Osteoporosis

Carrie Ye, Peter Ebeling, Gregory Kline

Osteoporotic fractures are one of the most common and consequential diseases of advanced ageing and many antifracture therapies are widely available but largely underused. This Seminar presents an updated approach to osteoporosis consultation, drawing upon published evidence and collaborative expert opinion to place the data in a pragmatic and useful context for clinicians. New evidence on osteoporosis screening recommendations, fracture-risk assessment, intervention decisions, nutrition-based therapies, and antiresorptive and anabolic therapies are discussed, along with practical approaches to treatment in the oldest old, those with chronic kidney disease, and patients who continue to fracture despite therapy. Patient safety is emphasised by providing an overview of advice on safe discontinuation of denosumab in those who require it.

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Medicine and Dentistry, University of Alberta, Edmonton, AB, Canada (C Ye MD); **Northern Alberta Osteoporosis Program, Alberta Health Service, Edmonton, AB, Canada** (C Ye); **Department of Medicine, School of Clinical Sciences at Monash Health, Monash University, VIC, Australia** (Prof P Ebeling MD); **Department of Medicine, University of Calgary, Calgary, AB, Canada** (Prof G Kline MD); **Dr David Hanley Osteoporosis Clinic, Alberta Health Services, Calgary, AB, Canada** (Prof G Kline)

Correspondence to:
Dr Gregory Kline, Dr David Hanley Osteoporosis Clinic, Alberta Health Services, Calgary, AB, T2T 5C7, Canada
gregory.kline@ahs.ca

Introduction

Bone loss and osteoporosis occur commonly with normal ageing, chronic diseases, and off-target drug therapy effects.[1] The technical description of osteoporosis as a state of low bone mass with microarchitectural deterioration includes mention of increased bone fragility and propensity to fracture,[2] often recurrently.[3] Low bone mass is asymptomatic, but osteoporotic fractures are common,[4] costly,[5,6] and often disabling events in the life of an older person.[7] Effective therapies to reduce the risk of such fractures are widely available, but often underused or mistargeted.[8,9]

Background

In many cases, the initial presentation leading to a diagnosis of osteoporosis is the occurrence of a major low-trauma fracture, typically of the wrist, shoulder, pelvis, or hip in postmenopausal women or older men. Vertebral collapse, or compression fracture, is also common, albeit often unrecognised, asymptomatic, or dismissed as a normal age-related x-ray finding.[10] A clinical fracture presentation represents the late-stage manifestation of an otherwise silent and continuous process of age-related bone loss, which can be detected earlier through dual x-ray absorptiometry, often called a bone mineral density (BMD) measurement. There are many factors that help determine an individual's typical (or peak) adult bone mass and subsequent rate of bone loss, for example genetics, nutrition, body weight, physical activity, reproductive hormone status, tobacco or alcohol use, medications (such as prednisone), and chronic diseases (such as diabetes or rheumatoid arthritis). Low or decreasing bone density is extremely common with advancing age; the rate of bone loss accelerates for a decade following menopause.[11] Therefore, depending on the presence or absence of such factors, some patients might develop osteoporosis with fractures at a relatively young age whereas others might maintain a comparatively robust bone health well into later life. Most atraumatic fractures occur in the context of a fall and therefore contributors to recurrent falls are also important, for example frailty, impaired mobility, chronic neurologic disease, dementia, poor vision, and environmental hazards.[12] A history of sustaining a low-trauma fracture is the most important signal for a high likelihood of having another low-trauma fracture within a few years.[13] Atraumatic fractures are very common in most countries globally,[14] and the rate of these increases as the population ages[4] and they contribute to acute and chronic health-care and personal costs, including those of persistent disability and institutionalisation.[6] Among the most vulnerable, a major osteoporotic fracture (MOF; which includes low-trauma or no-trauma fractures of the forearm, upper humerus, hip, or vertebrae) is often the initiating step for a sequence of events that lead to end of life. However, not every person with low bone density will sustain a fracture; or at least not in the near-to-mid-term future. Therefore, one of the primary tasks of the clinician is to assess the patient's bone health status and make an estimation of the resulting risk of fracture, usually over the next 10 years. This process typically involves use of a validated clinical fracture prediction tool, which might include BMD measurements. Concomitantly, the care provider will order a small number of routine laboratory tests, such as serum calcium, phosphate, alkaline phosphatase, or creatinine, to exclude other common medical causes of bone loss, such as hyperparathyroidism. Finally, for patients who are deemed to be at sufficiently high risk for fracture in the short-term future, or for those who wish to take a proactive approach to bone mass preservation, several therapeutic agents are available that can either maintain, or even build, bone mass.

Search strategy and selection criteria

Several author meetings were held to decide upon the primary topics to be selected for comprehensive review based upon the intended audience and educational focus of the proposed work. For each topic, the authors searched PubMed, OVID, and Epistomonikos databases for peer-reviewed publications and systematic reviews in English, published between Jan 1, 2018, and Feb 28, 2025, although older articles from searches of a study's reference list were not excluded from consideration if appropriate. Each topic was searched individually by one author per subtopic using the paper title as keywords. Articles retrieved were reviewed by all authors to gather consensus for relevance and importance before inclusion in the work.

Osteoclast-inhibiting antiresorptives, such as bisphosphonates or denosumab, are the most used antifracture agents worldwide; whereas osteoblast-stimulating anabolic agents, such as teriparatide, abaloparatide, and romosozumab, are higher cost therapies with variable availability.

Comprehensive, state-of-the-art reviews of osteoporosis clinical medicine were published by Compston and colleagues in 2019[15] and Reid and Billington in 2022,[16] and most of this content remains highly relevant. This Seminar has been designed with the general practitioner in mind and will therefore focus upon practice-changing developments in osteoporosis over the past 5 years, in addition to addressing practical questions commonly posed in referrals to osteoporosis clinics.[17] In some areas, such as case screening and pharmacotherapies, the evidence derives from robust randomised clinical trials and epidemiological models derived from retrospective cohort studies to inform fracture prediction tools. Other topics, such as shared decision-making, treatment of the oldest old, and how to approach a patient who fractures despite therapy, are included for their pragmatic necessity but derived from evidence-supported expert opinion.

