.