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Guideline No. 422g: Menopause and Osteoporosis

(En français : Directive clinique n° 422g : Ménopause et ostéoporose)

The English document is the original version. In the event of any discrepancy between the English and French content, *the English version prevails*

This clinical practice guideline was prepared by the authors and overseen by the Menopause Working Group. It was reviewed by the SOGC's Clinical Practice Gynaecology Committee, SOGC's Family Physician Advisory Committee, and the SOGC's Urogynaecology Committee and approved by the SOGC Guideline Management and Oversight Committee and SOGC Board of Directors.

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RECOMMENDED CHANGES IN PRACTICE

1. Anabolic therapy is recommended as first-line therapy in patients at high risk of an imminent fracture.
   a. Romosozumab, a monoclonal antibody to sclerostin, is an anabolic agent and has been approved for the treatment of postmenopausal osteoporosis for up to 1 year.
   b. Teriparatide, recombinant human parathyroid hormone 1-34, is an anabolic agent approved for the treatment of postmenopausal osteoporosis for up to 2 years
2. Following anabolic therapy, it is essential to initiate antiresorptive therapy to prevent reductions in bone mineral density that are associated with an increased risk of fracture.
3. Following 5 years of bisphosphonate therapy, a drug holiday should be considered in patients with an intermediate fracture risk, in the absence of a previous fragility fracture and provided their femoral neck T-score is greater than −2.5.
4. Osteonecrosis of the jaw is a rare complication of antiresorptive therapy in the doses used to treat osteoporosis (1 in 10 000 to 1 in 100 000 patient-years of exposure).
5. Atypical femoral fractures have been uncommonly reported with long-term use of antiresorptive therapy; they account for 1.1% of all femoral fractures, with an age-adjusted incidence of 1.8 cases per 100 000 person years for bisphosphonate exposure of less than 2 years increasing to 113 cases per 100 000 person years at 8−10 years of exposure. Number needed to harm is about 1 per 2000 per year of bisphosphonate use.

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This document reflects emerging clinical and scientific advances as of the publication date and is subject to change. The information is not meant to dictate an exclusive course of treatment or procedure. Institutions are free to amend the recommendations. The SOGC suggests, however, that they adequately document any such amendments.

Informed consent: Everyone has the right and responsibility to make informed decisions about their care together with their health care providers. In order to facilitate this, the SOGC recommends that health care providers provide patients with information and support that is evidence-based, culturally appropriate, and personalized.

Language and inclusivity: The SOGC recognizes the importance to be fully inclusive and when context is appropriate, gender-neutral language will be used. In other circumstances, we continue to use gendered language because of our mission to advance women's health. The SOGC recognizes and respects the rights of all people for whom the information in this document may apply, including but not limited to transgender, non-binary, and intersex people. The SOGC encourages health care providers to engage in respectful conversation with their patients about their gender identity and preferred gender pronouns and to apply these guidelines in a way that is sensitive to each person's needs.

Clinicians are encouraged to enquire about the presence of thigh or groin pain in patients on long-term antiresorptive therapy and, if present, evaluate further with bilateral full-femur X-ray and/or a bone scan.

KEY MESSAGES

1. Health care providers should carefully exclude secondary causes of bone loss before confirming a diagnosis of postmenopausal osteoporosis in all patients through laboratory testing (complete blood count [CBC], thyroid-stimulating hormone [TSH], serum calcium corrected for albumin and /or ionized calcium, phosphate, creatinine, 25-hydroxyvitamin D, parathyroid hormone [PTH], alkaline phosphatase [ALP], and serum immunoelectrophoresis). Further investigations can be completed as clinically indicated (i.e., celiac profile, adrenal function, and 24 hour urine calcium and creatinine).
2. Lifestyle modifications, with a daily weight-bearing exercise program, smoking cessation, and limitation of alcohol intake, are advised.
3. Health care providers should ensure adequate calcium intake (1200 mg of elemental calcium, preferably from dietary sources) and adequate vitamin D supplementation, aiming for a 25-hydroxyvitamin D level of 75−125 nmol/L in all patients with postmenopausal osteoporosis.
4. Patients with osteoporosis at an intermediate risk of fracture (10%−20% risk of major osteoporotic fracture) should be treated with pharmacotherapy, especially in the presence of diseases or drugs associated with an increased fracture risk or progressive bone loss.
5. All patients with a high risk of fracture (≥20% risk of major osteoporotic fracture or ≥3% risk of hip fracture over the next 10 years) should be treated with pharmacotherapy.
6. Patients at very high risk of fracture (recent fracture within the past 12 months or multiple fragility fractures or major osteoporotic fracture risk >30% or hip fracture risk >4.5%) should be considered preferably for an anabolic agent followed by antiresorptive therapy.
7. The benefits of pharmacotherapy for fracture prevention greatly outweigh any potential adverse effects.