Osteoporosis screening

Screening recommendations to identify pharmacotherapy candidates among those at risk for future fragility fractures are important elements in all osteoporosis guidelines.[18] Screening can involve only using major clinical risk factors, such as age, sex, and prior fragility fracture, although the addition of BMD, measured by dual-energy x-ray absorptiometry (DXA), improves the risk stratification accuracy.[19] However, effective treatment options are often initiated based on low BMD.[20] Since 2019, several societies have updated their fracture-risk screening recommendations, although most guidelines support BMD testing as part of treatment selection, there is no consensus on population-level screening (table 1).[21–27]

Many guidelines recommend DXA scans in all women over a specific age (table 1). Although osteoporosis is more common in women, it is also an important disease in men, with 40% of all fragility fractures occurring in males (panel 1).[32] Despite a scarcity of evidence to support population-level DXA screening in men, some societies do include age-based screening recommendations for males.[22,24]

The US Preventive Services Task Force, the North American Menopause Society, the American College of Obstetricians and Gynecologists, and the Bone Health and Osteoporosis Foundation recommend DXA scans in all women 65 years or older,[21,24–26] whereas Osteoporosis Canada recommends a minimum age for screening of 70 years in both men and women[22] and the Bone Health and Osteoporosis Foundation also recommends DXA screening for men 70 years or older.[24] Other guidelines use non-age-related criteria for DXA referral: The American Association Of Clinical Endocrinologists and American College of Endocrinology and the National Osteoporosis Guideline Group recommend referring both men and women for

	Publication year	Recommended age for screening (years)	
		Women	Men
US Preventive Services Task Force[21]	2025	≥65	None*
Osteoporosis Canada[22]	2023	≥70	≥70
National Osteoporosis Guideline Group[23]	2022	None*	None*
Bone Health and Osteoporosis Foundation[24]	2022	≥65	≥70
North American Menopause Society[25]	2021	≥65	None*
American College of Obstetricians and Gynecologists[26]	2021	≥65	None*
American Association of Clinical Endocrinologists and American College of Endocrinology[27]	2020	None*	None*

*There are no population dual-energy x-ray absorptiometry screening recommendations, but all guidelines recommend dual-energy x-ray absorptiometry testing in those with clinical risk factors for osteoporosis or fracture.

Table 1: **Comparison of population-screening guidelines on the use of dual-energy x-ray absorptiometry for risk stratification**

Panel 1: Osteoporosis in men

- Age-specific fracture risk is lower in older men (>70 years) than in similarly aged women, but fractures are associated with a higher mortality risk in men than women
- An important male-specific risk factor is androgen-deprivation therapy for prostate cancer
- All osteoporosis medications recommended for women have been shown to improve bone mineral density in men and zoledronic acid has been shown to reduce vertebral fractures in men[28,29]
- Some guidelines recommend checking serum free or total testosterone levels as part of the osteoporosis tests in men, based on studies that have shown increase in bone mineral density in men with hypogonadism treated with testosterone[28,30]
- A landmark randomised controlled trial of testosterone therapy in men with hypogonadism showed that there was an increase in fracture risk in the testosterone arm (hazard ratio 1·43, 95% CI 1·04–1·97);[31] although fracture outcomes were a secondary endpoint, and it did not specifically enrol men with osteoporosis
- Consider measuring testosterone only in settings where symptomatic testosterone deficiency is suspected and testosterone treatment anticipated

DXA only if clinical risk factors indicate an increased risk of fracture.[23,27]

Three randomised controlled trials (RCTs), which included a total of 57744 women, reported the effects of primary care and the Fracture Risk Assessment Tool (FRAX)-score selected and population-level risk screening (including of BMD) on clinical fracture outcomes.[33–36] None of these RCTs included male participants. Although individually the three trials did not show significant fracture benefit across the full trial population, a meta-analysis showed a reduction in MOFs (hazard ratio [HR]=0·91, 95% CI 0·84–0·98) and hip fractures (HR=0·80, 95% CI 0·71–0·91).[33] The number of individuals needing to be screened to prevent one fracture was 247 for osteoporotic fractures and 272 for hip fractures, leading to 113 bone densitometry examinations for osteoporotic fractures (resulting in treatment for 25 individuals) and 124 bone densitometry examinations for hip fractures (resulting in treatment for 28 individuals).[33]

Unfortunately, the COVID-19 pandemic saw rates of DXA scans decrease by more than 50% globally.[37] To address this decline in osteoporosis screening, some researchers have proposed repurposing existing imaging studies, such as abdominal and pelvic CT scans to extract BMD measurement at the lumbar spine and hip. This secondary use of routine CT scans is referred to as opportunistic CT-dual-energy x-ray absorptiometry (CT-DXA), an area of research that has accelerated due to the rapid advancements in artificial intelligence. Two systematic literature reviews and meta-analyses of opportunistic CT-DXA studies found that some models performed better than standard DXA.[38,39] Although additional research is necessary to validate these emerging models, they show the potential to opportunistically detect and classify osteoporosis, which can help close the fracture-risk screening and treatment gap. However, as it would not be appropriate to perform subsequent CT scans for the sole purpose of monitoring BMD given the higher radiation exposure compared with DXA, one current limitation of opportunistic CT-DXA is its comparative validity with subsequent DXA scans to detect change in BMD, for example during monitoring of treatment response.[40]

