ASBMR SECONDARY FRACTURE PREVENTION INITIATIVE: CONSENSUS CLINICAL RECOMMENDATIONS AND RATIONALES FROM A MULTISTAKEHOLDER COALITION

The following clinical recommendations represent the consensus of a broad multi-stakeholder coalition assembled by the American Society for Bone and Mineral Research (“ASBMR”) and the Center for Medical Technology Policy (“CMTP”) to develop a plan to prevent secondary fractures in patients with osteoporosis. They form the core foundation of the initiative, defining the target population and identifying the direct clinical actions that the Coalition believes should be taken in order to diminish patients’ risk of secondary fractures. Older people who have suffered a hip or vertebral fracture are at extremely high risk of another fracture, yet a majority of them do not receive appropriate treatments following their fracture — these recommendations are intended to help change this unacceptable situation.

The recommendations are not intended to address the clinical management of acute fractures and how best to optimize recovery — for example, how quickly a patient with a hip fracture should proceed to surgery or how best to treat back pain in a patient with vertebral fractures. Such issues are important and potentially could affect the risk of additional fractures but are beyond the scope of this document and this initiative.

Similarly, the recommendations do not speak to how they should be implemented. Many of the recommendations can be carried out through coordinator-based case management approaches, such as fracture liaison services, which have been repeatedly shown to be effective, but other approaches may also be effective and better suited to particular circumstances. Other parts of this secondary fracture prevention initiative focus on methods, implementation, and communication techniques — the how; these clinical recommendations focus on the substance — the what.

A core set of fundamental recommendations is provided first, followed by additional supporting recommendations. The fundamental recommendations focus on the primary underlying critical issues: improving communications — both with patients and also between healthcare providers, identifying and modifying patients’ risks of falling, offering patients effective pharmacotherapy to maintain or build bone strength, and providing appropriate monitoring and follow-up in recognition that osteoporosis is a chronic, lifelong condition.

It is important to bear in mind that these recommendations are intended to be used as general guidance only — they may not apply to all patients in all circumstances and they are not meant to replace clinical judgment and management decisions reached through informed discussions with patients.
Additionally, “consensus” means general agreement – it does not mean that every Coalition member approves of every specific element. In a consensus project it is expected that any given member’s preferences may occasionally diverge from the consensus.

Finally, the recommendations were developed to address the specific clinical situation in the US. Just as international ideas and experiences\(^1\) have informed their development, however, the Coalition hopes that the recommendations will in turn inform international efforts in the future.

Note on Methodology: Based on a review of existing clinical guidelines and recommendations, as well as a literature review, CMTP developed an initial set of draft recommendations for secondary fracture prevention, which were reviewed and edited by the Coalition Co-Chairs and ASBMR, the Coalition Steering Committee, and the full Coalition, sequentially. The cycle was repeated until consensus was reached. CMTP then prepared accompanying text that provided rationales, more detailed explanations of the recommendations, and supporting references. The full document underwent additional cycles of review and a small workgroup was assembled to work through issues on which the Coalition had not yet reached consensus. This final version resulted from further cycles of review and formed the basis of a peer-reviewed publication.

Although the recommendations do not include explicit assessment of the quality of supporting evidence, one of the Coalition’s fundamental principles was to follow the evidence and focus where the data are strongest. Because disagreements seem to occur most frequently when the scientific evidence is lacking or contradictory, we believed that consensus could be achieved even within a very diverse group by concentrating efforts where the evidence is clear and strong. Where Coalition members have substantially disagreed about the propriety of a proposed recommendation, we generally either removed the recommendation or stated that the most appropriate action is not known and then elaborated on the point in the accompanying text. The recommendations would lose credibility if they adopted strong positions on controversial issues based on opinion rather than on convincing evidence.
Summary of Consensus Clinical Recommendations

The following recommendations pertain to people aged 65 years or older with a hip or vertebral fracture. They are directed to all healthcare professionals who participate in the care of these patients (including, but not limited to, orthopaedic surgeons, rheumatologists, endocrinologists, family physicians and primary care providers, fracture liaison service coordinators, geriatricians, occupational therapists, physical therapists, rehabilitation therapists, emergency department physicians, gynecologists, hospitalists, infusion nurses, internists, neurosurgeons, nurse practitioners, oral and maxillofacial surgeons, pharmacists, physician assistants, radiologists, registered dietitian nutritionists, and chiropractors).

