Clinical Practice Guidelines for the Diagnosis and Management of Osteoporosis in Canada: Background and Technical Report

Authors:

Alexandra Papaioannou MD MSc[1], Suzanne Morin MD MSc[2], Angela M. Cheung MD PhD[3], Stephanie Atkinson PhD[4], Jacques P. Brown MD[5], Sidney Feldman MD[6], David A. Hanley MD[7], Anthony Hodsman MD[8], Sophie A. Jamal MD PhD[9], Robert G. Josse MD BS[10], Stephanie M. Kaiser MD[11], Brent Kvern MD[12], Kerry Siminoski MD[13], William D. Leslie MD MSc[14]; for the Scientific Advisory Council of Osteoporosis Canada

Correspondence to:

A. Papaioannou
St. Peter's Hospital
Alexander Pavilion, Juravinski Research Centre
88 Maplewood
Hamilton
Ontario L8M 1W9
Phone: 905-525-9140 Extension:77715
Fax 905-318-2654
papaioannou@hhsc.ca

[1] Professor, Department of Medicine, McMaster University

[2] Associate Professor, Department of Medicine, Division of General Internal Medicine, McGill University

[3] Associate Professor, Departments of Medicine and Medical Imaging, University of Toronto

[4] Professor, Department of Pediatrics and Biomedical Sciences, McMaster University

[5] Clinical Professor, Department of Medicine, Laval University

[6] Assistant Professor, Department of Family & Community Medicine, University of Toronto

[7] Professor, Departments of Medicine, Community Health Sciences, and Oncology, University of Calgary

[8] Professor, Department of Medicine, University of Western Ontario

[9] Associate Professor, Faculty of Medicine, University of Toronto

[10] Professor, Department of Medicine, University of Toronto

[11] Associate Professor, Division of Endocrinology and Metabolism, Dalhousie University

[12] Associate Professor, Department of Family Medicine, University of Manitoba

[13] Associate Professor, Departments of Radiology & Medicine, University of Alberta

[14] Professor, Departments of Medicine and Radiology, University of Manitoba

ABSTRACT

Summary: Since the publication of the 2002 Osteoporosis Canada guidelines, there has been a paradigm shift in the prevention and treatment of osteoporosis and fractures. This background document contains the technical reviews that were used to inform the development of the 2010 Clinical Practice Guidelines for the Diagnosis and Management of Osteoporosis in Canada.

Introduction: The focus is now on preventing fragility fractures and their negative consequences rather than treating low bone mineral density (BMD), which is viewed as only one of several risk factors for fracture. Current data suggests that many patients with fractures are not appropriately assessed or treated.

Results: Systematic reviews of the literature were conducted to update our knowledge in two key areas: 1) fracture risk assessment and 2) therapies for osteoporosis. Additional topics included were identified as important for the management of osteoporosis.

Discussion: The management of osteoporosis should be guided by an assessment of the patient's absolute risk of osteoporosis-related fractures. Given that certain clinical factors increase fracture risk independent of BMD, it is important to take an integrated approach and base treatment decision on the absolute risk of fracture.

INTRODUCTION

Since the publication of the 2002 Osteoporosis Canada guidelines[1], there has been a paradigm shift in the prevention and treatment of osteoporosis and fractures.[2] This background document contains the evidence and technical reviews that were used to inform the development of the 2010 Clinical Practice Guidelines for the Diagnosis and Management of Osteoporosis in Canada.[3] The guidelines summary was published in the Canadian Medical Association Journal in November of 2010 and can be viewed online at www.cmaj.ca/cgi/content/full/182/17/1864

The World Health Organization (WHO) has defined osteoporosis as a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. Based on epidemiological data linking low bone mass with increased fracture risk, a WHO Study Group developed a bone mineral density (BMD) definition of osteoporosis as a BMD T-score 2.5 or more standard deviations below peak bone mass.[4] Using this BMD definition, the Canadian Multicentre Osteoporosis Study (CaMos) estimated the prevalence of osteoporosis in those over age 50 to be 21.3% in women and 5.5% in men.[5] Since the publication of the last Osteoporosis Canada guidelines in 2002[1] there has been a paradigm shift in fracture risk assessment and treatment decisions. In 2005, Osteoporosis Canada adopted a system for ten-year absolute fracture risk assessment to be used in BMD reporting.[6] Our new guidelines focus on the clinical impact of fragility fractures; assessment and management of women and men at high risk for fragility fracture; and integrate a new absolute risk assessment model into an overall management approach.

Detailed background information and methods can be found in the Appendix 1, available at www.cmaj.ca/cgi/content/full/cmaj.100771/DC1.

DEVELOPMENT OF THE PRACTICE GUIDELINES

The development of these guidelines followed the Appraisal of Guidelines, Research and Evaluation (AGREE) framework (Appendix 1, Development of Guidelines and Methods).[7] Key stakeholders were surveyed to identify priorities for these guidelines. Based on these priorities, systematic reviews of the literature were conducted to update our knowledge in two key areas: 1) fracture risk assessment and 2) therapies for osteoporosis. Additional topics included were identified by experts and primary care clinicians as important for the management of osteoporosis (Appendix 1, Tables A1-A5). We convened a Best Practice Guidelines Committee consisting of participants from across Canada with methodological and content expertise. Literature searches in eight electronic databases were performed: Medline, EMBASE, Cochrane Database of Systematic Reviews, Database of reviews of Effectiveness (DARE), Controlled Trials Register (CENTRAL), ACP Journal Club, Health Technology Assessment Database, and NHS Economic Evaluation Database (Appendix 1, Table A6). We developed search strategies based on systematic reviews by the Cochrane Musculoskeletal Group, the PRESS (Peer Reviewed Electronic Search Strategy) checklist[8] and the Cochrane Collaboration Handbook. [9] The committee identified 35 papers for assessment of fracture risk, published from January 1990 to December 2009. To maintain currency, we incorporated further relevant data up to Sept. 19, 2010. We used the systematic review of osteoporosis therapies of MacLean and colleagues,[10] who included 76 randomized trials and 24 meta-analyses, supplemented with data from 30 randomized controlled trials

published since 2008. The PRISMA flow diagram for reporting purposes was used (Appendix 1, Figures A2, A3). We abstracted all papers, graded them for quality of evidence and assigned a level of evidence using established criteria (Appendix 1, Tables A15-A23). The committee then developed and graded initial recommendations. Recommendations were graded according to the system used to grade recommendations for the 2002 guidelines[1], which incorporates both level of evidence and expert consensus (Appendix 1, Table A4). Recommendations were assigned a grade of D when they were based only on committee consensus in the absence of clear supporting evidence or when evidence was weak.

An expert panel, consisting of members of the Osteoporosis Canada Scientific Advisory Council, members of stakeholder organizations, family physicians and experts from across Canada, met to discuss the initial recommendations (Appendix 1, Table A5). The group used a modified RAND/University of California, Los Angeles Delphi method for developing consensus to ensure clinical relevance and applicability.[11] The Guidelines Committee and the Executive Committee of the Osteoporosis Canada Scientific Advisory Council then reviewed the recommendations. The revised recommendations (presented in this report with grades in square brackets) are based on the feedback provided and were endorsed by the expert panel.

The target population of these guidelines is women and men 50 years and older and consequently the systematic reviews focused on this population. Although we acknowledge the importance of other populations with elevated risks for fracture (for

example, individuals with chronic kidney disease), in-depth reviews of these conditions were beyond the scope of these guidelines.

FRAGILITY FRACTURES

The most serious manifestation of osteoporosis is a fragility fracture, defined as a fracture occurring spontaneously or following minor trauma such as a fall from standing height or less.[12-14] Fragility fractures (which exclude craniofacial, hand, ankle and foot fractures) represent 80% of all fractures occurring in postmenopausal women age 50 years and older. [14] A fracture remains one of the most significant risk factors for predicting future fractures.[15, 16] Forty percent of women who experience a fracture have a history of prior fracture.[12] The risk of experiencing another clinical fracture in the year following a hip fracture is 5-10%[17, 18] and there is a 20% risk of having a second vertebral fracture in the year following of a vertebral fracture.[19]

Falls are major risk factors for subsequent fractures, with 5-10% of falls resulting in a fracture.[20] Of those who reported a fractured hip in the 2005 Canadian Community Health Survey, 92% occurred after a fall.[21] Over 80% of falls-related admissions to hospitals in Canadian seniors are due to fracture; 56% are of the femur, pelvis, hip or thigh, and 24% are of the upper or lower limb.[22]

The Significance of Fragility Fractures

The consequences of fracture include increased mortality, morbidity, institutionalization and economic costs.[23, 24] An individual with a hip fracture has a 25% risk of death in the year following the fracture and this excess risk continues into the second year

independent of age and co-morbidity.[25] For those residing in long-term care , the mortality one year post-hip fracture rises to 39%.[17] Women with vertebral fractures are at increased risk of death in the first year of follow-up (adjusted HR 3.7, 95% CI 1.1–12.8) as well as the second year (adjusted HR 3.2, 95% CI 1.2–8.1).[25] Post-fracture mortality and institutionalization rates are even higher for men than women.[26] The annual cost of hip fractures alone in Canada was estimated at $650 million in 1993 and is expected to increase to $2.4 billion by 2041.[24]

When compared to other chronic diseases in a population-based study of Canadians, osteoporosis was rated as having a greater impact on quality of life than chronic obstructive pulmonary disease (COPD), diabetes mellitus, or heart disease.[27] Loss of confidence and fear of falling have been reported with all types of fractures and less than 40% of those who experience a hip fracture return to their prior walking abilities.[28, 29] In women, clinical vertebral fractures negatively affect self-care and mobility and are associated with chronic pain.[30]

FRAGILITY FRACTURES
***Clinical Recommendation*:** **1.** Individuals over age 50 who have experienced a fragility fracture should be assessed [grade A].

Care Gaps

Despite the high rate of fracture in the Canadian population, less than 20% of individuals receive therapies to reduce future fracture within the year following fracture.[14, 31] A number of Canadian and international studies have identified similar diagnostic and therapeutic care gaps in postfracture care.[14, 32-35] The therapeutic care gap is even wider in men; less than 10% of Canadian men with fragility fractures receive any osteoporosis therapy.[36] Furthermore, treatment rates following a fracture are lower for those individuals who reside in long-term care.[37] This is in stark contrast to myocardial infarction which overcame a significant care gap over the past 15 years; 75% of individuals now receive beta blockers to help prevent recurrent myocardial infarction.[38, 39]

Those who receive a BMD diagnosis of osteoporosis are more likely to be treated, as most physicians now regard BMD as the main criterion for initiation of therapy.[14, 31, 33, 36, 40] However, many individuals who experience a fracture (and even multiple fractures) have BMD scores in the low bone mass (formerly called osteopenia) range. (T-score between –1 and -2.5). These individuals may not be appropriately identified as being at high risk of future fractures, and often do not receive osteoporosis therapy.[41, 42] Thus, over-reliance on BMD results is a missed opportunity to prevent future fractures. The additive impact of non-BMD risk factors (especially prior fracture and older age) on future fracture risk has not been widely appreciated, and underscores the value of a more comprehensive approach to fracture risk assessment as described below**.**

CLINICAL APPROACH TO OSTEOPOROSIS

Osteoporosis has no clinical manifestation until a fracture occurs. A history and physical examination should be performed with several objectives: 1) to identify factors (some of which may be reversible) that may be contributing to bone loss, 2) to identify factors that may be predictive of future fractures, and 3) to exclude secondary causes of osteoporosis[1, 43, 44] (Table 1).