ABSTRACT

Objective: Provide strategies for improving the care of perimenopausal and postmenopausal women based on the most recent published evidence.

Target Population: Perimenopausal and postmenopausal women.

Benefits, Harms, and Costs: Target population will benefit from the most recent published scientific evidence provided via the information from their health care provider. No harms or costs are involved with this information since women will have the opportunity to choose among the different therapeutic options for the management of the symptoms and morbidities associated with menopause, including the option to choose no treatment.

Evidence: Databases consulted were PubMed, MEDLINE, and the Cochrane Library for the years 2002−2020, and MeSH search terms were specific for each topic developed through the 7 chapters.

Validation Methods: The authors rated the quality of evidence and strength of recommendations using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. See online Appendix A (Tables A1 for definitions and A2 for interpretations of strong and weak recommendations).

Intended Audience: physicians, including gynaecologists, obstetricians, family physicians, internists, emergency medicine specialists; nurses, including registered nurses and nurse practitioners; pharmacists; medical trainees, including medical students, residents, fellows; and other providers of health care for the target population.

SUMMARY STATEMENTS:

1. Secondary causes of bone loss should be excluded before confirming the presence of postmenopausal osteoporosis (*moderate*).
2. The Fracture Risk Assessment Tool (FRAX) can be used to evaluate 10-year fracture risk (*high*). Alternatively, the Canadian Association of Radiologists and Osteoporosis Canada (CAROC) assessment tool may be used to evaluate the 10-year fracture risk (*moderate*).
3. Ensure patients with postmenopausal osteoporosis receive a calcium-enriched diet (1200 mg elemental calcium daily) and adequate vitamin D supplementation, aiming for a 25-hydroxyvitamin D level of 75−125 nmol/L (30−50 ng/mL) (*high*).
4. Health care providers should treat all patients with osteoporosis at intermediate risk with a 10%−20% risk of major osteoporotic fracture over the next 10 years with pharmacologic therapy (*high*).
5. Health care providers should treat all patients at high risk of fracture (with a ≥20% risk of MOF or ≥3% risk of hip fracture over the next 10 years with pharmacologic therapy (*high*).
6. Health care providers should treat all patients at very high fracture risk (recent fracture within the past 12 months or multiple fragility fractures or major osteoporotic fracture risk >30% or hip fracture risk >4.5%) preferably with an anabolic agent followed by an antiresorptive agent (*moderate*).
7. Patients taking bisphosphonates should be considered for a bisphosphonate drug holiday after 5 years of bisphosphonate therapy, if the fracture risk is intermediate and femoral neck T-score is better than −2.5 and in the absence of prior fragility fracture (*moderate*).
8. Atypical femoral fractures are associated with long-term bisphosphonate therapy and are uncommon. It is important to ask about thigh or groin pain in patients on antiresorptive therapy and the antiresorptive therapy should be stopped in the presence of an atypical femoral fracture (*moderate*).
9. Osteonecrosis of the jaw is a rare complication of antiresorptive therapy, and the incidence seen in patients prescribed antiresorptive therapy ranges from 1 in 10 000 to 1 in 100 000 patient-years (*high*).
10. Romosozumab, teriparatide, or denosumab should not be stopped without replacing these agents with an antiresorptive agent in order to prevent declines in bone mineral density and bone strength following cessation of drug therapy. (*high*).

RECOMMENDATIONS:

1. All adults ≥65 years should be screened for increased fracture risk by clinical evaluation and bone mineral density assessment. Community-based screening in older women may be effective in reducing the incidence of hip fracture (*conditional, moderate*).
2. In postmenopausal women <65 years, evaluate fracture risk clinically without bone mineral density assessment (FRAX without bone mineral density). A bone mineral density assessment should be considered for patients with diseases or drugs associated with an increased risk of fracture or in the presence of a prior fragility fracture (*conditional, low*). If the FRAX score for MOF without bone

mineral density is >10%, a bone mineral density assessment should also be considered.