An important overarching principle for the recommendations is that people aged 65 years or older with a hip or vertebral fracture optimally should be managed in the context of a multi-disciplinary clinical system that includes case management (one example is a fracture liaison service) to assure that they are appropriately evaluated and treated for osteoporosis and risk of future fractures.

Fundamental Recommendations

1. Communicate three simple messages to people aged 65 years or older with a hip or vertebral fracture (as well as to their family/caregivers) consistently throughout the fracture care and healing process:
   - their broken bone likely means they have osteoporosis and are at high risk for breaking more bones, especially over the next one to two years;
   - breaking bones means they may suffer declines in mobility or independence -- for example, have to use a walker, cane, or wheelchair, or move from their home to a residential facility, or stop participating in favorite activities -- and they will be at higher risk of dying prematurely;
   - most importantly, there are actions they can take to reduce their risk, including regular follow-up with their usual health care provider as for any other chronic medical condition.

2. Ensure that the usual healthcare provider for a person aged 65 years or older with a hip or vertebral fracture is made aware of the occurrence of the fracture. If unable to determine whether the patient’s usual healthcare provider has been notified, take action to be sure the communication is made.

3. Regularly assess the risk of falling of people aged 65 years or older who have ever had a hip or vertebral fracture.
   - At a minimum, take a history of their falls within the last year.
   - Minimize use of medications associated with increased fall risk.
   - Evaluate patients for conditions associated with an increased fall risk.
   - Strongly consider referring patients to physical and/or occupational therapists or a physiatrist for evaluation and interventions to improve impairments in mobility, gait, and balance, and to reduce fall risk.
4. Offer pharmacologic therapy for osteoporosis to people, aged 65 years or older, with a hip or vertebral fracture, to reduce their risk of additional fractures.
   - Do not delay initiation of therapy for bone mineral density ("BMD") testing.
   - Consider patients’ oral health before starting therapy with bisphosphonates or denosumab.
   - For patients who have had repair of a hip fracture or are hospitalized for a vertebral fracture:
     - Oral pharmacologic therapy can begin in the hospital and be included in discharge orders.
     - Intravenous and subcutaneous pharmacologic agents may be therapeutic options after the first two weeks of the postoperative period. Concerns during this early recovery period include:
       ▪ Hypocalcemia because of factors including vitamin D deficiency or perioperative overhydration.
       ▪ Acute phase reaction of flu-like symptoms following zolendronic acid infusion, particularly in patients who have not previously taken zolendronic acid or other bisphosphonates.
     - If pharmacologic therapy is not provided during hospitalization, then mechanisms should be in place to ensure timely follow-up.

5. Initiate a daily supplement of at least 800 IU vitamin D per day for people age 65 years or older with a hip or vertebral fracture.

6. Initiate a daily calcium supplement for people age 65 years or older with a hip or vertebral fracture who are unable to achieve an intake of 1200 mg/day of calcium from food sources.

7. Because osteoporosis is a life-long chronic condition, routinely follow and re-evaluate people aged 65 years or older with a hip or vertebral fracture who are being treated for osteoporosis. Purposes include:
   - reinforcing key messages about osteoporosis and associated fractures;
   - identifying any barriers to treatment plan adherence that arise;
   - assessing the risk of falling;
   - monitoring for adverse treatment effects;
   - evaluating the effectiveness of the treatment plan; and
   - determining whether any changes in treatment should be made, including whether any anti-osteoporosis pharmacotherapy should be changed or discontinued.