History

A history of dietary calcium intake and physical activity helps to tailor bone health strategies. Risk factors for fracture in those over age 50 should be assessed including: a fragility fracture after age 40; parental history of hip fracture; lifestyle factors such as smoking, excessive alcohol, and physical inactivity; weight loss since age 25 of greater than 10%, poor nutrition; and premature menopause.[45-48] Glucocorticoid use greater than 3 months in the prior year at a prednisone equivalent dose of greater than 7.5 mg daily is a major risk factor for fracture as early as 3-6 months after starting glucocorticoids.[49]

Integrating osteoporosis and falls risk assessment is critical in reducing the risk of fracture in the older adult, at both the individual and health system level. A history of falls in the last year is one of the most significant risk factors for predicting future falls,[50] as well as the inability to rise from a chair without using the arms and walk a few steps and return (Get up and Go test).[20, 50-54] Dementia and poor physical function have also been found to be associated with falls and fractures in older adults.[47, 51-53]

Physical Examination

Height and weight should be measured, as low weight and body mass index (BMI) are predictors of low BMD and fractures.[31, 46-48, 55, 56] Vertebral fracture is the most common manifestation of osteoporosis.[19] Two thirds of vertebral fractures are seemingly asymptomatic, but nonetheless associated with chronic back pain and decreased activity.[57] Because vertebral fractures are associated with an increased risk of future fractures, it is important that the clinicians identify patients with unrecognized vertebral fractures through a targeted physical examination.[58] Vertebral fractures can produce kyphosis, height loss, and reduced rib-pelvis distance.[49] Historical height loss of 6 cm (difference between the tallest recalled height and current measured height)[59, 60] or measured height loss of 2 cm (from two or more office visits within 3 years of each other)[61-63] are associated with the presence of vertebral fractures. If these height loss criteria are met, vertebral fracture should be investigated by means of a lateral spine radiograph (Table 1). Risk for fall and fracture can further be assessed by performing the Get Up and Go test or by simply asking the patient to get up from a chair without using their arms.[51-53, 64] A multifactorial falls assessment including environmental and functional assessment is recommended for those who have fallen (Appendix 1, Figure A4).[20]

Radiologic Investigations

Height loss should trigger further investigations including a lateral thoracic and lumbar spine radiograph. Unfortunately, a Canadian study of emergency department radiographs found that only 55% of vertebral fractures were mentioned in the radiology report, so it is very important for the ordering physician to specify that the radiograph is being ordered

to look for compression fractures.[65] Osteoporotic vertebral fractures are best recognized on radiograph as 25% or greater vertebral height loss with end-plate disruption. [66] Radiographic examinations of the spine that may be helpful for investigation of height loss and vertebral fracture detection are presented in Appendix 1, Table A9.

Screening for Secondary Causes of Osteoporosis

In primary care the prevalence of secondary osteoporosis is unknown, but is probably less than 20% in women[66, 67], and possibly as high as 50% in men.[68] Many diseases that contribute to low BMD have specific therapies and it is appropriate to assess for and treat these conditions before making a diagnosis of osteoporosis solely on the basis of low BMD.[1, 69]

Simple biochemical screening should be considered in all patients with documented osteoporosis prior to initiating pharmacologic treatment (Table 2). Recently published Osteoporosis Canada guidelines for vitamin D have emphasized the high prevalence of vitamin D insufficiency in the population and the importance of recommending supplements to ensure optimal vitamin D status. Vitamin D insufficiency should be considered in any patient with osteoporosis, particularly when there are recurrent fractures, bone loss despite therapy or when co-morbid conditions such as celiac disease or gastric bypass that affect vitamin D absorption or action are present. In individuals receiving pharmacologic therapy for osteoporosis, measurement of serum 25-OH-D should follow 3-4 months of an adequate supplementation dose and should not be repeated if optimal level (>75 nmoles/liter) is achieved.[70]

Among patients in whom a specific secondary cause of osteoporosis is identified (such as hyperparathyroidism, liver disease, celiac disease, multiple myeloma), blood and urine studies should be obtained before starting therapy. Some examples of additional testing that could be ordered based on clinical assessment are presented in Table 3. Routine measurement of testosterone in men who do not have signs or symptoms of hypogonadism is not recommended due to variability in the assay, lack of clarity concerning which assay to use (bioavailable, total, free), and the fact that testosterone levels are not consistently associated with increased fracture risk.[71]

CLINICAL ASSESSMENT

Summary Statements:

1. There is an important osteoporosis care gap in Canada[14, 32-34, 72] (Level 1).
2. A history of a fall in the past year is predictive of future falls[20, 50-54] (Level 1).

CLINICAL ASSESSMENT

Clinical Recommendations:

1. Individuals over age 50 who have experienced a fragility fracture should be assessed [grade A]. Measure height annually, and assess for the presence of vertebral fractures [grade A].
2. Assess history of falls in the past year. If there has been such a fall, a multifactorial risk assessment should be conducted, including the ability to get out of a chair without using arms [grade A].
3. Perform additional biochemical testing to rule out secondary causes of osteoporosis in selected patients, on the basis of the clinical assessment [grade D].

4. Measure serum level of 25-hydroxyvitamin D in individuals who will receive pharmacologic therapy for osteoporosis, those who have sustained recurrent fractures or have bone loss despite osteoporosis treatment, and those with co-morbid conditions that affect absorption or action of vitamin D [grade D].
5. Measure Serum 25-hydroxyvitamin D after three to four months of adequate supplementation and do not repeat if an optimal level (75 nmol/L) is achieved [grade B].
6. Serum 25-hydroxyvitamin D should not be measured in healthy adults at low risk of vitamin D deficiency, i.e., without osteoporosis or conditions affecting the absorption or action of vitamin D [grade D].
7. Perform lateral thoracic and lumbar spine radiography or vertebral fracture assessment by dual energy x-ray absorptiometry if clinical evidence is suggestive of a vertebral fracture [grade A].

FRACTURE RISK ASSESSMENT

Systematic Review of Risk Assessment Models

The systematic review of Risk Assessment Models identified and compared existing models for defining fracture risk and examined the level of evidence that supports the use of these models in Canada. The search identified 327 papers (prospective cohorts, meta-analyses, systematic reviews, and RCTs where the control arm was analyzed for fracture risk assessment). After removal of duplicates and screening of the abstracts, 35 papers were retained and examined in full text for data abstraction. Further analysis resulted in 18 papers excluded for the following possible reasons: it was the wrong study design[6, 73-

[75],or population[76, 77]; it did not describe a clinical risk assessment system[78, 79], it did not evaluate clinical risk factors[80, 81] or the system did not report absolute risk or fracture outcomes[82-85], it covered the wrong risk variable (such as the use of ultrasound)[86-88], or because it was a duplicate report.[89] The final review included 17 studies of absolute fracture risk assessment systems as summarized in Appendix 1, Figure A2.

The clinical risk factors included in each of the risk assessment models are summarized in Appendix 1, Table A17. This review focused on the following general principles for developing and validating risk prediction models[90]:

- Independence - "Was the model validated in a population other than the one in which it was initially derived?"
- Discrimination - "How well did the model perform in terms of risk stratification?"
- Calibration - "Was the observed fracture risk consistent with the predicted fracture risk?"

Since fracture rates vary markedly between different populations and countries[91, 92], and are also changing over time in Canada, [93] it is important to ensure that results from a risk assessment model can be applied to the Canadian population (Appendix 1, Figure A5). Some assessment systems, such as FRAX, must be specifically calibrated to the country in which it is going to be used. Therefore, Appendix 1, Table A15 separates those systems that have been directly tested in the Canadian population (candidates for clinical adoption and therefore graded) from those that have been evaluated in other populations (requiring additional Canadian testing before adoption and therefore not graded). There

are important similarities and differences between risk assessment systems, and the risk factors that are most consistently associated with fractures which may be of additional value in clinical decision making for individuals who are categorized as moderate risk.

Studies were identified in which the absolute risk of future osteoporotic fracture was predicted over a discrete time interval, usually five to 10 years, or as a fracture rate per 1000 person-years. Papers providing only relative or proportional risk models were not considered. Studies were done on populations in several parts of the world, including Canada[16, 94, 95], the USA[94, 96-99], Europe[77, 100-103] Australia[89, 104], and Japan.[76] FRAX was based upon pooling individual-level data from nine primary derivation cohorts (N=46,340 men and women) and included 9,101 Canadian participants from CaMos. Gradient of risk and receiver operating characteristic (ROC) area under the curve were similar in the original derivation cohorts and in an even larger pooled analysis from eleven validation cohorts (N=230,486).[105] Most studies recruited white postmenopausal women[16, 77, 89, 94, 96, 98, 99, 104, 106-108] although other ethnic groups[76, 94, 99] and men[16, 77, 103-105] were included in some reports.

While most authors have studied large cohorts of women, two studies comprised fewer than 2,000 women.[89, 104] Most models determined risk for the four major fragility fractures typical of osteoporosis, including fractures of the vertebra (clinical and/or radiographic), hip, forearm, and proximal humerus.[16, 76, 77, 100, 103-108] Four reports were limited to an assessment of hip fracture risk.[89, 97, 99, 101]

Eighteen papers were included in the analysis, covering 14 separate models. Thirty different variables were used in one or more of these models (Appendix 1, Table A17). Aside from BMD, the most commonly used clinical variables were age and gender (both used in all models), prior history of fracture (11 models), BMI or weight (seven models), parental history of hip fracture or osteoporosis (six models), and smoking history (six models). Four studies included the use of corticosteroids, three studies included the ability to rise from a chair without use of the arms, and the level of physical activity. Height or height loss, weight loss, fall history, self-reported health, and number of prior fractures were each used in two models. A number of variables were used in only one model, including rheumatoid arthritis, alcohol intake, walking speed, hip fracture in a sister, use of long-acting benzodiazepines, pulse rate, caffeine intake, anticonvulsant use, hyperthyroidism, depth perception, visual contrast sensitivity, vertebral fracture severity, energy level , grip strength, diabetes, race/ethnic group, and family history of fracture in a first-degree relative.

Of the 30 different variables used in one or more of the previously reviewed absolute risk assessment models, only the following were evaluated in four or more studies: age, sex, prior history of fracture, BMI (or weight), parental history of hip fracture or osteoporosis, smoking history and corticosteroid use. Age and gender are not amenable to further risk stratification. BMI (or weight) and smoking are not included in the CAROC system. WHO meta-analyses have shown that they are relatively weak risk factors for osteoporotic fractures after adjustment for age and BMD (risk ratio [RR] for BMI category from 0.91 to 1.07, RR 1.13 for current smoking).[109, 110] Family history of fracture is also not included in the CAROC system. A WHO meta-analysis found that

parental hip fracture was predictive of future osteoporotic fractures (BMD adjusted RR 1.54 [95% CI 1.25–1.88]) while any parental fracture was a weak risk factors only (RR 1.22 [95% CI 1.08–1.38]).[15] A subsequent analysis from CaMos found minimal gain in fracture prediction when parental hip fracture was added to prediction based upon age, BMD and prior fractures (RR 2.01 [95% CI 1.81–2.25] and AUC 0.69 versus 2.06 [95% CI 1.85–2.31] and AUC 0.70).(24) At the present time, fall history is not considered by either the FRAX or CAROC risk assessment systems. Therefore, fracture risk will be underestimated in those at risk for recurrent falls.

Changes in Risk Assessment

In 1994, the World Health Organization (WHO) expert panel set the operational definition of osteoporosis in postmenopausal white women as a bone mineral density (BMD) T-score of 2.5 or more standard deviations (SD) below the normal BMD for young healthy white women.[111] The WHO Collaborating Centre has recently provided guidance on the diagnosis of osteoporosis in older white and non-white women and men, designating BMD measurement made at the femoral neck with DXA as the reference standard.[112] The recommended reference range is the NHANES III reference database for femoral neck measurements in white women aged 20-29 years using a similar cut-off value for both men and women (BMD T-score 2.5 SD or more below the average for young adult women). The WHO position remains controversial and other groups advocate sex-matched reference data.[106, 113, 114] A recent report from CaMos supports the WHO position, and therefore this is now the recommendation for BMD reporting in Canada.[115]

BMD assessment with dual energy x-ray absorptiometry (DXA) is well established for the diagnosis of osteoporosis and for fracture risk assessment in postmenopausal women and men (see Table 4 for indications).[116, 117] Currently, a diagnosis of osteoporosis is made in older women and men who have a BMD T-score 2.5 or more SD below the normal BMD for young healthy white women,[4] with BMD measurement made at the femoral neck from DXA as the reference standard (see frequency of clinical risk factors included in the risk assessment models in Appendix 1, Table A17).[112] It is appropriate to consider a clinical diagnosis of osteoporosis in individuals who have sustained fragility fracture(s) even if BMD is not in the osteoporotic range, as the majority of fragility fractures occur in those who have a T-score above -2.5.[41]

Prior to age 50, the WHO T-score system is not appropriate, and age- and sex-matched Z-scores are preferred. For Z-scores, a value of -2.0 or lower is considered below the expected range for age and a value above -2.0 is considered within the expected range for age (Table 5).[118] Similarly, the models for fracture risk prediction discussed below should not be applied to individuals younger than age 50. Risk assessment and osteoporosis therapy considerations are complex in individuals less than age 50, particularly those with medical conditions that may have adverse skeletal consequences (Table 5), and often benefit from consultation with a specialist.