Fracture-risk assessment

Although the diagnostic criteria for osteoporosis for both men and women is historically based on a BMD threshold T-score of –2·5 SD or lower, most fractures occur in individuals with T-scores above this threshold.[15] Thus, the National Bone Health Alliance Working Group advocated to formally expand the criteria for making a diagnosis of osteoporosis to include the presence of specific low-trauma fractures or the determination of an elevated fracture risk, without a T-score of –2·5 or lower.[41] Thus, it is important that clinical risk factors are considered, with or without BMD, when estimating an individual's fracture risk. Several fracture-risk calculators are available; the most widely used and recommended in guidelines is FRAX.[18] Published in 2008, it calculates the 10-year probabilities of an MOF and hip fracture using clinical risk factors, such as age, sex, weight, height, prior low-trauma or no-trauma fracture, parental hip fracture history, and glucocorticoid use, with or without femoral neck BMD.[42] Other risk tools exist, including the Garvan Bone Fracture Risk Calculator,which calculates the 5-year and 10-year risk of osteoporotic fracture, and includes falls as a factor; The Bone Health and Osteoporosis Foundation's American Bone Health Fracture Risk Calculator, which includes additional clinical risk factors beyond FRAX; and QFracture, which does not include BMD, but can calculate fracture risk for time frames between 1 to 10 years. The advantages of FRAX are that it has been widely validated in many large populations, and has country-specific models that reflect the epidemiology of country-specific fracture and mortality rates.[42] Additionally, trabecular bone score, a surrogate marker of bone microarchitecture that can be derived from DXA images, can be incorporated into FRAX to further improve its accuracy.[43,44]

A 2019 meta-analysis of the discriminative performance of 14 fracture-risk calculators found that FRAX had been validated by the most studies, and QFracture, FRAX with BMD, and Garvan with BMD had the highest discriminative performance for predicting fracture with site-specific areas under the curve ranging from 0·65 to 0·88,[45] indicating modest-to-good predictive ability for these calculators. Although treatment recommendations are generally based on 10-year fracture-risk estimates, there is evidence that fracture risk could be highest shortly after an incident fragility fracture, with approximately half of all subsequent fractures occurring in the first 2 years after the initial fracture.[46] This concept, referred to as imminent fracture risk, is not well accounted for by most fracture-risk calculators, which provide linear, long-term fracture-risk estimates. The fracture-risk evaluation model tool, developed in Denmark and externally validated in Canada, can be used to estimate imminent fracture risk as it has been shown to stratify the 1-year and 5-year risk of MOF.[47,48] Conversely, there is no consensus on how best to consider fractures that occurred many years, or even decades, before a current assessment. A 2024 study showed that early adulthood fractures (eg, age 20–30 years) are associated with increased future fracture risk in later adulthood, with adjusted HRs of 1·51 (95% CI 1·42–1·60) to 2·12 (1·67–2·71);[49] thus, fractures that occurred in the long-term past remain relevant to future fracture risk, albeit less so than recent major fractures.

There is considerable debate regarding the development and use of race-specific fracture-risk calculators. An American Society for Bone and Mineral Research Task Force on clinical algorithms for fracture risk

For the **Fracture Risk Assessment Tool (FRAX)** see https://frax.shef.ac.uk/FRAX/index.aspx

For the **Garvan Bone Fracture Risk Calculator** see https://fracturerisk calculator.com.au/calculator/

For **The Bone Health and Osteoporosis Foundation's American Bone Health Fracture Risk Calculator** see https://americanbonehealth.org/fracture-risk-calculator-pro/

For the **QFracture calculator** see https://qfracture.org/

concluded that there is little justification for race-based adjustments and recommended against their use.[50,51] A subsequent position paper from the International Osteoporosis Foundation disagreed, asserting that omission of race would decrease FRAX's performance and expose individuals to unnecessary treatments given racial population differences in fracture risk for the same BMD.[52] Both agreed that data supporting any fracture-risk calculator should be representative of the intended user population.

For the **FRAXplus Calculator** see https://fraxplus.org/calculation-tool

There are ongoing efforts to improve the accuracy of FRAX. FRAXplus, a payment-required online tool, allows adjustments to FRAX outputs for recency of fracture, high-dose glucocorticoid exposure, type 2 diabetes, lumbar spine BMD, trabecular bone score, falls, and hip axis length.[42] There are currently no studies showing the comparative performance of FRAX versus FRAXplus and the combined accuracy of multiple additional adjustments is unknown.[53] There is considerable work being done to update the original FRAX tool, including additional cohorts that were previously unavailable, which should improve its generalisability and accuracy, and sex-specific and ethnicity-specific differences in the weight of the risk factors are being evaluated.[54] Promising research shows that machine learning and artificial intelligence could enhance contemporary fracture-risk prediction by using high-dimensional data derived from medical records, imaging, and wearable devices.[55] Ultimately, it is unlikely that any population-based prediction tool will perform with perfect accuracy at the individual level, therefore, clinicians must augment any fracture-risk estimation with clinical judgement, considering the unique array of risk factors in their specific patient.

	Year of cost estimate	10-year fracture-risk threshold for cost-effectiveness
USA		
Alendronate[59]	2005	3% for hip fracture
China		
Zoledronate[60]	2018	7% for MOF
UK		
Bisphosphonate[61]	2019	1% for MOF treated with oral bisphosphonate; 10% for MOF treated with intravenous bisphosphonate
Romosozumab to alendronate[62]	2024	18–35% for MOF
Switzerland		
Alendronate[63]	2012	14% for MOF
Portugal		
Antiresorptive[64]	2016	9% for MOF treated with oral bisphosphonate; 20% for MOF treated with intravenous bisphosphonate; 35% for MOF treated with denosumab
Teriparatide[64]	2016	78% for MOF
Singapore		
Alendronate[57]	2019	14% for MOF
Taiwan		
Alendronate[65]	2017	7% for MOF
India		
Alendronate[66]	2024	14% for MOF

MOF=major osteoporotic fracture.