**Additional Recommendations**

8. Consider referring people aged 65 years or older with a hip or vertebral fracture who have possible or presumed secondary causes of osteoporosis to the appropriate subspecialist for further evaluation and management.
9. Counsel people aged 65 years or older with a hip or vertebral fracture:
   • not to smoke or use tobacco;
   • to limit any alcohol intake to a maximum of two drinks a day for men and one drink a day for women; and
   • to exercise regularly (at least three times a week), including weight-bearing, muscle strengthening, and balance and postural exercises, depending on their needs and capabilities, preferably supervised by physical therapists or other qualified professionals.

10. When offering pharmacologic therapy for osteoporosis to people aged 65 years or older with a hip or vertebral fracture, discuss the benefits and risks of therapy, including, among other things:
   • the risk of osteoporosis-related fractures without pharmacologic therapy; and
   • for bisphosphonates and denosumab, the risk of atypical femoral fractures (“AFFs”) and osteonecrosis of the jaw (“ONJ”) and how to recognize potential warning signs.

11. First line pharmacologic therapy options for people aged 65 years or older with a hip or vertebral fracture, include:
   • the oral bisphosphonates alendronate and risedronate, which are generally well tolerated, familiar to health care professionals, and available at low cost; and
   • intravenous zoledronic acid and subcutaneous denosumab, if oral bisphosphonates pose difficulties.

For patients at high risk of fracture, particularly those with vertebral fractures, anabolic agents may be useful although consultation with or referral to a specialist would also be appropriate.

12. The optimal duration of pharmacologic therapy for people aged 65 years and older with a hip or vertebral fracture is not known.
   • General recommendations on stopping and restarting anti-osteoporosis drugs are available to individualize treatment for each patient.
   • Most published guidelines recommend that the need for therapy with bisphosphonates be reassessed after 3-5 years, based on their long half-life in bone and evidence suggesting that the risk of certain rare adverse events may increase with longer duration of treatment.
   • Stopping denosumab without starting another antiresorptive drug should be avoided because of the possibility of rapid bone loss and increased fracture risk. Similarly, patients stopping anabolic agents also should be placed on an antiresorptive therapy.

13. Primary care providers who are treating people aged 65 years and older with a hip or vertebral fracture may want to consider referral to an endocrinologist or osteoporosis specialist for those patients who, while on pharmacotherapy, continue to experience fractures or bone loss without an obvious cause, or who have comorbidities or other factors that complicate management (e.g., hyperparathyroidism, chronic kidney disease).
Recommendations and Rationales

The following recommendations pertain to people aged 65 years or older with a hip or vertebral fracture. They are directed to all healthcare professionals who participate in the care of these patients (including, but not limited to, orthopaedic surgeons, rheumatologists, endocrinologists, family physicians and primary care providers, fracture liaison service coordinators, geriatricians, occupational therapists, physical therapists, rehabilitation therapists, emergency department physicians, gynecologists, hospitalists, infusion nurses, internists, neurosurgeons, nurse practitioners, oral and maxillofacial surgeons, pharmacists, physician assistants, radiologists, registered dietician nutritionists, and chiropractors).

These clinical recommendations focus on a specifically-defined population — patients within a certain age range who have experienced certain osteoporotic fractures that come to clinical attention. The two criteria for identifying the target population — age and location of fracture — are simple and straightforward. No active case-finding or screening is required: patients with hip fractures usually present to an emergency department; patients with vertebral fractures may come to clinical attention because they are symptomatic and seek care (e.g., for back pain), have clinical signs (e.g., kyphosis), or have radiographically apparent signs that are incidentally detected. Thus, healthcare professionals should be able to readily identify the patients covered by these recommendations at all points along their care pathways.

Patients who have experienced one osteoporotic fracture are at significantly higher risk of a subsequent fracture, and the risk appears to be particularly high in older women during the first year following the index fracture (greater than five times the risk). Approximately 25% of older men and women who have a hip fracture will have a second fracture within one year, as will around 20% of older patients who have a vertebral fracture.