Since the 2002 Osteoporosis Canada guidelines, the importance of using multiple risk factors to predict quantitative (absolute) fracture risk has been recognized. Bone density T-scores are difficult for many patients to understand, and as outlined above, do not identify the majority of patients suffering fragility fractures. Calculating an absolute

10-year fracture risk may contribute to a more meaningful patient-physician dialogue over the risks and benefits of treatment, and was preferred to T-scores in a survey of physicians .[119] Accordingly, in 2005, Osteoporosis Canada adopted 10-year absolute fracture risk assessment as the preferred method for risk assessment and BMD reporting in women and men age 50 and older.[6] The original risk assessment model was developed as a collaboration of the Canadian Association of Radiologists and Osteoporosis Canada (referred to as the CAROC system). Since publication of the 2005 recommendations, several other risk assessment models have been developed, most notably the WHO fracture risk assessment tool (FRAX) as discussed below.[77] A systematic review was performed and forms the basis of guidelines regarding the most suitable risk assessment models for use in Canada. The clinical risk factors included in each of the risk assessment models, together with key methodological considerations and outcomes, are summarized in Appendix 1, Tables A15, A16.

Many clinicians are unaware of the large differences in osteoporotic fracture rates between countries (more than ten-fold)[91, 92], and the fact that fracture rates are changing over time in Canada and elsewhere.[93] Although it is beyond the scope of this document to explore the possible reasons behind these differences, it is important to ensure that results from a risk assessment model can be applied to the Canadian population. Therefore, our recommendations only consider those systems that have been directly tested and validated in the Canadian population.

Risk Assessment Systems Validated in Canada

WHO Fracture Risk Assessment (FRAX) tool: The WHO Collaborating Centre has identified clinical risk factors which, in addition to age and sex, contribute to fracture risk independently of BMD.[120] The fracture risk assessment (FRAX) tool, released in 2008, computes 10-year probability of major osteoporotic fracture (composite of hip, vertebra forearm and humerus) from sex, age, BMI, prior fracture, parental hip fracture, prolonged glucocorticoid use, rheumatoid arthritis (or secondary causes of osteoporosis), current smoking, alcohol intake (3 or more units daily) and femoral neck BMD.[121] Although FRAX also computes 10-year probability of hip fracture alone, the primary designation of risk for clinical decision-making should be the global assessment of major osteoporotic fracture probability. The online FRAX calculator and more details on how it is used can be found at: www.shef.ac.uk/FRAX.

As fracture rates are known to vary by more than an order of magnitude worldwide,[91] calibration for the FRAX tool is population/country specific (Appendix 1, Table A5). Using national fracture data, a FRAX model for Canada was recently constructed for the prediction of hip fracture risk and major osteoporotic fracture risk with and without use of BMD.[95, 122] Performance of this system was independently assessed in CaMos (4,778 women and 1,919 men) and a clinical cohort from Manitoba (36,730 women and 2,873 men).[123, 124] The Canadian FRAX tool generated fracture risk predictions that were generally consistent with observed fracture rates across a wide range of risk categories.[123-125] Fracture discrimination using FRAX with BMD was better than FRAX without BMD or BMD alone, as has been seen in other cohorts.[105]

Canadian Association of Radiologists/Osteoporosis Canada (CAROC): This risk assessment model provides a semi-quantitative (ordinal risk category) method for estimating 10-year absolute risk of a major osteoporotic fracture in postmenopausal women and men over age 50.[6] An individual's 10-year absolute fracture risk (combined risk for fractures of the proximal femur, vertebra [clinical], forearm, and proximal humerus) is stratified into three 10-year absolute fracture risk zones designated low risk (less than 10%), moderate risk (10-20%), and high risk (over 20%), similar to the absolute risk categories already used for cardiovascular risk assessment[126] (Figure 1). Other fractures attributable to osteoporosis (e.g., pelvic fractures and undiagnosed vertebral fractures) are not reflected in the CAROC or FRAX predictions, which will therefore underestimate the total osteoporotic fracture burden. Underestimation of fracture risk using CAROC and FRAX also occurs if the patient has suffered more than one fragility fracture, which markedly increases the 10-year risk.

An initial (basal) risk category is obtained from age, sex, and T-score at the femoral neck. The spine BMD is not considered in the initial risk assessment for either CAROC or FRAX. However, when determining the risk category, a patient with a T-score of the spine or hip ≤-2.5 should not be considered low risk (i.e. should be classified having at least moderate risk). Certain clinical factors increase fracture risk independently of BMD, the most important being: fragility fractures after age 40 (especially vertebral compression fractures)[66, 127]and recent prolonged systemic glucocorticoid use (e.g., at least 3 months cumulative during the preceding year at a prednisone equivalent dose greater than 7.5 mg daily).[127] The presence of either of these factors substantially elevates fracture risk independent of the basal risk category (estimated from age, sex and

BMD) and their effect is put into use by increasing the risk categorization to the next level: from low risk to moderate risk, or from moderate risk to high risk. When both factors are present (i.e., fragility fractures and prolonged systemic glucocorticoid use), the patient is considered to be at high fracture risk regardless of the BMD result. These clinical risk factors have been shown to enhance fracture prediction in Canadian women independent of age and BMD alone.[128] Recently, CAROC has been recalibrated using Canadian hip fracture data with an online tool that can be downloaded (Figure 1). The updated version of CAROC (2010 version) has been validated in two large Canadian cohorts and replaces the previous 2005 version of CAROC[95] The updated CAROC system shows a high overall degree of concordance in risk categorization (approaching 90% agreement) with the Canadian FRAX system.[95]

Summary: Appropriate utilization of interventions to prevent fractures is predicated on accurate identification of those at risk (presumed to be amenable to therapeutic intervention) and therefore most likely to benefit from treatment.[13, 129] Observed and predicted fracture rates under the Canadian FRAX or CAROC systems are generally in close agreement for women and men from the general population and also in those clinically referred for BMD testing[123]. FRAX is based upon a more complete set of clinical risk factors and can be used even without BMD results, but the calculations require access to the FRAX software or website. CAROC is less complete but captures the major risk factors for fracture, and is easy to apply using the tools provided in this document. Therefore, the choice of using FRAX or CAROC is largely a matter of personal preference and convenience.

Laboratory and Radiographic Risk Factors for Fracture

The preceding discussion concentrated on clinical risk factors that can be combined with BMD to assess absolute fracture risk. The potential value of laboratory measures, specifically bone turnover markers (BTM), and radiographic imaging of the spine including vertebral fracture assessment (VFA), was not systematically reviewed. The recommendations for clinical assessment can be found in Appendix 1, Table A7. These were recent topics of Osteoporosis Canada position statements.

Bone Turnover Markers (BTM)

The potential clinical role for BTMs was the subject of a joint review between Osteoporosis Canada, medical biochemists and clinical chemists. A number of prospective population-based studies have reported that increased levels of BTMs are associated with an approximately two-fold increased risk of fracture (vertebral and nonvertebral) compared to those with normal BTM levels, both in women 65 years of age or older[130, 131] and in those younger than 65 years.[132] The ability of BTMs to predict fracture was largely independent of, and complementary to, BMD. In estimating the 10-year absolute risk of hip fracture, the combination of an elevated resorption marker (urinary C-terminal telopeptide) with an osteoporotic BMD or a history of previous fracture resulted in a 70-100% higher risk than from BMD alone[133] (Appendix 1, Table A10). The value of BTMs in estimating future risk of fracture in individual patients needs further research. As a result, BTMs have not yet been integrated in any fracture risk assessment system.

Vertebral Fracture Assessment (VFA)

Vertebral fracture recognition and reporting by radiologists were the subject of a recent review by Osteoporosis Canada and the Canadian Association of Radiologists[66] (Appendix 1, Table A9). VFA is an available scanning and software option on bone densitometers which use a fan-beam scanning technology, and will identify moderate (>25% compression) or severe (>40%) vertebral deformities. Unequivocal vertebral fractures (>25% height loss with end-plate disruption) unrelated to trauma are associated with a 5-fold increased risk for recurrent vertebral fractures. Therefore, a fracture detected by VFA or radiograph (a morphometric vertebral fracture) should be considered a prior fracture under the FRAX or CAROC system. However, mild spinal deformities (<25% height loss without definite end-plate fracture) are not as strong predictors of future osteoporotic fractures or low bone density.[66] Canadian centres have been slow to adopt VFA technology despite its potential clinical value in identifying patients with previously unrecognized vertebral fractures. Like radiographic fractures, VFA-detected fractures predict future osteoporotic and hip fractures independently of age, weight, and BMD.[66, 134]

FRACTURE RISK ASSESSMENT AFTER AGE 50

Summary Statements:

1. Clinical risk factors (especially age, prior fragility fracture and prolonged glucocorticoid exposure) enhance fracture prediction independent of BMD alone[105, 108, 135, 136] [Level 1].
2. The Canadian FRAX tool and CAROC are well calibrated for prediction of major osteoporotic fracture risk[95, 123] [Level 1].

3. The CAROC model shows a high overall degree of concordance in risk categorization with the Canadian FRAX system[136] [Level 1].

FRACTURE RISK ASSESSMENT AFTER AGE 50

Clinical Recommendations:

1. Assessment of the absolute risk of fracture should be based on established factors, including age, bone mineral density, prior fragility fractures and glucocorticoid use [grade A].
2. The 2010 version of the Canadian Association of Radiologists and Osteoporosis Canada tool and the Canadian version of the WHO Fracture Risk Assessment tool should be used in Canada, because they have been validated in the Canadian population [grade A].
3. For purposes of reporting bone mineral density, the 2010 version of the Canadian Association of Radiologists and Osteoporosis Canada tool is currently the preferred national risk assessment system [grade D].
4. Only the T-score for the femoral neck (derived from the reference range for white women of the National Health and Nutrition Education Survey III) should be used to calculate risk of future osteoporotic fractures under either system [grade D].
5. Individuals with a T-score for the lumbar spine or total hip ≤ -2.5 should be considered to have at least moderate risk [grade D].
6. Multiple fractures confer greater risk than a single fracture. In addition, prior fractures of the hip and vertebra carry greater risk than fractures at other sites [grade B].

STRATEGIES FOR FRACTURE PREVENTION

There are many non-pharmacologic interventions available to promote bone health and pharmacologic therapies to reduce fracture risk. Available therapeutic options can reduce the risk of future fractures in high-risk individuals by up to 40-60% but are dependent on the site of fracture and nature of the treatment.[70]

Lifestyle Modifications

Several lifestyle interventions promote bone health including: appropriate dietary intake and where necessary, supplementation of calcium and vitamin D, exercise, fall prevention and avoidance of behaviours detrimental to bone health such as smoking and excessive alcohol consumption. Many of these interventions apply to other chronic diseases and the individual elements can be integrated into disease management and/or self-management programs.[137] For a summary of the studies on vitamin D and calcium reviewed for the development of the guidelines, see Appendix 1, Table A19.