Table 2: **Selected cost-effectiveness threshold estimates for antifracture therapies**

The shared decision to initiate an antifracture drug therapy

Virtually all osteoporosis guidelines include specific criteria or scenarios in which it is recommended to offer or initiate antifracture drug therapy. Most guidelines agree that in an older or osteoporotic patient incident hip or vertebral fractures should be indications for pharmacotherapy intervention, but beyond that, a systematic review of global guidelines showed little agreement.[56–58] Generally, recommendations might be imaging-based (ie, DXA–BMD thresholds), risk tool-based (ie, FRAX), purely clinical (ie, fracture or age-related), or a combination of all three. Economics-based intervention (cost-effectiveness) thresholds exist for many countries, but might not be globally generalisable or stable over time and will vary by pharmaceutical agent (table 2).[57,59–66]

Comparison of different models for proposed intervention suggests large variations in the number of patients treated, with subsequent wide variation in the predicted usage of DXA and number of fractures prevented per 1000 patients treated.[67,68] A Canadian study that modelled various population treatment thresholds reported that a FRAX-based 10-year MOF risk of 20% or more was the ideal balance between maximum fractures prevented versus minimum required percentage of individuals on therapy.[67] The 2022 UK-based guideline[23] considered cost-effectiveness estimates in their recommendation, which were dominated by assumed use of either oral or intravenous bisphosphonate. Patient history of prior fragility fracture and an age-specific nomogram for FRAX-based 10-year risk interpretation[69] was provided to assist the clinician with targeting therapy towards patients deemed likely to benefit from treatment in a similar magnitude to that seen in secondary prevention.[70] Importantly, patients often have preferences and values regarding treatment initiation that do not always align with guideline recommendations or cost-effectiveness analyses.[71] One osteoporosis programme, which focused on autonomous, educated patient decision-making, showed that less than 50% of women with an MOF risk of 20% or more chose treatment; yet 23% of women with an MOF risk of less than 20% still wanted to be treated.[72] Some patients at relatively low fracture risk might still choose to be treated to prevent bone loss; a strategy of infrequent infusion of zoledronic acid at 5-year intervals was shown to preserve bone

density and provide a 30% (95% CI 23–44%) relative risk (RR) reduction in any fracture over a 10-year period.[73] Although shunned for many years[74] after the initial Women's Health Initiative study results,[75] menopausal oestrogen therapy is now increasingly recognised as an inexpensive and effective means to preserve bone mass for several years after menopause,[76] with relatively small absolute risk of serious adverse events in carefully selected patients.[77] A systematic review concluded that the use of visual osteoporosis patient decision aids might assist in a shared decision-making process by reducing decisional conflict and improving patients' ability to understand fracture risk.[78] A 2024 National Institute for Health and Care Excellence shared-decision aid for menopausal hormone therapy is also available.[79] Treatment initiation that is supported by patient choice can improve long-term therapy adherence,[80] a crucial determinant of real-world antifracture efficacy.[81]

Nutrition and fracture-risk reduction

Vitamin D

Vitamin D plays an important role in calcium-phosphate homoeostasis and is necessary for bone growth and maintenance.[82] However, in populations with a low prevalence of vitamin D deficiency, general population screening is not cost-effective and should be reserved for those with risk factors for serious vitamin D deficiency (eg, malnutrition, malabsorption, chronic kidney disease [CKD], and institutionalisation) or evidence of metabolic bone disease.[82] Total serum 25-hydroxyvitamin D concentration, also known as 25(OH)D, is the accepted biomarker of vitamin D status, but there is no clear consensus on target levels, or the optimal dose for vitamin D supplementation.[82,83] Several guidelines define vitamin D deficiency as a serum 25-hydroxyvitamin D level of less than 50 nmol/L.[27,83–85]

Separate from the debate of what levels constitute normal or optimal vitamin D status is the question of whether vitamin D supplementation impacts the incidence of fractures. A 2023 systematic literature review in postmenopausal women without osteoporosis showed inconclusive results on the efficacy of vitamin D on BMD or fractures.[86] Since this systematic literature review was completed, two bone-health-related analyses were published from the Vitamin D and Omega-3 Trial (VITAL), a double-blind, placebo-controlled RCT of 25 871 adults.[87,88] These studies showed that vitamin D supplementation did not decrease falls (odds ratio [OR] 0·97, 95% CI 0·90–1·05) or fractures (HR 0·98, 0·89–1·08). In addition, the results from the double-blind, randomised, placebo-controlled D-Health trial of 21 315 participants confirmed that monthly doses of 60 000 IU of vitamin D3 had no effect on fracture risk (HR 0·94, 0·84–1·06), although the HR for total fractures appeared to trend downwards with increasing follow-up time.[89] These studies were conducted in healthy adults and in regions with adequate sun exposure. Thus, it is unknown whether these findings can be generalised to individuals with osteoporosis or those at risk of it or to global regions where vitamin D deficiency is prevalent.[90]

Calcium

Although vitamin D supplementation has not been shown to reduce the risk of fractures, a 2019 meta-analysis of six RCTs (comprising 49 282 participants, 5449 fractures, and 730 hip fractures) focusing on combined supplementation with vitamin D (daily doses of 400–800 IU) and calcium (daily doses of 1000–1200 mg) found a 6% reduced risk of any fracture (RR 0·94, 95% CI 0·89–0·99) and a 16% reduced risk of hip fracture (RR 0·84, 0·72–0·97).[91] However, the long term follow-up of the Women's Health Initiative CaD trial of 36 282 postmenopausal women, who were randomly assigned to 1000 mg of calcium carbonate with 400 IU of vitamin D3 daily or placebo, found no overall effect on hip fractures.[92] Although the association between calcium supplementation and cardiovascular disease to date has been inconsistent, the Women's Health Initiative CaD trial showed a 6% increase in cardiovascular mortality in the vitamin D and calcium supplementation arm.[92] These results are in line with a 2021 meta-analysis of 13 double-blind, placebo-controlled RCTs examining calcium supplementation and risk of cardiovascular disease, which also showed a significant increase in the risk of cardiovascular disease in the calcium supplementation group.[93] However, a limitation of these studies is that cardiovascular adverse events were generally trial safety endpoints rather than primary endpoints.