3. All patients with osteoporosis should be treated. After a fragility fracture, the risk of a subsequent fracture is highest in the next 12–24 months (imminent fracture risk). Pharmacologic therapy should be initiated after a fragility fracture without delay. (*strong, high*).
4. Bisphosphonates may be offered to patients with osteoporosis at an intermediate risk of fracture in the absence of contraindications, ideally for up to 5 years (*strong, high*). Fracture risk should be revaluated after 3 to 5 years of bisphosphonate therapy, and a drug holiday should be considered (*strong, moderate*).
5. Denosumab may be offered for up to 10 years in patients at high or very high risk of fracture in the presence of a normal serum calcium (adjusted for albumin or ionized calcium), normal vitamin D, and estimated glomerular filtration rate (eGFR) >15 mL/min/1.73 m^2. If denosumab is discontinued, it should be replaced with an alternative treatment option (*strong, high*).
6. Romosozumab may be offered to those at high or very high risk of fracture for up to 1 year (*strong, high*). After 1 year of therapy, romosozumab should be followed by an antiresorptive agent (*strong, moderate*). Romosozumab is contraindicated in the presence of a recent myocardial infarction or stroke or for patients with a high risk for major adverse cardiovascular events.
7. Teriparatide or abaloparatide (for up to 2 years) may be offered to patients with a high or very high risk of fracture and should be followed by an antiresorptive agent (*strong, high*). Teriparatide and abaloparatide are not advised in patients with a history of cancer, radiation exposure, hypercalcemia, or hyperparathyroidism.
8. Raloxifene or bazedoxifene may be offered to postmenopausal women with an intermediate risk of fracture who are at increased risk of breast cancer and at low risk of thromboembolic disease (*conditional, ungraded*).
9. Menopausal hormone therapy may be given to postmenopausal women experiencing menopausal symptoms at low, intermediate, or high fracture risk if they are under the age of 60 years, with no history of breast cancer or thromboembolic disease and at a low risk of cerebrovascular or cardiovascular disease (*conditional, moderate*).
10. A daily weight-bearing exercise program, as well as a calcium-enriched diet with adequate vitamin D supplementation, are advised (*strong, high*). Limitation of alcohol intake and smoking cessation should also be emphasized (*strong, moderate*).

INTRODUCTION

In Canada, postmenopausal osteoporosis is associated with significant morbidity, mortality, and health care costs.[1] Currently, a health care crisis has resulted from inadequate treatment of postmenopausal osteoporosis. Prevention of both primary and secondary fractures is inadequate, with treatment rates after a fracture ranging from 20% to 30%.[2] This update summarizes advances in the diagnosis and management of postmenopausal osteoporosis following the publication of the previous guidelines in 2014, and it is aligned with other recently published international guidelines.[3–6] See appendix B for a detailed explanation of the literature search strategy that was conduced to inform this update.

SCREENING

Whom to Screen to Prevent Osteoporotic Fractures

Screening for risk of osteoporosis-related fracture may assist in identifying those at increased risk of fracture, initiating therapy to improve bone mineral density (BMD), and lowering fracture risk. Two randomized controlled trials (RCTs) of moderate quality evaluated the effectiveness of screening for risk of osteoporosis-related fracture.[7,8] The studies included women over 65 years and had a mean follow-up of 5 years. The Screening for Osteoporosis in Older Women for the Prevention of Fracture (SCOOP) trial screened 12 483 women using either the Fracture Risk Assessment Tool (FRAX) or usual care. For those identified as at high risk by FRAX, BMD was evaluated by dual-energy X-ray absorptiometry (DXA) imaging. At 5-year follow-up, there was no statistically significant decrease in incidence of all osteoporosis-related fractures (hazard ratio [HR] 0.94; 95% confidence interval [CI] 0.85–1.03, $P = 0{\cdot}178$), clinical fractures (HR 0.94; 95% CI 0.86–1.03, $P = 0.183$), and mortality (HR 1.05; 95% CI 0.93–1.19, $P = 0.436$).[7] A statistically significant reduction in the incidence of hip fracture was observed in the screening group compared with a usual care group (2.6% vs. 3.5%; HR 0.72; 95% CI 0.59–0.89, $P = 0.002$).[7]

The Risk-stratified Osteoporosis Strategy Evaluation (ROSE) trial evaluated the effectiveness of a population-based, two-step screening program for the prevention of major osteoporotic fracture (MOF) in 34 229 women aged 65–80 years.[8] The screening program consisted of a fracture risk assessment (self-reported) and DXA imaging. No statistically significant difference was observed between the intervention and control groups. Among women with FRAX ≥15%, there were no statistically significant reductions in MOF, hip fractures, and all fractures in those undergoing DXA compared with usual care. However, hip fracture was significantly reduced in the screening program group (adjusted sub-hazard ratio [SHR] 0.741; $P = 0.007$).[8] Overall, screening for osteoporosis fracture risk did not have a significant effect on fracture incidence compared with usual care.