Vitamin D

There is evidence that vitamin D supplementation is associated with increases in bone mineral density[138-140] and reductions in fractures[141], particularly when combined with adequate calcium intake.[142] A meta-analysis that combined data from five trials (N=9,829) that used 17.5-20 µg (700-800 IU) of vitamin D_3 reported a 23% reduction in nonvertebral fractures. A fracture risk reduction was associated with higher serum 25-OH-D levels, particularly when these exceeded 75 nmol/L. [141] An update of this meta-analysis found that the combined relative risk from six trials (N= 45,509) of vitamin D_3 (10-20 µg [400-800 IU]) combined with calcium was 0.82 (95% CI, 0.71, 0.94),

consistent with an 18% (95% CI, 6-29) reduction in hip fractures.[143] Greater treatment effects are noted in institutionalized elderly patients where there is supervision of medications. [144]

A recent review and guideline statement from Osteoporosis Canada[70] recommends increased vitamin D supplementation for low risk adults (under age 50 without osteoporosis or conditions affecting vitamin D absorption) from 10 μg (400 IU) daily to 10-25 μg (400-1,000 IU) daily. In adults over age 50, and those at high risk for adverse outcomes from vitamin D insufficiency (e.g., recurrent fractures or osteoporosis and co-morbid conditions that affect vitamin D absorption) recommendations have been increased from 20 μg (800 IU)/day to 20-50 μg (800-2,000 IU) daily; some of these patients need doses higher than 50 μg (2000 IU) daily, and monitoring of the serum 25-OH-D response is appropriate. The optimal level of serum 25OH-D for musculoskeletal benefits is estimated to be at least 75 nmol/L.[70] Supplemental vitamin D of at least 700 IU daily has also been found to reduce falls risk by 19% in both community and institutionalized elderly.[141] The risk of hip and nonvertebral fractures was also reduced when vitamin D was given daily in combination with calcium.[141, 144]

Serum 25-OH-D should only be measured in situations where deficiency is suspected, or would affect response to therapy, e.g. individuals with impaired intestinal absorption, or in patients with osteoporosis requiring pharmacologic therapy. The half-life of 25-OH-D in the body is 15-20 days[145] and the serum 25-OH-D response to standard-dose supplementation plateaus after 3-4 months.[146] Therefore, serum 25-OH-D should be checked no sooner than 3 months after commencing standard-dose supplementation in

patients who have osteoporosis. Monitoring of routine supplement use, and routine testing of otherwise healthy individuals as a screening procedure, are not necessary.[70]

Calcium

Dietary calcium exerts a mild suppressive effect on bone turnover and this has a beneficial impact on BMD.[147, 148] In a meta-analysis it was concluded that calcium with or without vitamin D resulted in fewer fractures.[142] However, there is controversy regarding the potential adverse effects of high-dose calcium supplementation on renal calculi and cardiovascular events in older women[147, 149, 150] and prostate cancer in older men. Health Canada defines adequate calcium intake (from diet and supplements) as 1200 mg daily with an upper tolerable level of 2500 mg per day for adults age 50 and older.[151] The upper tolerable levels were derived from historical concerns over the development of milk-alkali syndrome in individuals who consumed large doses of calcium. High doses of calcium supplements are difficult to achieve as individuals experience gastrointestinal symptoms such as constipation. These symptoms may have contributed to compliance rates of 40% or less in the majority of randomized controlled trials (RCTs) on calcium supplementation.[147, 152]

VITAMIN D AND CALCIUM
Summary Statements:
1. Vitamin D_3 with calcium supplementation increases bone density in postmenopausal women and men over age 50 [138-140] and reduces the risk of fractures[142] (Level 1).

2. Vitamin D_3 at daily doses of 20 µg (800 IU) with calcium (1000 mg) reduces the risk of hip and nonvertebral fractures in elderly populations in institutions[141, 142, 153] (Level 1). The evidence in community-dwelling individuals is less strong[154] (Level 2).
3. There is evidence that daily 20 µg (800 IU) vitamin D_3 reduces fall risk, particularly in trials that adequately ascertained falls[154] (Level 2).
4. A daily intake of 25 µg vitamin D_3 (1000 IU) - a commonly available safe dose - will raise serum 25-OH-D level on average by 15-25 nmol/L[146] (Level 2).

VITAMIN D AND CALCIUM

Clinical Recommendation:

1. The total daily intake of elemental calcium (through diet and supplements) for individuals over age 50 should be 1200 mg [grade B].
2. For healthy adults at low risk of vitamin D deficiency, routine supplementation with 400–1000 IU (10–25 µg) vitamin D3 daily is recommended [grade D].
3. For adults over age 50 at moderate risk of vitamin D deficiency, supplementation with 800–1000 IU (20–25 µg) vitamin D3 daily is recommended. To achieve optimal vitamin D status, daily supplementation with more than 1000 IU (25 µg) may be required. Daily doses up to 2000 IU (50 µg) are safe and do not necessitate monitoring [grade C]. For individuals receiving pharmacologic therapy for osteoporosis, measurement of serum 25-hydroxyvitamin D should follow three to four months of adequate supplementation and should not be repeated if an optimal level (75 nmol/L) is achieved [grade D].

Exercise and Falls Prevention

Exercise is often recommended for individuals with osteoporosis. Programs that are at least one year in duration and include aerobic exercises and strength training have demonstrated positive effects on BMD but have limited evidence for fracture reduction. A systematic review found these programs ranged from 2 to 5 days a week with session durations from 20 to 60 minutes, and included strength training for the extremities and trunk, jumping, aerobic exercise (such as walking), stretching and balance.[155] A meta-analysis of cohort studies has demonstrated that moderate to vigorous exercise has demonstrated reduced hip fractures and supports the importance of healthy lifestyle promotion for bone health[156].

Thoracic kyphosis may be reduced by a program that includes muscle strengthening, range of motion, and postural alignment exercises.[155] Quality of life associated with exercise has been shown to improve in those with osteoporosis, with and without fractures, particularly in the domains of physical function, pain and vitality.[157] Refer to Appendix 1, Table A13 for exercise advice to patients.

An integrated approach to osteoporosis treatment and falls interventions is also beneficial for exercise interventions. In a systematic review, exercise-focused interventions reduced falls for community-dwelling older people.[158] Tai chi, gait and balance training were effective in reducing falls.[159-161] Home safety assessment was only effective in those with severe visual impairment and in others at high risk for falls.[159] Removal of the first cataract has been demonstrated to reduce falls.[159]

Hip protectors have been shown to be ineffective for those older adults residing in the community.[162, 163] A modest reduction in hip fractures was demonstrated in two meta-analyses of elderly long-term care residents.[162, 164] A recent Canadian analysis found hip protectors were cost effective in reducing hip fractures in long-term care.[165] Compliance with wearing hip protectors poses a challenge and may be responsible for the ineffectiveness of this intervention.[162] A subsequent RCT found no protective effect with a type of hip protector that is not used in clinical practice.[166]

OTHER NON-PHARMACOLOGIC THERAPIES

Summary Statements:

1. Exercises for individuals with osteoporosis should include weight bearing, balance and strengthening exercises[156, 167, 168] (Level 2).
2. Exercise-focused interventions improve balance and reduce falls in community-dwelling older people[159, 169] (Level 2).
3. Hip protectors may reduce the risk of hip fractures in long-term care residents, however compliance with their use may pose a challenge for the older adult[162, 164] (Level 2).

OTHER NON-PHARMACOLOGIC THERAPIES

Clinical Recommendations:

1. Exercises involving resistance training appropriate for the individual's age and functional capacity and/or weight-bearing aerobic exercises are recommended for those with osteoporosis or at risk for osteoporosis [grade B].

2. Exercises to enhance core stability and thus to compensate for weakness or postural abnormalities are recommended for individuals who have had vertebral fractures [grade B].
3. Exercises that focus on balance, such as tai chi, or on balance and gait training should be considered for those at risk of falls [grade A]. Use of hip protectors should be considered for older adults residing in long-term care facilities who are at high risk for fracture [grade B].

Pharmacologic Therapy For Fracture Prevention

When deciding to initiate pharmacologic therapy, the clinician should take into consideration the benefit to harm ratio, particularly in patients at low risk. When choosing between therapies, the patient's individual risk, co-morbid conditions, preferences and lifestyle should be considered. First-line osteoporosis therapies with evidence for fracture prevention are summarized in Appendix 1, Table A11.

A systematic review of 76 randomized trials and 24 meta-analyses graded the quality of the evidence for various osteoporosis therapies.[10] A number of therapies demonstrated good evidence for fracture prevention in high risk groups which included individuals with ≥1 fracture at baseline, BMD in the osteoporotic range, transplant populations, and those with neuromuscular impairment (stroke, Alzheimer's disease). Subsequently, several other systematic reviews have been published and are summarized in Appendix 1, Table A19. Although the reviews differ in their inclusion criteria, a T-score above -2.0 was generally used to define lower risk, while a T-score below -2.0 and/or prior vertebral fractures was considered higher risk. Thirty more RCTs have been published since the

last systematic review search date and are summarized in Appendix 1, Table A18. The results of the RCTs are consistent with those previously reported.[10]

For vertebral fracture prevention, the following agents have good evidence to support their use for individuals at high risk of fracture: alendronate, risedronate, etidronate, zoledronic acid, denosumab, teriparatide, raloxifene and estrogen. There is fair evidence for the use of calcitonin in vertebral fracture prevention. For hip fracture prevention, the following therapies have good evidence: alendronate, risedronate, zoledronic acid, denosumab and estrogen. For nonvertebral fracture prevention, there is good evidence for alendronate, zoledronic acid, risedronate, denosumab, teriparatide, and estrogen.[10] Both calcitonin and teriparatide may decrease the pain associated with vertebral fractures.[170, 171]

Because vertebral and hip fractures are associated with increased risk of mortality, one might expect that the clinical trials of osteoporosis drugs would show a reduction in mortality. However, most subjects recruited in clinical trials are recruited on the basis of good health except for the presence of increased fracture risk. The only clinical trial providing evidence that fracture prevention can reduce mortality was in participants receiving zoledronic acid within 90 days of hip fracture; mortality was analyzed as a secondary outcome and biases may have limited the validity of the results (e.g., not all participants were followed for the entire 36 months).[172] However, a recent meta-analysis also reported a 10% reduction in mortality in older individuals at high risk of fractures treated with osteoporosis therapies.[150] Prescribing information for osteoporosis pharmacologic agents is summarized in Table 6.

Antiresorptive Agents

Most pharmacologic agents used in osteoporosis prevention and therapy reduce bone resorption or slow the overall rate of bone turnover. These include bisphosphonates, denosumab, calcitonin, estrogen, and the selective estrogen receptor modulators.

Bisphosphonates

A meta-analysis of 11 studies representing 12,068 postmenopausal women with osteoporosis receiving at least one year of alendronate [173] showed significant reductions in vertebral fractures (RR 0.55, 95% CI 0.43–0.69) across the range of fracture risk whether women were at low or high risk of fractures based on bone mineral density and the presence of clinical risk factors[174] for 5 years of treatment (For number needed to treat, NNT, see Appendix 1, Table A19). Significant reductions were also found for the secondary prevention of nonvertebral fractures (RR 0.77 95% CI, 0.64 to 0.92), wrist fractures (RR 0.50, 95% CI, 0.34 to 0.73) and hip fractures (RR 0.47 95% CI, 0.26 to 0.85).

Etidronate demonstrated a relative risk reduction of 41% for vertebral fractures across eight studies (RR 0.59, 95% CI 0.36 to 0.96) and greater efficacy in secondary prevention trials (RR 0.47, 95% CI 0.32 to 0.87), there were no significant reductions for nonvertebral fractures (RR 0.98, 95% CI 0.68 to 1.42), hip fractures (RR 1.20, 95% CI 0.37 to 3.88) or wrist fractures (RR 0.87, 95% CI: 0.32 to 2.36).[175] It was concluded that cyclical etidronate is beneficial in the secondary prevention of vertebral fractures.