Effective interventions for preventing secondary fractures in this population have also been convincingly demonstrated. Several systematic reviews, for example, have concluded that bisphosphonates reduce the risk of vertebral fractures in numerous populations as well as the risk of hip and non-vertebral fractures in patients who have already experienced a fracture. Other effective pharmacologic therapies, including RANK ligand inhibitors and anabolic drugs, are also available. In terms of non-pharmacologic interventions, the Centers for Disease Control and Prevention have assembled a compendium of interventions that have been shown to reduce falls in older adults, to provide one example. Finally, a variety of studies have shown that people with hip and vertebral fractures are not receiving these effective interventions (treatment rates ranging from 8.3% to 30%).

While this particular set of clinical recommendations is focused on a specifically-defined population and its circumstances, it is critical to emphasize that fracture prevention is also needed for other high-risk populations. These recommendations are not intended to compromise other fracture prevention efforts, but rather to complement them and to serve as a foundation for future endeavors.

The recommendations are directed to a wide variety of healthcare professionals, reflecting the multitude of entry points to the relevant care pathways, both acute and chronic, and the diversity of the steps along the pathways themselves. The partial listing of disciplines is intended to illustrate this broad
range and to prompt reflection on and recognition of the roles we all can assume. Each professional involved has the ability to help ensure that their patients receive appropriate secondary fracture prevention interventions, as well as the ethical and moral obligation to do so.\textsuperscript{13}

\textit{An important overarching principle for the recommendations is that people aged 65 years or older with a hip or vertebral fracture optimally should be managed in the context of a multi-disciplinary clinical system that includes case management (one example is a fracture liaison service) to assure that they are appropriately evaluated and treated for osteoporosis and risk of future fractures.}

The recommendations primarily identify what actions to take rather than how to take them. However, a substantial and still growing body of literature demonstrates that the most effective organizational approach to secondary fracture prevention (and one that is effective in a number of different environments) is a multi-disciplinary case management approach that frequently takes the form of a fracture liaison service (“FLS”).\textsuperscript{13–20} One of the key features of an FLS is a dedicated case manager who coordinates patients’ evaluation, treatment plan development, and follow-up.\textsuperscript{13,14,16} FLSs function to help close the gap between acute fracture care and chronic osteoporosis care and optimally involve all relevant disciplines, including those aimed at addressing the psychosocial issues commonly associated with fractures that potentially significantly limit the success of treatment (e.g., depression, cognitive changes, and changes in social relationships\textsuperscript{21–24}). FLS programs have been shown to be cost-effective or cost-saving in several settings,\textsuperscript{17} and have been broadly and successfully adopted internationally, including as national policy in the UK National Health Service.\textsuperscript{25,26} Several organizations, both within the US and internationally, have developed resources to assist with establishing and sustaining FLSs, such as best practices, business case models, implementation toolkits, and training and mentoring programs, to name just a few.\textsuperscript{27–31} (The American Orthopaedic Association’s “Own the Bone,”\textsuperscript{28} the National Osteoporosis Foundation’s FLS Training and Certificate Program,\textsuperscript{31} and the International Osteoporosis Foundation’s “Capture the Fracture”\textsuperscript{29} are three prominent examples.) Although there may be settings where FLS programs cannot be fully implemented, the Coalition strongly recommends that institutions attempt to establish them.