The Stichting Artsen Laboratorium and Trombosedienst (SALT) study randomly assigned 11 032 women aged 65–90 years with 1 or more clinical risk factors for fracture to receive screening for BMD and vertebral fracture assessment or usual care.[9] Screening program success was dependant on adherence to screening and adherence to treatment. Therefore, screening is only advised in postmenopausal women over the age of 65 years.[10] In younger women, it is indicated only in patients who have diseases or who are receiving drugs associated with bone loss, or in those with a previous fragility fracture, particularly if the fracture occurred in the previous 2 years.

How to Screen for Osteoporosis Fracture Risk

Secondary causes of bone loss should be excluded before confirming the presence of postmenopausal osteoporosis. Prospective observational studies have evaluated the accuracy of screening for fracture risk with various screening tools (FRAX, FRAX adjusted for trabecular bone score [TBS], BMD, FRAX with BMD, and Garvan bone fracture risk calculator).[11–13] The Garvan screening tool calculates fracture risk based on sex, age, previous fractures since the age of 50 years (excluding fractures related to major trauma), history of falls in the past year, and BMD.[14,15]

The usefulness of FRAX and the Garvan screening tool in identifying fracture risk was evaluated in 64 739 postmenopausal women between the ages of 50 and 64 years. Self-reported MOF and incident hip fractures

ABBREVIATIONS

AFF:	atypical femoral fracture
BMD:	bone mineral density
CAROC:	Canadian Association of Radiologists and Osteoporosis Canada assessment tool
DXA:	dual-energy X-ray absorptiometry
eGFR:	estimated glomerular filtration rate
FN:	femoral neck
FRAX:	Fracture Risk Assessment Tool
MACE	major adverse cardiovascular events
MHT:	menopausal hormone therapy
MOF:	major osteoporotic fracture
PTH:	parathyroid hormone
TBS:	trabecular bone score

were measured over a 10-year follow-up period.[16] The area under the curve (AUC) for predicting hip fractures was 0.68 (95% CI 0.65−0.70) for FRAX and 0.62 (95% CI 0.59−0.65) for the Garvan tool. The AUC for predicting MOF was 0.58 (95% CI 0.57−0.59) for FRAX and 0.57 (95% CI 0.57−0.58) for the Garvan tool.[16] FRAX without BMD is a good predictor of hip fractures in women (AUC 0.81; 95% CI 0.78−0.83).[17] Self-reported falls are a significant predictor of hip fracture in women over age 70 years (HR 1.64; 95% CI 1.20−2.24).[17] Falls have been reported to be an important determinant of fracture risk in the frail elderly.[18]

FRAX adjusted for TBS is a better predictor of fracture than FRAX alone.[19] In a prospective cohort study of 2000 community-dwelling women above the age of 65 years, TBS-adjusted FRAX was a better predictor of incident MOF than FRAX alone.[20]

The Canadian Association of Radiologists and Osteoporosis Canada (CAROC) assessment tool integrates age, sex, history of previous fracture, steroid use, and BMD. It has been externally validated in 1 study and has a sensitivity of 0.54 (95% CI 0.52−0.56) for women at high risk of fracture. The specificity for CAROC is 0.75 (95% CI 0.74−0.75) among postmenopausal women.[21]

We recommend evaluating fracture risk by FRAX (with or without BMD) and incorporating the TBS if available. The CAROC tool may also be used to assess fracture risk.