Similarly, a meta-analysis assessing the efficacy of risedronate in the prevention of osteoporotic fracture in postmenopausal women found that 5 mg per day was associated with a 39% relative risk reduction (RR: 0.61, 95% CI, 0.50 to 0.76), 5% ARR for

secondary prevention of vertebral fractures versus an overall reduction of 37% (CI 0.51 to 0.77) for vertebral fractures when primary and secondary prevention trials were combined. For nonvertebral fractures, risedronate demonstrated a 20% relative risk reduction (RR: 0.80, 95% CI, 0.72 to 0.90), 2% ARR, and 26% relative risk reduction (RR: 0.74, 95% CI, 0.59 to 0.94), 1% ARR for hip fractures, but no significant risk reduction for wrist fractures.[176] In 2 trials with zoledronic acid there was evidence of vertebral (RR 0.33, CI 0.274 to 0.4), nonvertebral (RR 0.75, CI 0.66 to 0.85) and hip fracture (RR 0.62, CI 0.47 to 0.83) reduction.[176]

Other Antiresorptives

Hormone therapy (HT) was found to reduce overall fractures with a relative risk reduction of 30%. Benefit was seen for vertebral fractures (RR 0.67, CI 0.48 to 0.93), nonvertebral fractures (0.73, CI 0.64 to 0.81) and hip fractures (RR 0.60 CI 0.42 to 0.93).[177] A number of organizations have recommended that the primary indication for HT is moderate to severe vasomotor symptoms and should be used at the lowest effective dose. However, low dose HT(< 0.625 conjugated estrogen) has not been demonstrated to reduce fractures. In those individuals who have adverse effects and/or are intolerant of other osteoporotic therapies, continuation of HT may be an option after discussion of risks and benefits.[178, 179] Raloxifene (RR 0.64, CI 0.54 to 0.78)[180] and calcitonin (RR 0.65, CI 0.48 to 0.88) were found to reduce the risk of vertebral fractures, but not nonvertebral fractures.[177]

Denosumab is a human monoclonal antibody to the receptor activator of nuclear factor-kappa B ligand (RANKL) that blocks its binding to RANK, inhibiting the development and activation of osteoclasts. In an RCT of 7868 women, denosumab given twice yearly

reduced the risk of hip fracture by 40% compared to placebo (hazard ratio, 0.60; 95% CI, 0.37 to 0.97; ARR 0.5%).[181] Denosumab also reduced the risk of nonvertebral fracture by 20% (hazard ratio, 0.80; 95% CI, 0.67 to 0.95; ARR 1.5%).[181]

Anabolic Agents

Osteoporosis Canada completed a systematic review of the efficacy of the human parathyroid hormone product, teriparatide (hPTH 1-34), and found good evidence that its use reduced the risk of vertebral fractures; there was insufficient evidence that teriparatide prevented hip or wrist fractures.[182, 183] A more recent meta-analysis[177] included additional trials and concluded that both vertebral fractures (RR 0.36, CI 0.23 to 0.57) and nonvertebral fractures (RR 0.49, CI 0.27 to 0.87) were reduced by teriparatide.

Combination Therapy

The combination of therapies such as HT or raloxifene with a bisphosphonate [184-189] have demonstrated a greater improvement in BMD. However, there are no RCTs demonstrating additional benefit in reduction of fractures. The combination of antiresorptive agents is not recommended for fracture reduction.

Testosterone and Men

There is no evidence to date that testosterone reduces fractures in men, [10]
nor is there evidence that hypogonadal men respond differently than eugonadal men to bisphosphonate therapy in the presence of osteoporosis.[118] [77]

In an RCT in which one-third of men were hypogonadal, defined by low serum free testosterone, the BMD response from alendronate was similar regardless of baseline testosterone level.[190] In a meta-analysis of alendronate therapy, men with hypogonadism responded to treatment with a lower odds ratio for incident vertebral fractures of 0.44 (95% CI 0.23, 0.83)[191] with similar response to eugonadal men. Studies to date have not been powered to determine efficacy of testosterone in reducing nonvertebral fractures in eugonadal or hypogonadal men.

Length of Therapy

There is very little evidence to support any recommendation regarding the questions of how long to treat, use of drug holidays, and the effectiveness of resuming treatment after discontinuation of therapy. There have been no studies comparing the effects of various drug holiday regimens and holiday lengths, and no studies have examined the effectiveness of resuming therapy after a holiday. The possible benefits of a drug holiday include reduction of potential adverse events and costs. [192, 193]

In the FLEX (Fracture Intervention Trial Long-Term Extension) trial [194], after five years of treatment with alendronate, participants either continued on alendronate for five additional years, or were randomized to placebo for five years. At the end of the extension phase, the 5-year clinical vertebral fracture rates were decreased by 55% in those who continued on alendronate (for a total of 10 years) compared to those randomized to placebo (i.e., received five years alendronate and five years placebo). There were no differences in nonvertebral fractures or radiographic vertebral fractures.[194]

In an RCT with risedronate, participants who had been on treatment for three years (risedronate or placebo) discontinued their study medication and continued on calcium and vitamin D for an additional year. At the end of one year off treatment, BMD decreased in those who had been on risedronate previously, but remained higher than baseline in placebo treated subjects. [195]

Discontinuation of HT results in BMD loss of 3-6% during the first year with fracture risk similar to those who have never been prescribed HT.[196]

Adverse Events

Adverse events have been noted in RCTs that assess treatment efficacy for all currently available osteoporotic drugs.[10] Evidence from RCTs, systematic reviews, and case reports on adverse events are found in Appendix 1, Tables A21-A23. Oral bisphosphonate therapy, has been shown to be associated with upper gastrointestinal events.[10] Flu-like symptoms, reported in up to 10% of patients following zoledronic acid infusion, are most prominent after the first dose and are self limited.[174] Major adverse events associated with raloxifene include an increased risk of pulmonary embolism, and an increased risk of thromboembolic events.[10]

Adverse events from RCTs and postmarketing surveillance include reports of osteonecrosis [197, 198] of the jaw and atypical femur fractures associated with bisphosphonates[199] (Appendix 1, Table A23). It is important to note that the adverse events reported outside of the pivotal trials should be interpreted with caution.

PHARMACOLOGIC THERAPIES

Summary Statements:

1. Alendronate prevents vertebral, nonvertebral, hip, and wrist fractures in postmenopausal women[173, 200] (Level 1).
2. Cyclical etidronate prevents vertebral fractures, but has not demonstrated risk-reductions for other nonvertebral fracture types[175] (Level 1).
3. Risedronate prevents vertebral, nonvertebral, and hip fractures in postmenopausal women[176] (Level 1).
4. Zoledronic acid prevents vertebral, nonvertebral, hip in men and women[177] (Level 1).
5. Hormone therapy prevents vertebral, nonvertebral, and hip fractures, but is recommended for women with moderate to severe vasomotor symptoms[194] (Level 1).
6. Raloxifene and calcitonin reduce vertebral fractures, but have not demonstrated risk-reductions for nonvertebral fractures[180] (Level 1).
7. Teriparatide reduces vertebral and nonvertebral fractures[182, 183] (Level 1).
8. Combination of osteoporosis therapies does not show greater fracture reduction than a single agent[184-188] (Level 1).
9. Denosumab reduces vertebral, nonvertebral fractures and hip fractures in postmenopausal women[181] (Level 1).

PHARMACOLOGIC THERAPIES

Clinical Recommendations:

1. For menopausal women requiring treatment of osteoporosis, alendronate, risedronate, zoledronic acid and denosumab can be used as first-line therapies for prevention of hip, nonvertebral and vertebral fractures [grade A].

2. For menopausal women requiring treatment of osteoporosis, raloxifene can be used as a first-line therapy for prevention of vertebral fractures [grade A].
3. For menopausal women requiring treatment of osteoporosis in combination with treatment for vasomotor symptoms, hormone therapy can be used as first-line therapy for prevention of hip, nonvertebral and vertebral fractures [grade A].
4. For menopausal women intolerant of first-line therapies, calcitonin or etidronate can be considered for prevention of vertebral fractures [grade B].
5. For men requiring treatment of osteoporosis, alendronate, risedronate and zoledronic acid can be used as first-line therapies for prevention of fractures [grade D].
6. Testosterone is not recommended for the treatment of osteoporosis in men [grade B].
7. The potential benefits and risks of the prescribed agents should be discussed before therapy is initiated, to support informed decision-making [grade D].

Special Groups

It is beyond the scope of these guidelines to address all special groups at risk of osteoporosis. However, a number of key co-morbidities and relevant RCTs evaluating osteoporosis therapies have demonstrated a fracture reduction.

Patients with Long-Term Glucocorticoid Use

Osteoporosis therapies are often initiated in patients on long-term glucocorticoid therapy to prevent fractures.[10] Long-term use of glucocorticoids (≥ 3 months) has resulted in 30-50% incidence of fractures, particularly in those over the age of 40 and those using high doses.[49] Both alendronate [201, 202] and risedronate[203, 204] have demonstrated a reduction in morphometric vertebral fractures compared to placebo in patients who are treated with

glucocorticoids. There is evidence that etidronate is protective against bone loss at the spine but fracture prevention was only seen in sub-group analysis.[10, 205] A non-inferiority study comparing zoledronic acid to risedronate demonstrated a greater improvement in lumbar spine BMD with zoledronic acid, however the study was not powered to detect differences in fracture reduction.[206]

Other therapeutic options include teriparatide and calcitonin. Teriparatide treatment resulted in fewer new radiographic vertebral fractures compared to those receiving alendronate (ARR 5.5%); although the incidence of nonvertebral fractures was not significantly different between the groups.[207] A meta-analysis of trials with calcitonin compared to placebo did not find a significant effect for the prevention of vertebral or nonvertebral fractures for individuals treated with glucocorticoids.[10] There was evidence that calcitonin prevented bone loss at the spine but not at the hip compared to placebo.[201, 208]

Patients with Breast or Prostate Cancer

Women with breast cancer receiving aromatase inhibitor (AI) therapy may have increased BMD loss and fractures.[209-211] Zoledronic acid, denosumab[212, 213], and risedronate have been demonstrated to reduce AI-associated BMD loss.[214] Up-front zoledronic acid prevented AI-associated BMD loss with early breast cancer more effectively than delaying therapy until BMD loss or fracture occurs.[215] As well, the addition of zoledronic acid to adjuvant endocrine therapy improves disease-free survival in premenopausal patients with estrogen-responsive early breast cancer.[216] For patients taking adjuvant anastrozole for early breast cancer, risedronate resulted in significant increase in lumbar spine and total hip BMD.[217]

Men who receive androgen deprivation therapy (ADT) for prostate cancer are at higher risk for fracture.[218, 219] and should be assessed for pharmacologic therapy. [220] There was insufficient fracture data in studies with bisphosphonates and SERMs; however, denosumab showed a decreased cumulative incidence of new vertebral fractures at 36 months (ARR 2.4%).[213] .

SPECIAL GROUPS

Summary Statements:

1. Osteoporosis therapies including alendronate, risedronate, and teriparatide reduce the risk of vertebral fractures and maintain BMD in those prescribed glucocorticoids > 3 months[10, 201-204] (Level 1).
2. Etidronate, zoledronic acid and calcitonin maintain BMD in those prescribed glucocorticoids > 3 months[10, 201, 205, 206, 208] (Level 2).
3. Bisphosphonates maintain BMD in women prescribed aromatase inhibitors and men prescribed androgen deprivation therapy[209-211, 213-215] (Level 2).

SPECIAL GROUPS

Clinical Recommendations:

1. For individuals over age 50 who are on long-term glucocorticoid therapy (three months cumulative therapy during the preceding year at a prednisone-equivalent dose > 7.5 mg daily), a bisphosphonate (alendronate, risedronate, zoledronic acid) should be initiated at the outset and should be continued for at least the duration of the glucocorticoid therapy [grade A].

2. Teriparatide should be considered for those at high risk for fracture who are taking glucocorticoids (three months cumulative therapy during the preceding year at a prednisone-equivalent dose > 7.5 mg daily) [grade A].
3. For long-term glucocorticoid users who are intolerant of first-line therapies, calcitonin or etidronate may be considered for preventing loss of bone mineral density [grade B].
4. Women who are taking aromatase inhibitors and men who are undergoing androgen-deprivation therapy should be assessed for fracture risk, and osteoporosis therapy to prevent fractures should be considered [grade B].

Testosterone and Men

There is no evidence to date that testosterone reduces fractures in men,[10] nor is there evidence that hypogonadal men respond differently than eugonadal men to bisphosphonate therapy in the presence of osteoporosis.[77, 118]

In an RCT in which one-third of men were hypogonadal, defined by low serum free testosterone, the BMD response from alendronate was similar regardless of baseline testosterone level.[190] In a meta-analysis of alendronate therapy, men with hypogonadism responded to treatment with a lower odds ratio for incident vertebral fractures of 0.44 (95% CI 0.23, 0.83)[191] with similar response to eugonadal men. Studies to date have not been powered to determine efficacy of testosterone in reducing nonvertebral fractures in eugonadal or hypogonadal men.

TESTOSTERONE IN MEN
Summary Statement: 1. Testosterone maintains BMD in hypogonadal men but has not been shown to reduce the risk of fractures[10] (Level 2).

INTEGRATED MANAGEMENT

An integrated risk assessment and treatment model is desirable to ensure that there is a consistent approach to overall management. This should involve a participatory approach to clinical decision-making, with patient and health care provider reviewing the patient's risk for osteoporotic fracture and health care preferences, leading to the formulation of an individualized care plan (Figure 2).

General Principles of Therapy

To achieve the most dramatic reduction in future fracture rates and orthopaedic health care costs, healthcare providers must first target those patients who have already fractured because they are the ones at highest risk for more fractures (Figure 3).