Current guidelines recommend 700–1200 mg/day of calcium, preferably through diet.[21–25,27,94] There is likely little to no benefit of calcium supplementation if dietary intake is adequate. If calcium supplementation is required, calcium carbonate should be taken with food, as it is more effectively absorbed when there is acid in the stomach.[95] In the setting of proton pump inhibitors and higher stomach pH, calcium citrate is better absorbed than calcium carbonate.[95] Calcium lactate and calcium gluconate are less concentrated forms of calcium and not ideal oral supplements.[95] Regardless of the type of calcium supplement, the maximum dose of calcium supplement that should be taken at a time is 500 mg.[95]

Vitamin K

There is some evidence that vitamin K could be beneficial to bone health, but there has been controversy in this area as several publications in this field have been retracted.[96] Nonetheless, a 2022 meta-analysis of 16 RCTs examining the efficacy of vitamin K2 in treating osteoporosis, which did not include any retracted papers, found that vitamin K2 supplementation led to significant improvement in lumbar spine BMD (mean difference 1·02% change, 95% CI 0·30–1·75; p=0·0006).[97] Six of these studies reported fracture incidence (all fractures were considered in the meta-analysis) and the overall effect test showed

For the **visual osteoporosis patient decision aids** see https://osteoporosisdecisionaid.mayoclinic.org/ and https://frax.canadiantaskforce.ca/

that vitamin K2 did not reduce the incidence of fractures (RR 0·56, 0·28–1·11; p=0·10). After excluding one heterogeneous study, a significant reduction in fracture incidence was observed (RR 0·38, 0·20–0·76; p=0·006).[97] However, the majority of included studies were conducted in Japan and the generalisability of these results to other populations is unknown.

Factors influencing treatment modality

In selecting a treatment modality, osteoporosis severity, as well as patient-specific medical comorbidities, are important considerations. Osteoporosis severity has led to the concept of goal-directed therapy.[98] This approach sets treatment targets, determined according to each patient's individual risk profile, including the recency, site, number, and severity of prior fragility fractures, and the severity of densitometric osteoporosis. The selection of initial treatment modality should consider the more rapid fracture-risk reduction and BMD increases seen with anabolic versus antiresorptive therapy. When choosing bisphosphonate therapy, one large retrospective cohort study suggested intravenous zoledronic acid could be associated with a 25% lower fracture risk compared with oral alendronate,[99] but a meta-analysis of several smaller studies failed to show any difference in BMD or bone turnover markers between the two.[100]

In older patients, comorbidities need consideration. With age-related declines in kidney function, treatment options become restricted. Among patients with CKD stages 3–4, antifracture drugs might reduce the risk of vertebral fracture. However, as only small studies examining effects of alendronate or denosumab on BMD in patients with CKD stage 5 and patients with CKD stage 5 on dialysis (stage 5D) have been performed, there are no data on antifracture efficacy in this group.[101] Bisphosphonates are contraindicated in patients with an eGFR of less than 30–35 ml/min. However, in one study, about half the usual dose of oral alendronate (40 mg/week) in patients with CKD stage 5D maintained the same level of hip BMD compared with placebo.[102] The use of half-dose bisphosphonates in CKD stages 4–5 therefore has minimal evidence and would be considered off-label use in most countries. When considering the use of an antiresorptive drug in CKD stages 4–5D, adynamic bone disease should be excluded (ie, adynamic bone disease is unlikely if serum parathyroid hormone >1·6×upper limit of normal or bone-specific alkaline phosphatase in the upper third of normal range or above).[103] In patients with CKD stage 5D usual bisphosphonate doses can be used. In patients with CKD, high calcium intake might be associated with increased vascular calcification, so the recommended daily calcium intake from food and supplements should be 800–1000 mg and not exceed 1500 mg.[104] Vitamin D nutrition should be optimised for patients with CKD. Denosumab treatment in patients with CKD stages 4–5D has been associated with hypocalcaemia (sometimes severe and prolonged), even when baseline calcium and vitamin D are normal.[105] Hypocalcaemia can be prevented or treated with active vitamin D (eg, calcitriol), particularly in patients on long-term denosumab treatment whose renal function has declined over time. Romosozumab treatment reduces vertebral fracture compared with placebo or alendronate in patients with an eGFR of 30–59 mL/min as well as in patients with a higher eGFR.[106] In patients with comorbid cardiovascular disease, only romosozumab is contraindicated in patients with a history of myocardial infarction or stroke. Teriparatide was previously contraindicated in patients at risk of osteogenic sarcoma (eg, patients with prior skeletal radiation, Paget's disease of bone, unexplained elevation of alkaline phosphatase, or in adolescents) and for treatment limited to 2 years; however, pharmacovigilance and registry studies since initial market release in 2003 have not shown an increased osteogenic sarcoma risk in humans.[107,108]

Update on denosumab therapy

Denosumab is a human monoclonal antibody that prevents osteoclast-mediated bone resorption via inhibition of receptor activator nuclear factor kappa β ligand (RANK-L) binding to osteoclast-expressed nuclear factor kappa β receptor activator (RANK). After bisphosphonates, denosumab is the second most prescribed osteoporosis therapy.[109] It is also commonly used as part of treatment protocols to reduce bone loss or prevent fractures in selected oncology settings.[110] Several prospective clinical trials have shown robust antifracture efficacy and bone density improvements; a 2019 meta-analysis of ten clinical trials on denosumab and bisphosphonates suggested a marginally higher BMD was achieved with denosumab than bisphosphonates after 1 year of treatment. A single trial reported a lower fracture rate at 2 years in the denosumab-treated group (RR 0·51, 95% CI 0·27–0·97).[111] Denosumab is well tolerated, easily administered in community settings, convenient for patients (with subcutaneous dosing every 6 months), and with a very low incidence of adverse effects in healthy postmenopausal women. Use for up to 10 years is supported by data from the 7-year open-label extension of the original 3-year FREEDOM trial,[112] completed by 34% of the original participants. New vertebral and non-vertebral fractures were uncommon (0·9–2·5% per year) and serious adverse events were rare (two atypical femur fractures and 13 cases of osteonecrosis of the jaw). However, with broader medical experience, two denosumab-related concerns have emerged that are crucial for providers to consider before prescribing. Although denosumab is not renally metabolised and does not appear to have any adverse effect upon renal function, numerous cases of severe hypocalcaemia have been reported in patients with advanced CKD or those on dialysis, often requiring prolonged hospital admission for intravenous calcium