SUMMARY STATEMENTS 1 AND 2 & RECOMMENDATIONS 1 AND 2

TREATMENT

Whom to Treat

Postmenopausal women at a very high fracture risk (recent fracture within the past 12 mo or multiple fragility fractures or MOF risk >30% or hip fracture risk >4.5%) should be treated aggressively preferably with an anabolic agent first (romosozumab, teriparatide or abaloparatide) followed by an antiresorptive agent (denosumab or bisphosphonates).[22−24]

Postmenopausal women at a high risk of fracture (10-y risk of MOF ≥20%, as calculated by FRAX or CAROC, or risk of hip fracture ≥3%, as calculated by FRAX) should be treated with pharmacologic therapy (anabolic therapy or denosumab or bisphosphonate or menopause hormone therapy [MHT]), as the benefit in terms of reduction in fracture risk is significant and far greater than the potential risks of therapy.[25−28]

Postmenopausal women with osteoporosis at an intermediate risk of fracture should be treated with pharmacologic therapy (bisphosphonate or MHT or selective estrogen receptor modulator [SERM]), especially if they have progressive bone loss, are receiving medications or have conditions associated with an increased risk of fracture, or have had falls in the previous 2 years.[29−36]

Fracture risk should be re-evaluated after 3−5 years of bisphosphonate therapy. If fracture risk is high, drug therapy should be continued.[37] If fracture risk is intermediate (10%−20% over the next 10 y), there is no previous fragility fracture, and the femoral neck (FN) T-score is higher than −2.5, then a bisphosphonate drug holiday should be offered.[31] See (Appendix C).[37,38]

SUMMARY STATEMENTS 4, 5 AND 6 & RECOMMENDATIONS 3,4,5 ,6,7, 8 AND 9

How to Treat

Adequate calcium intake is essential for achieving and maintaining optimal skeletal health.[39,40] We advise that postmenopausal women obtain 1200 mg of elemental calcium from dietary sources or from supplements (if dietary intake is inadequate), in the form of calcium carbonate or calcium citrate.[41] Daily weight-bearing exercise, limited alcohol intake and smoking cessation should be emphasized.[42−45]

It is important to measure serum calcium and correct for albumin to ensure that this level is normal before starting pharmacologic therapy for osteoporosis. Vitamin D is essential for skeletal mineralization and can be obtained from supplements, starting at 800−2000 IU daily.[41,46,47] Vitamin D levels should also be measured, and achieving a normal serum 25-hydroxyvitamin D level of 75−125 nmol/L is advised before starting pharmacologic therapy.[48−52]

SUMMARY STATEMENT 3 AND RECOMMENDATION 10

Bisphosphonates

Bisphosphonates (oral alendronate or risedronate) can be offered to patients with an intermediate to high risk of fracture under the following conditions: serum calcium and and vitamin D levels are normal, estimated glomerular

filtration rate (eGFR) is >30−35 mL/min/1.73 m^2, there is no gastroesophageal reflux disease, and the patient can follow the instructions for the use of oral bisphosphonates.[53] Oral bisphosphonate therapy may also be offered to patients at very high fracture risk as an alternative therapy if more potent therapy is not possible. Intravenous (IV) bisphosphonate (zoledronate) can be offered to patients with gastroesophageal reflux disease and an intermediate to very high risk of fracture, if the patient's serum calcium and vitamin D levels are normal and the eGFR is >35 mL/min/1.73 m^2.[54] Prospective RCTs have demonstrated reductions in vertebral, non-vertebral, and hip fracture risk for 3 years with IV zoledronate and up to 5 years with oral bisphosphonate therapy.[26,27,38,55] Following 3 years of annual IV zoledronate infusions or 5 years of oral bisphosphonate use, a "drug holiday" may be offered to those at an intermediate risk of fracture, as bisphosphonates have long-term skeletal retention. During the drug holiday, the bisphosphonate is stopped, and the patient is followed every 2−3 years for up to 5 years.[37] If the patient's BMD is stable and there have been no prior fragility fractures, the drug holiday can be continued. In those at a high fracture risk, ongoing therapy is required, and therapy may be switched to teriparatide, romosozumab, or denosumab as long-term bisphosphonate therapy beyond 5 years has not been shown to consistently reduce non-vertebral fracture risk.[56] If an alternative to bisphosphonates is not possible due to a contraindication or intolerance, then ongoing therapy with bisphosphonates is advised.