\textit{Fundamental Recommendations}

1. \textit{Communicate three simple messages to people aged 65 years or older with a hip or vertebral fracture (as well as to their family/caregivers) consistently throughout the fracture care and healing process:}
   - \textit{their broken bone likely means they have osteoporosis and are at high risk for breaking more bones, especially over the next one to two years;}
   - \textit{breaking bones means they may suffer declines in mobility or independence -- for example, have to use a walker, cane, or wheelchair, or move from their home to a residential facility, or stop participating in favorite activities -- and they will be at higher risk of dying prematurely;}
   - \textit{most importantly, there are actions they can take to reduce their risk, including regular follow-up with their usual health care provider as for any other chronic medical condition.}
The occurrence of a hip or vertebral fracture in women or men, aged 65 years or older, is diagnostic for osteoporosis in the absence of another metabolic bone disease,\textsuperscript{13,32–35} regardless of bone mineral density (“BMD”), and as previously noted is one of the strongest risk factors for subsequent fractures. The risk of subsequent fracture is significantly elevated, especially in the first one to two years following a fracture, for all of these patients, even in patients with high/normal BMD.\textsuperscript{36–39} Most patients, however, do not believe they are at risk for another fracture, do not believe osteoporosis caused their fracture, and are unaware of interventions that have been shown to reduce their risk.\textsuperscript{40} If patients do not understand their medical condition and its meaning, they are not likely to take appropriate steps to address it.\textsuperscript{41} The recommendation reflects the need for all health care professionals to provide consistent and sustained messaging throughout the care pathway, emphasizing outcomes that matter most to patients, in order to communicate these messages effectively.\textsuperscript{13,14} These communications to patients should begin at the time of diagnosis, whether in the emergency department, an urgent care clinic, the hospital, the office, the rehabilitation facility, or some other setting, and be consistently repeated.

Although clinicians tend to focus on the risks of mortality and additional fractures, those outcomes are not necessarily the ones that resonate most with patients. Several members of the Coalition observed that hip fracture patients, for example, are often of advanced age and concerned more about losing their independence and autonomy than about mortality. Emerging evidence, including data gathered for the development of patient-reported outcome instruments, illustrates the importance of physical function (e.g., mobility, physical activity, ability to self-care) to patients with osteoporosis or fractures.\textsuperscript{42}

The impact of hip fractures on physical functioning is substantial. Approximately half of hip fracture patients who survive to one year do not regain their prior functionality\textsuperscript{43} nor does their health status return to pre-fracture levels.\textsuperscript{44} With respect to mobility specifically, only about one-third to one half of hip fracture survivors regain prior ambulatory function\textsuperscript{24,45,46} and around 13% may be unable to ambulate at all.\textsuperscript{47} Of those patients surviving one year who needed no walking aids before hip fracture, approximately 40% come to require assistance.\textsuperscript{47}

Loss of autonomy and independence is also reflected in changes of residential settings following fracture. In a cohort of more than 43,000 Medicare patients who experienced a hip fracture between 2005 and 2010, 20% of patients who had been living in the community had moved into long-term care at one year following the fracture.\textsuperscript{43} Perhaps even more strikingly, because of the expense of long-term care in the US, 80% of those patients became destitute.\textsuperscript{43} Finally, the one-year mortality for hip fracture patients ranges from 15%-30% for community-dwelling residents\textsuperscript{24,43,48} to 40%-55% for long-term care facility residents.\textsuperscript{43,48}

The recommendation emphasizes the importance of communicating these messages not only to patients but also to their family/caregivers. Fracture patients often are hospitalized, in pain, undergoing surgery, potentially somewhat disoriented – not ideal circumstances for promoting message comprehension. Providing key information to persons who will be involved with the patients’ care will increase the likelihood that patients receive it as well. Mentioning how patients can reduce their risk provides a positive message and sets the stage for additional counseling and interventions. Emphasizing the connection between fracture and osteoporosis elevates the fracture from an unfortunate accident to a sentinel event indicative of an important underlying chronic disorder.
2. Ensure that the usual healthcare provider for a person aged 65 years or older with a hip or vertebral fracture is made aware of the occurrence of the fracture. If unable to determine whether the patient’s usual healthcare provider has been notified, take action to be sure the communication is made.