The integrated model emphasizes three fracture risk categories that are in general alignment with treatment requirements: low risk (usually not requiring pharmacologic treatment), moderate risk (consider additional clinical risk factors to determine need for pharmacologic treatment) and high risk (should be considered for pharmacologic treatment). Under the FRAX or CAROC risk assessment systems, these categories are

determined from sex, age, femoral neck BMD and a set of clinical risk factors.[6, 120] For those at moderate fracture risk, it may be helpful to consider additional clinical risk factors that are not already considered in the risk assessment system to refine assessment of risk within that category (Appendix 1, Table A12).

General nutrition includes optimizing total (dietary and supplements) calcium and vitamin D intake, regular weight bearing, balance and strengthening exercises, and smoking cessation. In older patients, falls prevention should be considered, including a multifactorial assessment for contributing causes. In general, these measures are sufficient for individuals at low fracture risk who do not already have low BMD or risk factors for rapid BMD loss.

Pharmacologic Therapy

There is consistent evidence from randomized clinical trials for vertebral fracture prevention in individuals with osteoporosis as defined by a T-score $\leq$-2.5, and some (but not all) interventions have also been shown to prevent nonvertebral and/or hip fractures as discussed elsewhere.[221] Patients with prior low trauma fractures affecting vertebrae or hip benefit from pharmacologic intervention.[222, 223] For fractures involving a site other than vertebrae or hip (e.g., wrist fracture), there is inconsistent evidence for benefit from pharmacologic therapy in those who do not also have osteoporotic T-scores.

Pharmacologic therapy should be offered to patients at high absolute risk (>20% probability for major osteoporotic fracture over 10 years). Post hoc analysis from two clinical trials found greater fracture reduction at higher FRAX

fracture probabilities.[224, 225]. The US (National Osteoporosis Foundation) has identified a 10-year risk of a major osteoporotic of >20% as a cost-effective intervention point.[226, 227]

Additional Considerations in Decision-Making

For those with moderate fracture risk and no other risk factors, treatment should be individualized and may include pharmacologic therapy, or basic bone health with monitoring. Patient preference and additional clinical risk factors that are not already incorporated in the risk assessment system will also help to guide management decisions.

Practical considerations limit the complexity and number of factors included in a risk assessment system. Although some of these additional factors appear to add little in terms of fracture prediction at the population level, they may still have important effects on fracture risk for the individual. In individuals at moderate fracture risk, refining the risk assessment based on consideration of additional features of risk factors within an existing model (e.g., number and site of prior fractures, glucocorticoid dose) or additional risk factors not included in that model (e.g., recurrent falls or spine T-score in the FRAX or CAROC systems) will help to guide the clinician in treatment decisions.

History of fracture and glucocorticoid use are considered as dichotomous (yes/no) under the FRAX or CAROC systems, but they have been shown to have dose-dependent effects. Multiple fractures confer greater risk than a single fracture,[89 104] and in particular multiple vertebral fractures confer a stronger risk than a single vertebral fracture.[66] Individuals with more than one low-trauma fracture should therefore be regarded as at particularly high risk for future fracture. In addition, prior fractures of the hip and

vertebra carry greater risk than other fracture sites.[108, 183] Notably, in the Canadian Multicentre Osteoporosis Study, radiographic vertebral fractures were strongly associated with future osteoporotic fractures independently of prior clinical fractures.[16] Together these findings emphasize that more than one low-trauma fracture, or a low-trauma fracture of hip or vertebra, justifies a recommendation for pharmacotherapy. As noted elsewhere, vertebral fracture assessment (VFA) predicts future osteoporotic and hip fractures independent of age, weight, and BMD.[40, 41] Lateral radiographs or VFA of the thoracolumbar spine to diagnose unrecognized vertebral compression fractures will also assist in further stratifying risk and clinical decision making.

A WHO meta-analysis of corticosteroid use did not have sufficient details to stratify according to dose or duration[42], but other large studies have confirmed that higher dose (prednisone or equivalent at 15 mg daily or greater) and recent exposure (within the last 3-6 months) indicate a higher risk subgroup. Corticosteroid-induced bone loss is believed to be most rapid in the first few months of treatment, especially within the spine. In 244,235 oral corticosteroid users and 244,235 controls (average age 57 years) from the UK General Practice Research Database (GPRD) the adverse effect of corticosteroids appeared to develop quickly (within 3-6 months) with a rapid decline in fracture risk toward baseline after cessation, and increased risk was seen with prednisone doses as low as 2.5-7.5 mg daily.[43] From the same GPRD cohort of oral corticosteroid users aged 40 years and older, a simplified scoring system was developed for absolute 5-year and 10-year fracture risk prediction.[44] Osteoporotic fractures were independently predicted by corticosteroid dose (but not duration), age, gender, fall history, fracture history, BMI, smoking, specific medical diagnosis, indication for corticosteroid treatment, other

medications and recent hospitalizations (information on BMD was not available). Adverse effects of glucocorticoids on bone develop quickly (within 3-6 months), with increased fracture risk for prednisone doses as low as 2.5-7.5 mg daily, although fracture risk rapidly declines toward baseline after cessation.[49] These findings justify intervention in individuals recently started on therapeutic long-term or repeated systemic glucocorticoids (oral or parenteral), even before they meet the conventional criteria for prolonged systemic glucocorticoid use (e.g., at least 3 months cumulative during the preceding year at a prednisone equivalent dose greater than 7.5 mg daily). This recommendation does not apply to the use of glucocorticoid therapy for appropriate physiologic adrenal glucocorticoid replacement.

Individualized Decision-Making

Cost-effectiveness models and guidelines typically do not consider personal preferences and health priorities. It has been suggested that integration of individual-specific with population-specific factors could ideally lead to ‘‘individualized intervention thresholds’’, thus aiding clinicians to maximize benefits to patients and society.[228]

Monitoring

The major objective of follow-up testing is to identify individuals with continued BMD loss, despite appropriate osteoporosis treatment. Measurement error must be considered when interpreting serial BMD assessments in order to determine whether the change is real and not simply random fluctuation or artifact. Each centre should determine its precision error in order to estimate the least significant change (LSC) (i.e., the change in BMD required to have 95% confidence that the change is real).[229] Continued BMD loss

exceeding the LSC may reflect poor adherence to therapy, failure to respond to therapy or previously unrecognized secondary causes of osteoporosis (e.g., vitamin D insufficiency). However, most osteoporosis therapies do not cause large increases in BMD, and the antifracture effect of treatment is only partly explained by the relatively small changes in BMD.[16] Stable BMD is consistent with successful treatment.

Once a decision to initiate osteoporosis drug therapy has been made, the expectation is that patients will experience antifracture benefits similar to those reported in clinical trials. Therapeutic benefit is reduced or eliminated if there is suboptimal adherence to the regimen, including frequently missed doses, failing to take the medication correctly to optimize absorption and action, or discontinuation of therapy.[230-232] Compliance rates at one year in the range 25-50% with oral osteoporosis agents are commonly reported, and are only marginally better with less frequent dosing regimens.[230, 233]

Several approaches can be considered to ensure that patients are adherent to therapy and to confirm treatment response. These include a combination of reminders, information, counseling, simplifying dosing regimen, and self-monitoring. The most effective monitoring strategy and the role of BMD in facilitating adherence are uncertain.[234] In part, this reflects conflicting data on the usefulness of BMD change as an independent risk factor for fracture[232, 235], relatively low sensitivity to identify short-term BMD changes[236], and a variable relationship between fracture risk reduction and BMD change (i.e. an increase in BMD during antiresorptive therapy accounts for a relatively small proportion of the observed reduction in the risk for fractures).[79, 193, 237, 238]

Measurement of BMD is commonly done to monitor the response to a pharmacologic therapy or to document the stability of bone density in untreated patients at risk for bone loss. No randomized trials have directly assessed the value of repeat BMD testing on persistence with medication or fracture reduction. Notwithstanding the lack of conclusive data, many patients and clinicians find value in an objective measurement that documents the effect of treatment.[193] If used correctly, serial BMD testing can be a helpful clinical tool.[6] Depending on the clinical situation, BMD scans are usually repeated every 1 to 3 years, with a decrease in testing once therapy is shown to be effective. In those at low risk without additional risk factors for rapid BMD loss, a longer testing interval (5-10 years) may be sufficient.[239, 240] As noted in "Risk Assessment", individuals with a T-score of the spine or hip $\leq$-2.5 should be considered as having at least moderate risk and a repeat BMD measurement should be obtained after 1-3 years to monitor for rapid bone loss. If BMD is stable then less frequent monitoring can be considered.

BMD monitoring can be used to guide initiation of osteoporosis drug therapy in those at moderate fracture risk undergoing basic care. Some, but not all, studies show that more rapid BMD loss in untreated individuals is an independent risk for fracture.[5, 241]; others have questioned the value of repeated BMD measurements to determine the rate of loss and suggest that it is the actual BMD level at any given time that predicts fracture risk rather than the rate of bone loss.[232, 242, 243]

Bone turnover markers have the potential to provide evidence of treatment effect much earlier than BMD (within the first 3-6 months), though further confirmation in clinical

trials and overcoming challenges of measurement variability within individuals are required before these can be endorsed as a clinical routine (Appendix 1, Table A10).

Referral for Specialist Care

Recognizing that there may be situations in which the management of osteoporosis can be complicated, primary care physicians should consider referral where specialized consultation and care is required (see Table 7).

Areas of Uncertainty

Trials showing benefit for empirical treatment based upon a low trauma fracture of the vertebra or hip have not stratified results by bone density. Consequently, there is some uncertainty over whether there is an antifracture benefit when the T-score is above -1.5. On the one hand, fracture prevention has been demonstrated with zoledronic acid given to elderly hip fracture patients without assessment of BMD. On the other hand, it is not known whether patients with a history of low-trauma fracture (other than vertebra or hip) benefit from osteoporosis drug treatment in the absence of concomitant low BMD, as there are no clinical trials of osteoporosis therapies using such fractures as a sole entry criterion. This is particularly relevant to patients younger than age 65 presenting with wrist fractures and no other major risk factors.[244] Wrist fractures contribute close to half of the low-trauma fracture burden in some series.[244]

TREATMENT INITIATION

Summary Statements:

1. Multiple fractures confer greater risk than a single fracture[89, 104] [Level 1].
2. Prior fractures of the hip and vertebra carry greater risk than other fracture sites[16, 66, 108, 183] [Level 1].
3. Pharmacologic intervention, when based on prior fragility fractures affecting the vertebra or hip, has shown fracture benefit in clinical trials[222, 223] [Level 1].
4. In patients who initiated glucocorticoids, fractures can occur quickly (within 3-6 months) with prednisone doses as low as 2.5-7.5 mg daily with a rapid decline in fracture risk toward baseline after cessation[49, 245] [Level 1].
5. Rapid BMD loss in untreated individuals may be an independent risk for fracture[235, 241] [Level 2].

TREATMENT INITIATION

Clinical Recommendations:

1. Initiation of pharmacologic treatment for osteoporosis should be predicated on an assessment of absolute fracture risk by means of a validated fracture prediction tool [grade D].
2. Pharmacologic therapy should be offered to patients at high absolute risk (> 20% probability for major osteoporotic fracture over 10 years) [grade D].

3. Individuals over age 50 who have had a fragility fracture of the hip or vertebra and those who have had more than one fragility fracture are at high risk for future fractures, and such individuals should be offered pharmacologic therapy [grade B].
4. For those at moderate risk of fracture, patient preference and additional risk factors (Appendix 1, Table A12) should be used to guide pharmacologic therapy [grade C].
5. Individuals at high risk for fracture should continue osteoporosis therapy without a drug holiday [grade D].
6. Clinicians should avoid simultaneously prescribing more than one antiresorptive agent for fracture reduction [grade D].

KNOWLEDGE TRANSLATION

Despite a number of osteoporosis updates and position papers since the 2002 Osteoporosis Canada guidelines were published, [6, 45, 46, 66, 183, 246-248] an osteoporosis care gap remains. Translation of evidence to improve clinical care in osteoporosis needs to be addressed, with a particular emphasis on those at high risk for fracture.