SUMMARY STATEMENT 7 & RECOMMENDATION 4

Denosumab

Denosumab, a monoclonal antibody to receptor activator of nuclear factor κB ligand (RANKL), is a potent antiresorptive agent and is offered to postmenopausal women at a high risk of fracture. It can safely be given if the patient's serum calcium and vitamin D levels are normal and the eGFR is >15 mL/min/1.73 m^2.[57,58] The prospective FREEDOM trial demonstrated reductions in vertebral, non-vertebral, and hip fracture risk with denosumab use for up to 10 years.[29] After 10 years of denosumab therapy, other options may be considered, or denosumab may be continued. If denosumab is discontinued, it should be replaced with an alternative treatment option, as cessation of denosumab therapy is associated with progressive bone loss and an increased risk of fracture.[59,60]

SUMMARY STATEMENT 10 & RECOMMENDATION 5

Teriparatide and Abaloparatide

Teriparatide, a recombinant human parathyroid hormone (PTH) 1-34, and abaloparatide, a modified PTH-related peptide (not yet approved in Canada), are anabolic agents and can be offered to those at a very high risk of fracture. Contraindications to their use include previous cancer, radiation exposure, hypercalcemia, high PTH level, or unexplained elevations in alkaline phosphatase.[22,59,61−63] Teriparatide and abaloparatide can be offered for up to 2 years. Following treatment with either teriparatide or abaloparatide, an antiresorptive agent should be offered to prevent declines in BMD.[64−69]

SUMMARY STATEMENT 10 & RECOMMENDATION 7

Romosozumab

Romosozumab is a humanized monoclonal antibody to sclerostin and has a dual mechanism of action. It increases bone formation and reduces bone resorption. It was approved for use in Canada in October 2019. It is indicated for those at a very high risk of fracture and is of particular benefit to those with a high risk of imminent fracture (in the next 2 y), as it has a rapid onset of action, resulting in significant reductions in the risk of vertebral, non-vertebral, and hip fracture after 1 year of therapy.[23,70−73] It is given monthly for up to 1 year. It is not advised for patients with coronary artery disease, cerebrovascular disease, or multiple risk factors for major adverse cardiovascular events (MACE). One study showed a higher incidence of MACE with romosozumab compared with alendronate (2% per year in the romosozumab arm vs. 1.1% per year in the alendronate arm).[23] However, this slight increase in the risk of MACE was not observed with romosozumab in comparison with placebo.[70]

SUMMARY STATEMENT 10 & RECOMMENDATION 6

Selective Estrogen Receptor Modulators

Raloxifene and bazedoxifene are SERMs that have been demonstrated to reduce the risk of vertebral fractures only,[74−77] not of non-vertebral or hip fractures. These

molecules can be offered to postmenopausal women who are at an increased risk of breast cancer and have a low or intermediate risk of fracture.[78–81]

RECOMMENDATION 8

Menopausal Hormone Therapy

MHT with estrogen alone or estrogen plus progesterone is effective in reducing the risk of vertebral as well as non-vertebral fractures.[82,83] It is recommended in postmenopausal women under the age of 60 years experiencing menopausal symptoms. Contraindications include a history of breast cancer or thromboembolic disease. Those at an increased risk of cardiovascular or cerebrovascular disease may be offered alternative treatment options for postmenopausal osteoporosis.[84] A summary of medications, contraindications and side effects are listed in the supplementary Table in Appendix D.

RECOMMENDATION 9

Special Circumstances

Atypical Femoral Fractures

These are stress fractures of the femoral shaft with specific radiographic features, including short oblique or transverse fracture line, as well as cortical thickening.[85,86] They have been associated with long-term use of bisphosphonates, and the risk appears to be 1 in 1000 patient-years of use following 10 years of bisphosphonate therapy.[87] Stopping bisphosphonate therapy has been associated with a 70% decline in the risk of an atypical femoral fracture (AFF). These fractures can also occur in the absence of any drug therapy, as is the case in approximately 20% of such fractures.[88,89] Two AFFs per approximately 6000 patients were observed with long-term denosumab therapy (up to 10 y).

The majority of patients with AFF have had thigh or groin pain for several weeks to months before the development of an AFF. It is advisable to ask all patients on bisphosphonate or denosumab therapy about thigh or groin pain. If thigh or groin pain is present, bilateral full femur X-rays are advised. If an AFF is found, bisphosphonate or denosumab therapy should be stopped, and teriparatide may be offered to affected patients, in the absence of contraindications.[90–92]

SUMMARY STATEMENT 8

Osteonecrosis of the Jaw

Osteonecrosis of the jaw is defined as exposed bone in the oral cavity that does not heal within 8 weeks.[93] It has been associated with dental trauma as well as high (oncological) doses of bisphosphonates or denosumab.[93,94] The absolute risk seen with the low doses of antiresorptive therapy used in osteoporosis ranges from 1 in 10 000 to 1 in 100 000 patient years. Other risk factors include diabetes, steroid therapy, periodontal disease, denture use, smoking, and antiangiogenic agents. In patients with osteoporosis on antiresorptive therapy, treatment can be withheld following a dental procedure until the surgical site has healed, which usually occurs within 6 to 8 weeks.