therapy.[113,114] Discontinuation or delayed administration of denosumab is now recognised as being associated with a phase of rapid (known as rebound) osteoclastic bone resorption and the risk of, sometimes multiple, vertebral fractures in the following year in up to 8–10% of cases.[115] The risk of such rebound bone loss appears to be related to duration of denosumab therapy[116] and is highest in those with previous vertebral fractures.[117] This rebound risk might be lower in those who used bisphosphonate before denosumab, but due to their retrospective observational nature the data are not clear. New guidelines have recommended that patients stopping denosumab should have a planned transition to a bisphosphonate, either zoledronic acid (preferred) or an oral bisphosphonate.[118] It is noted that if markers of osteoclast activity (eg, C-telo-peptide) are used to monitor for rebound osteoclastic activity, it might be necessary to give more than one infusion of zoledronic acid in the first 12 months off of denosumab. Concerningly, even this more aggressive approach has not been shown to reliably prevent bone loss and fracture in all cases.[119]

Update on anabolic therapies

Anabolic versus antiresorptive in fracture risk reduction

Anabolic therapies for osteoporosis act by either stimulating the parathyroid hormone receptor-1 (PTHR1; teriparatide and abaloparatide) or via sclerostin inhibition (romosozumab). Studies have shown the superiority of anabolic over antiresorptive therapy for both fracture reduction and increasing BMD. RCTs have shown that over 24–33 months, teriparatide reduces vertebral (HR 0·44, 95% CI 0·29–0·68) and clinical fractures (HR 0·48, 0·32–0·74) compared with risedronate;[120] romosozumab reduces vertebral (RR 0·52, 0·40–0·66), clinical (RR 0·73, 0·61–0·88), non-vertebral (RR 0·81, 0·66–0·99), and hip fractures (RR 0·62, 0·42–0·92) compared with alendronate;[121] and romosozumab reduces vertebral fractures (OR 0·45, 0·27–0·76) compared with denosumab.[122] A large network meta-analysis of RCTs in postmenopausal women showed bisphosphonates were less effective than PTHR1 agonists in reducing clinical fractures (OR 1·49, 1·12–2·00).[123] Bisphosphonates were also less effective than both PTHR1 agonists (OR 2·51, 1·82–3·46) and romosozumab (OR 2·06, 1·40–3·03) in reducing vertebral fractures, irrespective of baseline fracture risk.[123] Denosumab was less effective than PTHR1 agonists (OR 1·85, 1·18–2·92) and romosozumab (OR 1·56, 1·02–2·39) in reducing clinical fractures.[123] However, it should be noted that the effects of teriparatide on BMD at cortical bone sites (femoral neck and radius) are less than with antiresorptive drugs and there is little evidence that teriparatide reduces hip fractures.

Comparison between anabolic agents

Comparisons have also been made between anabolic drugs. In postmenopausal women with osteoporosis previously treated with oral bisphosphonates for 3 years, romosozumab increased BMD more than teriparatide.[124] Hip volumetric cortical bone mineral content increased with romosozumab but not teriparatide.[124] Although the ACTIVE trial showed similar vertebral fracture reductions for abaloparatide and teriparatide, abaloparatide had greater clinical and MOF reductions, with larger hip BMD increases.[125] This trial had several limitations, including open-label teriparatide use. A network meta-analysis, the highest level of evidence for measuring relative effectiveness across different interventions, also showed abaloparatide was more preventative for both non-vertebral (OR 0·87, 95% CI 0·80–0·95) and hip fractures (OR 0·81, 0·71, 0·93) than teriparatide.[126] However, such studies have limitations, including potential bias, complexity, and poor quality of included studies.

Therapy switches between anabolic and antiresorptive agents

An ideal treatment sequence is anabolic drugs first, followed by antiresorptive drugs. This has been shown for transitions from romosozumab to denosumab,[127] alendronate,[121] or zoledronic acid;[128] from abaloparatide to alendronate;[129] and from teriparatide to denosumab[130] in RCTs. All transitions were associated with either further improvements, or stability in spine and hip BMD. The reverse sequence of an antiresorptive drug first, followed by anabolic drug, is likely less ideal, although much more common in clinical practice. In an RCT, pretreatment with an oral bisphosphonate for 3 years attenuated spine and hip BMD to both romosozumab and teriparatide treatment by about one-third over 12 months, but BMD at the spine and hip were lower for teriparatide.[124] In another RCT, pretreatment with denosumab followed by teriparatide resulted in transient decreases in spine and hip BMD over 12 months with partial recovery by 24 months.[130] This outcome is likely due to an early additive effect of denosumab withdrawal and teriparatide to increase bone resorption. In a phase 2 trial extension, when romosozumab was started after denosumab treatment, BMD increases were attenuated compared with that seen when romosozumab was given without prior denosumab.[131] Observational studies using an overlapping sequential approach administering romosozumab 3 months after the last dose of denosumab and restarting denosumab at 6 months[132] or adding on romosozumab to denosumab[133] have both been described. The approach of adding on romosozumab to denosumab led to spine BMD increases similar to romosozumab alone, whereas with the overlapping sequential approach hip BMD also increased. Another potential approach is to give zoledronic acid at the time of the missed denosumab dose and then start romosozumab 12 months later, but evidence is currently scarce.