Educational Strategies Targeting Patients and Health Care Professionals

A systematic review of osteoporosis disease management tools found that interventions which targeted both the physician and patient and that were multifaceted, such as reminders, education and risk assessment in either paper or electronic format, improved both appropriate use of BMD and treatment.[249] Reminders in conjunction with education, targeted to physicians and patients, have demonstrated an increase in BMD testing (RR range 1.43 to 8.67) and osteoporosis medication use (RR range 1.60 to 8.67) and in one study reduced fractures.[250] Point-of-care tools that are evidenced-based and facilitate

diagnosis and treatment at the time of care have also been demonstrated to improve care. These include computer-based algorithms, access to diagnostic tools, guidelines (either electronic or printed copies). [251] However, there is limited research with point of care tools and osteoporosis management.[249] In an educational strategy targeting over 3000 primary care physicians, the Canadian quality circles[44, 252] involved a multifaceted program that included tools to assist in applying guidelines.[253] The outcome of this program was an improvement in the appropriate use of BMD and in the management of high risk individuals.[252]

Chronic Disease Management Models

Patients' perceptions of future fracture risk are influenced by whether or not they believe they have osteoporosis. Furthermore, up to 46% of individuals who had experienced a fragility fracture did not believe that they were at an increased risk for a future fracture. Other barriers to postfracture care include lack of integration between those providers who deliver fracture care, such as orthopedic surgeons, and those who provide osteoporosis and falls management care. To address these barriers, Ontario Ministry of Health and Long-Term Care in partnership with Osteoporosis Canada has developed an integrated care delivery model to improve postfracture care -- one of the first comprehensive strategies in the world (logic model and tools available at http://www.osteostrategy.on.ca).

Several Canadian RCTs have demonstrated the effectiveness of multi-faceted approaches using case managers to co-ordinate care. In an economic analysis, compared with usual care, the case management strategy was dominant: for every 100 patients case managed,

six fractures (four hip fractures) were prevented, four quality-adjusted life-years were gained, and CAD$260,000 was saved by the health care system.[254]

KNOWLEDGE TRANSLATION

Summary Statements:

1. Educational initiatives targeting both physicians and patients improve osteoporosis management for those individuals who experienced a fragility fracture[255, 256] (Level 2).
2. Case managers associated with high volume orthopedic clinics are cost effective in improving appropriate management for patients who have experienced a fragility fracture[254] (Level 1).

KNOWLEDGE TRANSLATION

Clinical Recommendations:

1. Following a fragility fracture, an educational initiative should be targeted at both the patient and the primary care physician [grade B].
2. Case management is recommended as an effective approach to post-fracture care, to improve both the diagnosis and the management of osteoporosis [grade A].
3. Point-of-care tools and other targeted strategies are recommended to support the implementation of osteoporosis guidelines in clinical practice [grade B].

COMPARISON WITH OTHER GUIDELINES

The use of an absolute 10-year fracture risk assessment system as a guide for treatment intervention is a recent development in osteoporosis management. The US National Osteoporosis Foundation (NOF) and the UK National Osteoporosis Guideline Group (NOGG) describe two different approaches to using fracture risk estimates from FRAX to determine treatment intervention thresholds. Both derive from cost-effectiveness analyses.

The NOF Clinician's Guide states that postmenopausal women or men over 50 with a T-score of ≤-2.5 at the hip or spine, should be treated, regardless of prior fracture status.[61, 62] Similarly, patients with a prior hip or spine fracture should be treated regardless of BMD. In addition, based on risk calculations from the US FRAX tool, patients with low bone mass (T-score between -1.0 and -2.5 at the femoral neck, total hip or spine) should be treated when there is a 10-year probability of hip fracture that is ≥3% or a 10-year probability of a major osteoporosis related fracture that is ≥20%.

NOGG suggests an age-dependent intervention threshold which varies from a 10-year probability of a major osteoporotic fracture of 7.5% at age 50 years to 30% at the age of 80 years.[63] Assessment thresholds for testing individuals with BMD are also proposed by NOGG and would apply to 6–9% of the population at the age of 50 years, rising to 18–36% at the age of 80 years. The overall use of the NOGG thresholds in a case-finding strategy was projected to identify 6–20% women as eligible for BMD testing and 23–46% as eligible for treatment, depending on age.[63]

The NOF approach would treat a much larger proportion of the population than under the NOGG guidelines, even after the recent downwards re-calibration in the US FRAX tool risk estimates; thus NOF guidelines are estimated to treat 40.5% of white women over age 50, rising to 67.9-90.8% after age 70.[64, 65] For comparison, a women age 68 or older with femoral neck T-score -2.4 and no other risk factors would be recommended for treatment under the NOF guidelines but not under the NOGG guidelines.

It is unclear which approach would be better suited to the Canadian context. Cost-effectiveness studies using Canadian cost data and the currently proposed Canadian FRAX and CAROC tools are required. The choice of an intervention threshold of 20% risk of major osteoporotic fractures under the CAROC system is therefore an evolving target that may change as additional information emerges.

Notes:

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Table 1: Clinical examination of individuals at risk of osteoporosis

History	Identify risk factors for low BMD, fractures and falls • Parental hip fracture, glucocorticoid use (> 3 months in the prior year at a prednisone equivalent dose greater than 7.5 mg daily), current smoking, high alcohol intake (3 or more units per day), and rheumatoid arthritis • Inquire about falls in the previous 12 months • Inquire about gait and balance
Physical Examination	Measure weight and compare with weight at age 25 In postmenopausal women and men 50 years and older, low body weight (< 60 kg) and major weight loss (>10% of weight at age 25 years) are associated with low BMD and fractures.[45, 257]
Diagnosis of Vertebral fractures	Measure Height Prospective loss of > 2cm over 3 years is associated with vertebral fractures and should be investigated by a lateral thoracic and lumbar spine x-ray Rib to pelvis distance to identify lumbar fractures Assessment of the distance between the costal margin and the pelvic rim (measured on the anterior axillary line) can help identify occult[258]. A measurement of < 2 fingerbreadths is associated with vertebral fractures Occiput to wall distance and kyphosis to identify thoracic spine fractures Measure the distance between the wall and the patient's occiput as the individual stands straight with heels and back against the wall. Vertebral fractures should be suspected if distance between the wall and the occiput >5 cm[58, 259] .
Falls	Assess ability to get out of chair without using the arms, walk, several steps and return; Get Up and Go Test[260, 261]

Table 2: Recommended biochemical tests for patients being assessed for osteoporosis

Calcium, corrected for albumin
Complete blood count
Creatinine
Alkaline phosphatase
Thyroid-stimulating hormone
Serum protein electrophoresis (for patients with vertebral fractures)
25-Hydroxyvitamin D*

* Should be measured after three to four months of adequate supplementation and should not be repeated if an optimal level (at least 75 nmol/L) is achieved.

Table 3: Additional biochemical testing to be considered, based on clinical assessment

Condition or Disease	Test
Hyperparathyroidism - if persistently elevated serum calcium	PTH
Multiple myeloma - in patients with multiple or atypical vertebral fractures	Protein electrophoresis Immunoelectrophoresis
Celiac disease - if symptoms/signs of malabsorption or non-response to vitamin D therapy	Antibodies associated with gluten enteropathy
Hypogonadism - in men with signs and symptoms of androgen deficiency	Testosterone (free and total) Serum prolactin
Hypercalciuria - consider in patients with history of kidney stones or high dose glucocorticoids for prolonged periods	24 hour urine for calcium

Table 4: Indications for measuring bone mineral density

Older adults (age ≥ 50 yr)	Younger adults (age < 50 yr)
Age ≥ 65 yr (both women and men)	Fragility fracture
Clinical risk factors for fracture (menopausal women, men age 50–64 yr)	Prolonged use of glucocorticoids*
Fragility fracture after age 40 yr	Use of other high-risk medications†
Prolonged use of glucocorticoids*	Hypogonadism or premature menopause (age < 45 yr)
Use of other high-risk medications†	Malabsorption syndrome
Parental hip fracture	Primary hyperparathyroidism
Vertebral fracture or osteopenia identified on radiography	Other disorders strongly associated with rapid bone loss and/or fracture
Current smoking	
High alcohol intake	
Low body weight (< 60 kg) or major weight loss (> 10% of body weight at age 25 yr)	
Rheumatoid arthritis	
Other disorders strongly associated with osteoporosis	

*At least three months cumulative therapy in the previous year at a prednisone-equivalent dose ≥ 7.5 mg daily.
†For example, aromatase inhibitors or androgen deprivation therapy.

Other disorders strongly associated with osteoporosis include:

- Primary hyperparathyroidism
- Type I diabetes
- Osteogenesis imperfecta in adults
- Untreated long-standing hyperthyroidism, hypogonadism or premature menopause (<45 years)
- Cushing's disease
- Chronic malnutrition or malabsorption
- Chronic liver disease
- Chronic inflammatory conditions (e.g., inflammatory bowel disease).

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Table 5: Diagnostic categories for both men and women based on bone densitometry

Age	Category	Criteria *
Less than 50 years	Below expected range for age	Z-score ≤ -2.0
	Within expected range for age	Z-score > -2.0
50 years and older	Severe (established) osteoporosis	T-score ≤ -2.5 with fragility fracture
	Osteoporosis	T-score ≤ -2.5
	Low bone mass	T-score between -1.0 and -2.5
	Normal	T-score ≥ -1.0

* Notes:

1) T-score is the number of standard deviations that BMD is above or below the mean normal peak BMD for young white women (NHANES III for hip measurements). Z-score is the number of standard deviations that BMD is above or below the mean normal BMD for sex, age and (if reference are available) race/ethnicity.

2) Osteoporosis cannot be diagnosed by BMD alone below age 50.

3) Based upon lowest value for lumbar spine (minimum two vertebral levels), total hip, and femoral neck. If either the lumbar spine or hip is invalid, then the forearm should be scanned and the distal 1/3 region reported.

4) Fracture risk assessment under the FRAX / CAROC (2010 version) is based upon the femoral neck T-score only.

Figure 1: Assessment of basal 10-year risk of fracture with the 2010 tool of the Canadian Association of Radiologists and Osteoporosis Canada

The T-score for the femoral neck should be derived from the National Health and Nutrition Education Survey III reference database for white women. Fragility fracture after age 40 or recent prolonged use of systemic glucocorticoids increases the basal risk by one category (i.e., from low to moderate or moderate to high). This model reflects the theoretical risk for a hypothetical patient who is treatment-naive; it cannot be used to determine risk reduction associated with therapy. Individuals with a fragility fracture of a vertebra or hip and those with more than one fragility fracture are at high risk of an additional fracture.

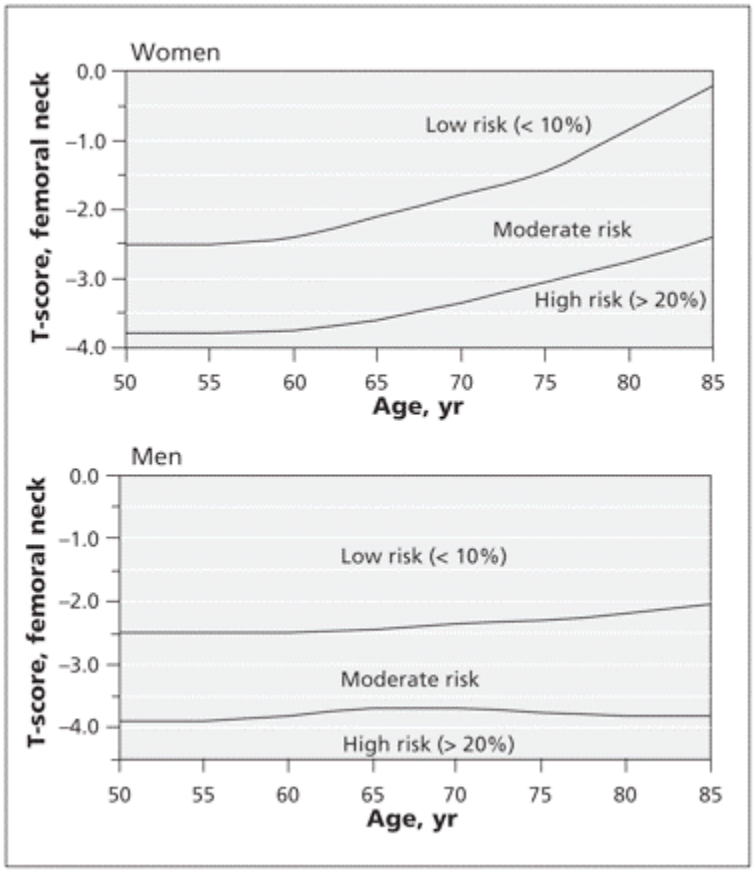

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Table 6: Prescribing information for osteoporosis pharmacologic agents