Lack of communication with patients’ usual healthcare providers has consistently been identified as one of the key barriers to providing appropriate management for secondary fracture prevention. If usual healthcare providers are not aware of the occurrence of a fracture and the diagnosis of osteoporosis, they cannot take steps to provide the long-term care that this lifelong, chronic condition requires. Vertebral fractures, in particular, are seldom noted in medical records and reports and, if they are mentioned, are often reported with ambiguous or confusing terminology. It is not sufficient to hope that patients will inform their physicians at their next routine follow-up – as noted above, many patients do not understand the long-term significance and importance of their fracture. Additionally, patients are at highest risk for another fracture in the months immediately following the initial hip or vertebral fracture and steps need to be taken on an urgent basis to reduce that risk. The recommendation applies to each healthcare professional along the care pathway, beginning at diagnosis and continuing throughout, because each has the opportunity to significantly affect patient outcomes. Taking action, when unable to determine whether the patient’s usual healthcare provider has been notified, might entail calling the provider, for example, or sending an email or letter. Documenting the action in the patient’s medical records ensures better continuity of care.

3. Regularly assess the risk of falling of people aged 65 years or older who have ever had a hip or vertebral fracture.
   - At a minimum, take a history of their falls within the last year.
   - Minimize use of medications associated with increased fall risk.
   - Evaluate patients for conditions associated with an increased fall risk.
   - Strongly consider referring patients to physical and/or occupational therapists or a physiatrist for evaluation and interventions to improve impairments in mobility, gait, and balance, and to reduce fall risk.

About one-third of community-dwelling persons aged 65 years or higher fall each year, with the incidence steadily increasing until age 80. Up to 10% to 15% of falls in older adults result in fractures, and about 1% result in a hip fracture, which suggests that the circumstances and biomechanics of falling substantially affect the risk. Although not all falls produce fractures, many fractures are due to falls — around 90% of hip fractures result from a simple fall from standing height or less, for example. Particular medication classes also are associated with a higher chance of falling and are often referred to as “fall-risk-increasing drugs” or “FRIDs.” A recent series of systematic reviews and meta-analyses investigated published literature on FRIDs and concluded that the following classes of drugs are significantly associated with increased risk of falling: loop diuretics, antipsychotics, antidepressants,
benzodiazepines, antiepileptics, and opioids. With these classes of medications, however, fall risk may vary with the particular agent – thus short-acting benzodiazepines and selective serotonin reuptake inhibitors may be safer in terms of fall risk than other drugs within their categories and the selectivity of beta-blockers may be a relevant factor. Although polypharmacy is often mentioned in the literature as an independent risk factor for falling, some recent research suggests that the key element may be the number of FRIDs as opposed to the number of drugs overall.

While the association between fall risk and FRIDs is clear and it would seem logical that minimizing the number or dosage of FRIDs would reduce falls and therefore fractures, the evidence actually demonstrating the effectiveness of FRID withdrawal is not robust. At least one prospective cohort study has shown that withdrawing or reducing the doses of FRIDs as a single intervention in people aged 65 years or older with a history of falls can reduce the risk of falling by about 50%. Medication reduction is also often one part of multifactorial interventions that have been demonstrated to reduce falls.

It seems unlikely that any randomized controlled trials will be performed in the future, however, because published clinical guidelines (including those of the American Geriatrics Society/British Geriatrics Society and the European Geriatric Medicine Society) already recommend minimizing FRID use, particularly psychotropic medications, and therefore assigning patients to a control group in which FRIDs would not be withdrawn would raise significant ethical concerns. Although a protocol for a systematic review and meta-analysis of randomized controlled trials of the efficacy of FRID withdrawal on the prevention of falls and fall-related complications has been published, the review has yet to be completed. Pharmacists can be helpful for clinicians who want to review their patients’ medications with an eye towards reducing FRID use.

Several other risk factors for falls also have been identified, including: age; deficits in visual, proprioception, and vestibular systems; decline in lower extremity physical performance; comorbidity burden; nutritional status, hypoglycemia in patients with type 2 diabetes, fear of falling, and various environmental factors.