SUMMARY STATEMENT 9

CONCLUSION

Postmenopausal osteoporosis is a common condition resulting in fragility fractures. It is associated with significant morbidity and mortality as well as health care costs. Effective therapy is available and can significantly reduce fracture risk. Benefits of therapy are far greater than their potential adverse effects. Careful patient evaluation, with exclusion of secondary causes of osteoporosis, should be followed by assessment of fracture risk. Management strategies include appropriate lifestyle changes, adequate calcium intake, vitamin D supplementation, and pharmacologic therapy.

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APPENDIX A

Table 1. Key to Grading of Recommendations, Assessment, Development and Evaluation Quality of Evidence

Grade	Definition
Strength of recommendation	
Strong	High level of confidence that the desirable effects outweigh the undesirable effects (strong recommendation for) or the undesirable effects outweigh the desirable effects (strong recommendation against)
Conditional [a]	Desirable effects probably outweigh the undesirable effects (weak recommendation for) or the undesirable effects probably outweigh the desirable effects (weak recommendation against)
Quality of evidence	
High	High level of confidence that the true effect lies close to that of the estimate of the effect
Moderate	Moderate confidence in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Limited confidence in the effect estimate: The true effect may be substantially different from the estimate of the effect
Very low	Very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a] Do not interpret conditional recommendations to mean weak evidence or uncertainty of the recommendation.Adapted from GRADE Handbook (2013), Table 5.1.

Table 2. Implications of Strong and Conditional recommendations, by guideline user

Perspective	Strong Recommendation • "We recommend that. . ." • "We recommend to not. . ."	Conditional (Weak) Recommendation • "We suggest. . ." • "We suggest to not. . ."
Authors	The net desirable effects of a course of action outweigh the effects of the alternative course of action.	It is less clear whether the net desirable consequences of a strategy outweigh the alternative strategy.
Patients	Most individuals in the situation would want the recommended course of action, while only a small proportion would not.	The majority of individuals in the situation would want the suggested course of action, but many would not.
Clinicians	Most individuals should receive the course of action. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Recognize that patient choices will vary by individual and that clinicians must help patients arrive at a care decision consistent with the patient's values and preferences.
Policymakers	The recommendation can be adapted as policy in most settings.	The recommendation can serve as a starting point for debate with the involvement of many stakeholders.

Adapted from GRADE Handbook (2013), Table 6.1.

APPENDIX B – LITERATURE SEARCH METHODOLOGY

Four databases (Embase, MEDLINE, PubMed, and Cochrane Library) were systematically searched for articles published from 2014 to 2021 to provide an update on screening for osteoporosis to prevent fractures and pharmacologic therapy for osteoporosis. The search strategy was adapted according to the Cochrane Collaboration Handbook.[1] Selection of studies for the research questions "*whom to screen for osteoporotic fracture risk*" and "*how to screen for osteoporosis fracture risk*" included 1) women ≥50 years with no history of fracture or secondary causes of osteoporosis, 2) validated risk assessment tool, 3) primary outcome of diagnostic accuracy, and 4) randomized control trial (RCT) design. Two investigators independently screened studies based on title and abstract (2478 citations), followed by full text articles (106 citations). Two RCTs for screening of osteoporosis and 7 cohort studies for how to screen were identified. Selection of articles for the research questions "*whom to treat for osteoporosis*" and "*how to treat for osteoporosis*" was based on the following criteria: 1) postmenopausal women with osteoporosis; 2) pharmacologic therapy, including bisphosphonates, denosumab, teriparatide, abaloparatide, romosozumab, raloxifene, or bazedoxifene, or MHT, 3) assessed fracture as outcome of interest; and 4) prospective design. A total of 2745 articles were screened by title and abstract, and 25 studies evaluating pharmacologic therapy were identified. Cross-sectional studies, case-control studies, retrospective cohort studies, and studies with non-validated fracture risk assessments were excluded. Data were extracted, and quality of evidence and recommendations were developed using the GRADE approach.[3] Risk of bias and applicability of diagnostic accuracy studies were evaluated using the QUADAS-2 tool.[2]

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APPENDIX C

Supplemental Figure. Osteoporosis treatment algorithm.