Drug Class	Drug and dosing schedules	Patient instructions and precautions	Adverse Events
Oral bisphosphonates	Alendronate (Fosamax®, Fosavance®): 10 mg daily, 70 mg weekly Risedronate (Actonel®): 5 mg daily, 35 mg weekly, 150 mg monthly Etidronate (Didrocal®): Cyclical therapy of daily 200 mg for 14 days followed by calcium supplements for 10 weeks	Alendronate and risedronate must be taken first thing in morning with plain water, at least 1/2 hour before eating. It is best to avoid taking a calcium supplement with breakfast on that day. Patients must refrain from lying down following the intake of the medication. These medications are contraindicated in patients whose creatinine clearance is below 30 ml/minute	Upper gastrointestinal symptoms (established association - 10% of trial participants) Severe bone, joint and/or muscle pains, distinct form the acute flu-like reaction that sometimes accompanies the initial administration of iv bisphosphonates (established association - rare) Esophageal ulceration (established association - rare) Esophageal cancer [262-265](uncertain association – very rare) Osteonecrosis of the jaw* (probable association - very rare in patients who take bisphosphonates for osteoporosis, less than 1 per 100,000 patient-years) Atypical subtrochanteric and diaphyseal femoral fractures (uncertain association – very rare) Atrial fibrillation (no association found after re-analyses by the Food and Drug Agency of data from all clinical trials on bisphosphonates)
Intravenous bisphosphonate	Zoledronic Acid (Aclasta®): 5 mg intravenously once yearly	Vitamin D must be administered in appropriate doses for a minimum of 2	Acute flu-like reaction (acute phase response) (established association - 10% of trial participants following the first

		weeks prior to the infusion. This medication is contraindicated in patients with hypocalcemia and in those whose creatinine clearance is below 35 ml/minute. Patients should be warned about the possibility of flu-like symptoms; acetaminophen can be given prior to the infusion and up to 48 hours after, to reduce (or prevent) the severity of the reaction. Elderly patients, those on diuretics or who have impaired renal function should be encouraged to drink 500 ml of water prior to or during the infusion	infusion. Incidence decreases with subsequent infusions) Severe bone, joint and/or muscle pains distinct form the acute flu-like reaction (established association - rare) Hypocalcemia (established association - less than 1% of trial participants) Osteonecrosis of the jaw* (probable association - very rare in patients who take bisphosphonates for osteoporosis,: less than 1 per 100,000 patient-years) Atypical subtrochanteric and diaphyseal femoral fractures (uncertain association – very rare) Atrial fibrillation (no association found after re-analyses by the FDA of data from all clinical trials on bisphosphonates)
Selective estrogen receptor modulators (SERM)	Raloxifene (Evista®): 60 mg daily	This medication is contraindicated in women who have a history of thromboembolic events.	Hot flashes and leg cramps (established association - <10% of trial participants) Venous thromboembolic events (established association – 0.02-0.5% of trial participants)
Calcitonin	Calcitonin (Miaclacin®): 200 IU intra-nasally daily	This medication is well tolerated	
Parathyroid hormone	Teriparatide (Forteo®):	This medication is	Headaches, nausea and dizziness

	20 mcg subcutaneously daily	contraindicated in patients who have a history of bone malignancy, hypercalcemia and active hyperparathyroidism. There is warning on this medication's package (black box warning) about very rare occurrences of osteosarcomas in growing rats that were given high doses of teriparatide during preclinical studies. Extensive postmarketing surveillance has not documented excess osteosarcomas in patients prescribed this medication compared to the general population.	(established association- 3 to 8% of trial participants) Asymptomatic hypercalcemia (established association – 10% of trial participants) Renal calculi (established association - 0.37-1.4% of trial participants)
Calcium	All formulations	Total daily intake of calcium (from diet and supplements) should not exceed 1200 mg per day	Cardiovascular events, mostly myocardial infarctions but also stroke (uncertain association – rare) Renal calculi (established association - rare if total intake less than 1500 mg daily)

* Bisphosphonate-associated osteonecrosis of the jaw is defined "as an area of exposed bone in the maxillofacial region that does not heal within 8 weeks after identification by a healthcare provider, in a patient who is receiving or has been exposed to a bisphosphonate and has not had radiation therapy to the craniofacial region

Figure 2: Integrated approach to management of patients who are at risk for fracture

BMD = bone mineral density. Dashed arrow indicates that evidence for benefit from pharmacotherapy is not as strong in this instance as for other recommendations.

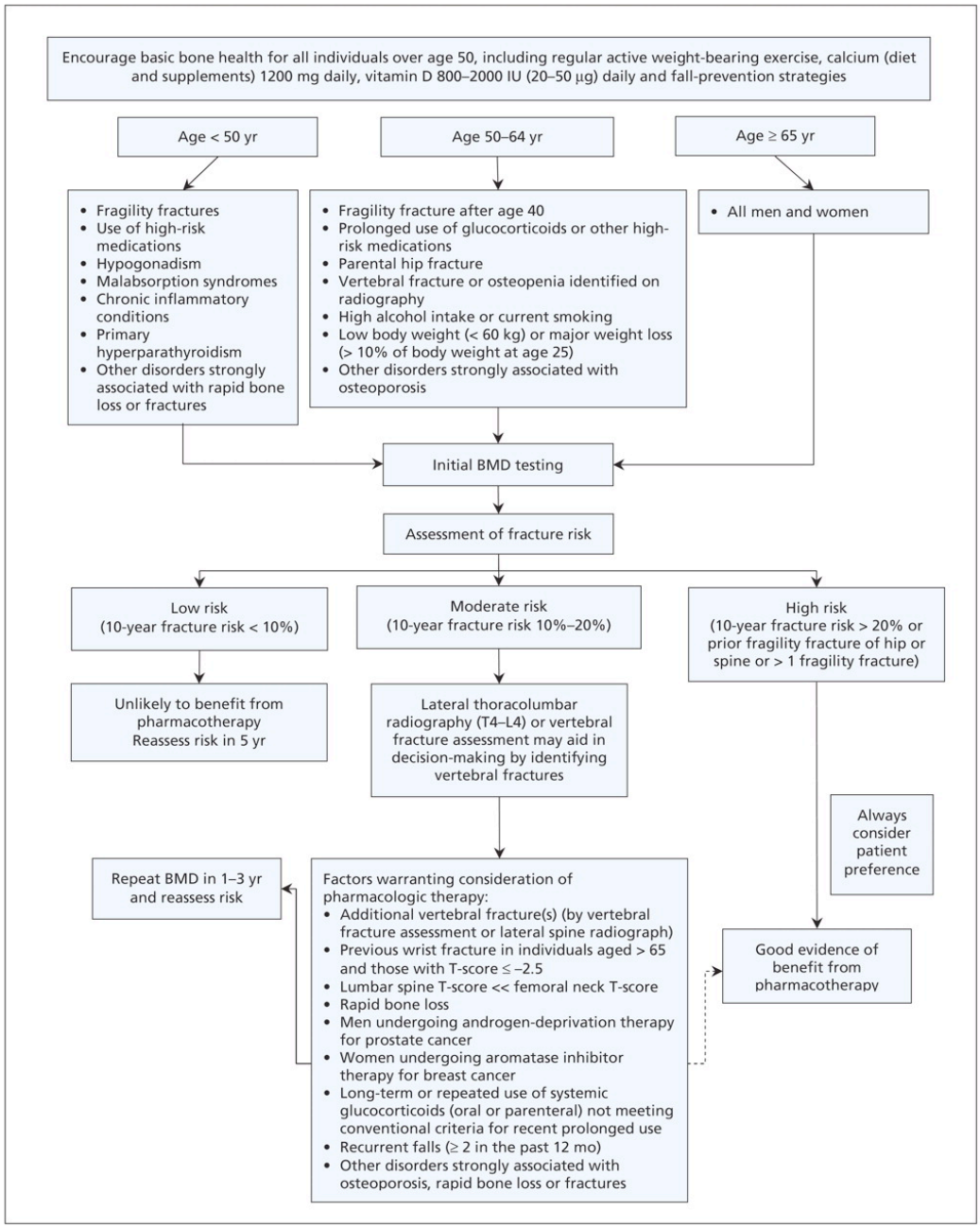

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Figure 3: Fracture Pyramid

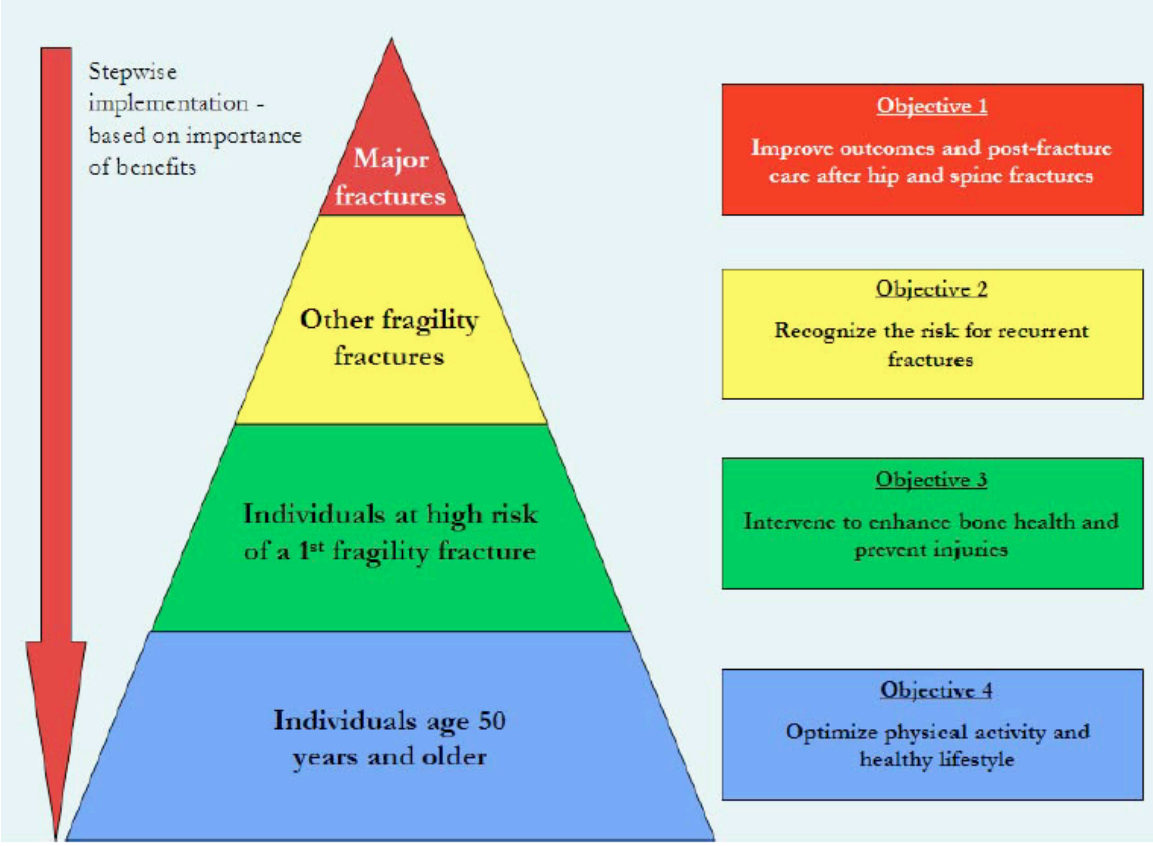

Table 7: When to refer patients for specialized consultation and care

1. Fracture on first line therapy with optimal adherence
2. Significant loss on follow-up BMD on first line therapy with optimal adherence
3. Intolerance of first and second line agents
4. Special populations:

    a) referrals to physicians with an interest or expertise in osteoporosis

    - Secondary causes of osteoporosis outside the comfort zone of the individual primary care physician
    - Patients with extremely low BMD

    b) referrals to other specialists

    - Complex individuals with multiple co-morbidities, such as those with frequent falling, Alzheimer's disease, stroke, and Parkinson's disease

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