The use of more than one course of romosozumab has been reported in small phase 2 trial extension studies.[134] A second year of romosozumab treatment resulted in

small BMD increases and is not recommended. A possible strategy would be to have a 12-month course of a bisphosphonate before a second course of romosozumab, but evidence is currently scarce.

Safety of anabolic therapies

The cardiovascular safety of anabolic drugs has been examined. Major adverse cardiovascular events were marginally increased in postmenopausal women treated with romosozumab versus alendronate in the first year of the Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk of Fracture, whereas no difference was seen compared with placebo in the first year of the Fracture Study in Postmenopausal Women with Osteoporosis.[121,135] However, real-world studies have not shown an increase in rates of major adverse cardiovascular events during romosozumab therapy.[136–138] These findings should be further validated by larger pharmacoepidemiological studies. Until then it seems prudent to treat cardiovascular risk factors before prescribing romosozumab and avoiding its use in those with a recent stroke or myocardial infarction or those at high risk of major adverse cardiovascular events. A Bayesian network meta-analysis of RCTs showed abaloparatide had the lowest likelihood of cardiac adverse events compared with placebo, whereas romosozumab was more likely to have an increased risk.[139]

Treatment in the oldest old

A common question is whether there is an upper age limit at which antifracture drug therapy is no longer effective or recommended. Arguments against drug therapy include the risks of polypharmacy at older age,[140] the issue of recurrent falls (in which fractures can be independent of BMD),[141] the safety of intervention in view of multiple competing morbidities, and the general recommendation for deprescribing drugs of low value in patients with a short expected lifespan.[142] With respect to deprescribing drugs, a 2022 time-to-benefit meta-analysis of pooled bisphosphonate clinical trial data suggested that 12·4 months (95% CI 6·3–18·4) of therapy was the minimum required to prevent one non-vertebral fracture in 100 treated women and 20·3 months (11·0–29·7) of therapy was the minimum required to avoid one hip fracture in 200 treated women.[143] However, these numbers might be different for parenteral antiresorptives and anabolic therapies, which have more rapid antifracture effects and shorter time to benefit.[144] The oldest old (those >85 years) are under-represented in clinical trials but are the group in which disabling fractures are the most frequent and devastating, therefore effective intervention can have high value.

Use of fracture risk prediction tools, such as FRAX, might be inappropriate in a healthy older person, given that the tool accounts for the competing risk of mortality at advanced age, resulting in a paradoxical decline in 10-year fracture risk in the oldest old.[145] Although this model whereby competing mortality is factored in can inform treatment priorities at a population health level, it might discriminate against patients who do live long enough to sustain a fracture and whose personal 10-year risk of fracture might be much higher than their non-surviving peers. For this reason, use of alternative risk prediction tools with shorter prediction windows, such as QFracture or Garvan, could be considered in the older population who are in good health.[146] Real-world effectiveness studies from Sweden show that in those 80 years or older, bisphosphonates increase BMD and likely decrease hip and non-vertebral fracture incidence compared with untreated propensity-matched controls or pre-treatment time periods.[147,148] The magnitude of the effect was at least as great or greater than that seen in younger women and clinical trials involving postmenopausal women. Therefore, as part of a patient and family-shared decision, antifracture drug therapy is reasonable and likely valuable for those with life expectancy beyond 6–12 months. The value of serial BMD measurements in monitoring this treated patient group is unknown. Close attention to renal function is important, especially when using intravenous bisphosphonates or denosumab.[149,150]

Fracture during therapy

Although antifracture drug interventions have been shown to reduce the risk of fracture, no intervention can be expected to prevent all future fractures. Active treatment arms in large clinical trials still showed fracture rates of 1–11% within 2–5 years of therapy (table 3),[73,151–156] despite being effective at reducing risk of fracture compared with no treatment. Therefore, it is inevitable that some patients using antifracture therapy

	Intervention, duration	Clinical vertebral fracture rate	Hip fracture rate	Non-vertebral fracture rate
Cummings et al, 1998[151]				
Without prexisting vertebral fractures	Alendronate, up to 5 years	2·1%	0·9%	11·8%
With prexisting vertebral fractures	Alendronate, 3 years	2·3%	1·1%	11·9%
McClung et al, 2001[152]	Risedronate, 3 years	NA	2·8%	9·4%
Harris et al, 1999 (with prexisting vertebral fractures)[154]	Risedronate, 3 years	11·3%	NA	5·2%
Lyles et al, 2007[153]	Zoledronic acid, 2 years	1·7%	2·0%	7·6%
Black et al, 2007[155]	Zoledronic acid, 3 years	0·5%	1·4%	8·0%
Bolland et al, 2025[73]	Infrequent zoledronic acid, two doses over 10 years	6·3%*	NA	11·6%†
Cummings et al, 2009[156]	Denosumab, 3 years	2·3%	0·7%	6·5%

NA=not applicable. *Morphometric vertebral fractures. †Reported as major osteoporotic fracture.

Table 3: **Fracture rates in treatment arms of the largest antiresorptive randomised controlled trials where significantly reduced fracture risk was shown versus placebo**

will still sustain a fracture; although this does not necessarily imply treatment failure, it does represent an appropriate time to review treatment (panel 2). Although the overall value of pre-treatment biochemical investigation is uncertain,[157] expert opinion suggests that fracture during therapy is an indication to ensure conditions such as primary hyperparathyroidism, myeloma or other malignancy, hyperthyroidism, and hypophosphataemia have been excluded. If the clinical scenario is compatible with possible severe vitamin D deficiency (coeliac disease, short-gut syndrome, etc) or hypercortisolism, these should be investigated. The pre-fracture adherence to therapy and duration of therapy should be carefully determined. Antifracture efficacy likely requires at least 6–12 months of continuous treatment, and in the case of oral bisphosphonate, dose-adherence rates in excess of 70–80% during the course of treatment.[158] When the patient has been on therapy for a minimum of 12 months, consideration might be given to repeat a BMD measurement as a marker of treatment response—although, with antiresorptives, BMD stability is well within the expected normal effect. Prolonged immobilisation or substantial weight loss are common explanations for a large observed decrease in BMD despite therapy.[159] Meaningful BMD changes in shorter time intervals (ie, 1–3 years) can be impossible to discern within the expected range of random variation between BMD measurements.[160]