APPENDIX D

Table. Osteoporosis Medications: Special Considerations and Contraindications

Name of drug	Dose	Adverse effects	Contraindication
Anabolic therapy			
Romosozumab	210 mg/mo SC (for 12 mo)	Arthralgias, injection site reaction	Prior MI or stroke, uncorrected hypocalcemia
Teriparatide	20 µg/d SC (for up to 2 y)	Nausea, orthostatic hypotension, leg cramps, mild hypercalcemia	Cancer, external beam radiation therapy, hypercalcemia, Paget's disease, bone metastases or skeletal malignancies, unexplained elevated ALP, prior radiation therapy involving the skeleton, severe renal impairment,[b] pregnancy and breast feeding
Abaloparatide[a]	80 µg/d SC (for up to 2 y)	Nausea, orthostatic hypotension, leg cramps, mild hypercalcemia	Hypercalcemia, Paget's disease, bone metastases or skeletal malignancies, elevated ALP, prior radiation therapy involving the skeleton
Antiresorptive therapy			
Bisphosphonates (oral)		Hypocalcemia, abdominal distention, GERD, constipation, diarrhea, musculoskeletal pain, ONJ (rare), AFF (rare)	GERD, esophageal abnormalities, history of AFF, hypocalcemia, inability to stand or sit for at least 60 min
Alendronate	70 mg/wk	See above	• See above • eGFR <35 mL/min
Risedronate	35 mg/wk 150 mg/mo	See above	• See above • eGFR <30 mL/min
Denosumab	60 mg SC every 6 mo	Hypocalcemia, dermatitis, eczema, headaches, arthralgia, ONJ (rare), AFF (rare)	• Hypocalcemia, history of AFF, pregnancy • Use with caution in severe renal impairment eGFR <15 mL/min
Zoledronic acid	5 mg IV (1 dose may provide skeletal protection for up to 5 y)	Hypocalcemia, hypertension, nausea, acute phase reaction-like symptoms, fatigue, headache, arthralgia, myalgia, ONJ (rare), AFF (rare)	• Hypocalcemia, pregnancy, breast feeding, history of AFF • eGFR <35 mL/min

(*continued on next page*)

Table. (*Continued*)

Name of drug	Dose	Adverse effects	Contraindication
SERMs		Hot flashes, leg cramps, edema, infection, arthralgia, flu-like symptoms, muscle spasm	Previous venous thromboembolic disorder (PE, DVT, retinal vein thrombosis), pregnancy
Raloxifene	60 mg/d oral	See above	See above
Bazedoxifene	20 mg/d oral	See above	See above
MHT, *suggested doses:*		Edema, breakthrough bleeding, breast tenderness, depression, arthralgia	Prior MI, stroke or venous thromboembolic disorder, breast cancer, undiagnosed abnormal vaginal bleeding, estrogen-dependent tumours, hepatic impairment, thrombophilic disorders, breastfeeding, endometrial hyperplasia[b]
Estrogen			
Conjugated estrogen	0.625 mg/d		
17β-estradiol (oral)	1 mg/d		
17β-estradiol (patch)	50 µg twice weekly		
17β-estradiol (gel)	2 metered doses/actuation daily (Estrogel)		
	1 mg packets daily (Divigel)		
Progestogen			
Micronized progesterone	100 mg/d oral (continuous regimen)		
	200 mg/d oral for 12–14 d/mo (cyclic regimen)		
Medroxyprogesterone acetate	2.5 mg/d oral (continuous regimen)		
	5 mg/d oral for 12–14 d/mo (cyclic regimen)		
Combined patches			
17β-estradiol/ norethindrone acetate	50/140 µg twice weekly patch (continuous regimen)		
	50/250 µg twice weekly patch for 12–14 d/mo (cyclic regimen)		

[a] Pending Canadian approval.

[b] Canadian labelling.

AFF: atypical femoral fracture; ALP: alkaline phosphatase; DVT: deep vein thrombosis; eGFR: estimated glomerular filtration rate; GERD: gastroesophageal reflux disease; IV: intravenous; MHT: menopausal hormone therapy; MI: myocardial infarction; ONJ: osteonecrosis of the jaw; PE: pulmonary embolism; SC: subcutaneous; SERM: selective estrogen receptor modulator.