Serum bone-turnover markers, such as C-telopeptide (which reflects osteoclastic activity) or procollagen 1 intact N-terminal propeptide (which reflects osteoblastic activity), have long been suggested as alternative biomarkers of drug effect that respond quickly to successful therapy.[161,162] However, minimal availability, sensitivity to pre-collection conditions, post-fracture bone remodelling effects, and wide intraindividual variation have precluded common use of such tests outside of specialised bone clinics and research settings. Those who fracture on oral bisphosphonates might consider a switch to a parenteral agent, which has been shown to result in a small increase in BMD.[163] However incremental fracture-risk reduction data are scarce. In some cases of fracture during therapy, patients might opt to switch from antiresorptive therapy to anabolic therapy given the evidence of better antifracture efficacy.[124,130,164–166] Extra caution should be taken when switching from denosumab to anabolic therapy, given the DATA-SWITCH trial results that suggested teriparatide therapy might not be sufficient to prevent denosumab discontinuation-related bone loss.[130] It might be reasonable for a patient to continue on their original therapy, anticipating a reduced risk of yet another fracture by remaining on treatment. Bisphosphonates do not need to be withdrawn for healthy fracture healing[167] except in the atypical femur fracture setting.[168] Attention to fall prevention, nutrition, and possible deprescribing of medications associated with increased fracture risk, especially in combination (ie, sedative hypnotics, opioids, selective serotonin reuptake inhibitors, and glucocorticoids), should also be part of ongoing management.[169,170]

***Panel* 2: Assessment of an osteoporosis patient who has sustained fracture during therapy**

- Consider testing to rule out hyperparathyroidism (calcium and parathyroid hormone), myeloma (protein electrophoresis and kappa and lambda light chain ratio) or malignancy, hypophosphatemia (phosphate), hyperthyroidism (thyroid stimulating hormone), hypercortisolism (24-h urine cortisol), or severe vitamin D deficiency (25(OH)D)
- Assess therapy duration to date; 6–12 months of antiresorptive use is the minimum for expected treatment effect
- Assess treatment adherence (and technique if oral bisphosphonate administration); a minimum of 70–80% adherence is the minimum for any expected treatment effect
- Consider repeat bone density measurement (if on therapy for ≥3 years) to ensure stability versus pre-treatment
- Consider measurement of bone turnover and resorption markers at least 3–6 months post-fracture (ie, serum C-telopeptide) to assess antiresorptive drug effect; typically, successful treatment leads to C-telopeptide levels within the lower half of normal premenopausal reference range
- If using oral bisphosphonate, consider switching to parenteral intravenous bisphosphonate or denosumab
- If using oral or intravenous bisphosphonate, consideration of a switch to anabolic therapy with teriparatide, abaloparatide, or romosozumab is reasonable
- Continuation of existing therapy remains a reasonable option after discussion of all the above

Care gap and future outlook

Many barriers to treatment uptake and adherence exist in osteoporosis. The most important is the identification of patients with fragility fractures in the health-care system, where less than 20% are initiated on pharmacological treatment. Fracture liaison services identify and provide care for patients with a fragility fracture to reduce subsequent fracture risk. Despite proven benefits, implementation of fracture liaison services has been scarce across health-care systems globally.[171] One crucial barrier is the minimal reimbursement for fracture liaison service-related programmes, which reduces the health care institutions' ability to implement them and results in missed opportunities for improved patient outcomes, as well as future cost savings. A systematic review of the cost effectiveness of fracture liaison services serving patients older than 50 years with fragility fractures showed a USD$10·49 return for each $1·00 invested.[172] Additionally, fracture liaison services that incorporate primary care and make treatment recommendations yielded the highest return on investment.

Treatment adherence is also crucial to reduce fractures and to avoid the adverse effects of stopping a reversible antiosteoporosis treatment, such as denosumab. The relationship between the health-care provider and patient is probably the most important factor, but other

monitoring tools have been used to provide patient feedback and to improve adherence. Studies evaluating bone turnover markers as an intervention failed to show any effect on adherence.[173] Regarding BMD monitoring in patients with high adherence, only a small minority will lose bone over time, thus questioning the role of multiple serial DXA for monitoring.[174] Additionally, a retrospective cohort study reported that when a mid-treatment DXA showed a decline in BMD over the first 3 years of treatment, adherence improved in the following 3 years, but fracture rates continued to be higher in this group than in patients with high adherence from the start.[175] This finding indicates treatment adherence is best addressed at the commencement of antiosteoporosis therapy and not by waiting to see a BMD decrease. Few data exist on interventions to improve adherence with anabolic therapy. In practice, most patients on anabolic therapy will have severe osteoporosis or treatment failure on antiresorptive drugs, so patients are often highly motivated to adhere. All antifracture therapies are likely underused among patients at high risk of disabling fracture. A meaningful reduction in fracture risk will require long-term therapy adherence and follow-up.

Contributors

GK conceived the article structure, supervised the writing team, co-wrote the initial draft, and critically revised the final version. CY and PE co-conceived the article structure, co-wrote the initial draft, and critically revised the final version.

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CY declares peer-reviewed research grants relating to bone health (Canadian Institutes of Health Research, University Hospital Foundation, and Cancer Research Society) and membership on the Scientific Advisory Council of Osteoporosis Canada. PE declares institutional research grants from Amgen, Alexion, and Sanofi and presentation honoraria from Amgen, Alexion, and Kyowa Kirin. PE has unpaid leadership roles with Healthy Bones Australia and the International Osteoporosis Foundation. GK declares no competing interests.

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