Because the immediate cause of around 90% of hip fractures is a fall, several entities stress that the best way to prevent hip fractures is through preventing falls. For example, of the five main actions the CDC recommends to prevent hip fractures, four relate to fall prevention and one to osteoporosis screening. The CDC has published a compendium of 41 effective fall prevention interventions for community-dwelling older adults that it divides into two main categories: single interventions (including exercise, home modification, and clinical interventions) and multi-faceted interventions that address multiple fall risk factors. It also has devoted significant resources to developing a Stopping Elderly Accidents, Deaths, and Injuries (“STEADI”) program based on guidelines from the American Geriatric Society and British Geriatrics Society that includes a toolkit, algorithm, training videos, and checklists to help clinicians discuss the risk of falling with their patients and adopt effective fall prevention strategies. In a recent study conducted in a health care system in upstate New York, Medicare-aged patients at high risk for falls whose primary care providers used STEADI to develop fall plans of care for them had 40% fewer fall-related hospitalizations compared to high risk patients without fall plans of care. Parts of the STEADI program, including the screening toolkit, are still in the process of refinement and testing but it appears to be a reasonable starting point for obtaining guidance on evaluating and treating patients.

The US Preventive Services Task Force (“USPSTF”) has also provided recommendations for preventing falls in community-dwelling older adults. The USPSTF primarily emphasizes exercise interventions, which it concluded can have a moderate benefit in preventing falls, although it supports multifactorial interventions when provided to selected patients. Additional information on fall prevention is available.
through the NIH, which highlights fall prevention as a key part of a multifactorial approach to reducing the risk of fractures.78

Because front-line clinicians are often already overextended and are not generally trained in exercise modalities,42 the Coalition recommends that they consider referring patients at potential high risk for falls to physical or occupational therapists or to physiatrists for evaluation and intervention. Patients who report fear of falling or imbalance may also benefit from using an assistive device.

4. **Offer pharmacologic therapy for osteoporosis to people, aged 65 years or older, with a hip or vertebral fracture, to reduce their risk of additional fractures.**
   
   - **Do not delay initiation of therapy for bone mineral density (“BMD”) testing.**
   - **Consider patients’ oral health before starting therapy with bisphosphonates or denosumab.**
   - **For patients who have had repair of a hip fracture or are hospitalized for a vertebral fracture:**
     - Oral pharmacologic therapy can begin in the hospital and be included in discharge orders.
     - Intravenous and subcutaneous pharmacologic agents may be therapeutic options after the first two weeks of the postoperative period. Concerns during this early recovery period include:
       - **Hypocalcemia because of factors including vitamin D deficiency or perioperative overhydration.**
       - **Acute phase reaction of flu-like symptoms following zoledronic acid infusion, particularly in patients who have not previously taken zoledronic acid or other bisphosphonates.**
     - **If pharmacologic therapy is not provided during hospitalization, then mechanisms should be in place to ensure timely follow-up.**

As noted previously, there is strong evidence that pharmacologic therapy for osteoporosis reduces the risk of fracture in older patients who have already experienced a hip or vertebral fracture. An important aspect of this recommendation is that the occurrence of hip or vertebral fracture is sufficient to establish a diagnosis of osteoporosis regardless of BMD and, therefore, treatment initiation should not be delayed for testing. As previously mentioned, the risk of subsequent fracture is significantly elevated for patients at all levels of BMD36–39 and patients with BMD results that fall outside the “usual” diagnostic parameters for osteoporosis have also been shown to benefit from pharmacotherapy. Most medical societies and professional organizations urge physicians to offer treatment on the basis of the clinical fracture alone (including the American Association of Clinical Endocrinologists and American College of Endocrinology,33 the National Osteoporosis Foundation,70 the American College of Physicians,32 the American Academy of Family Physicians,34 the Endocrine Society,79 the UK National Osteoporosis Guideline Group,80 the International Osteoporosis Foundation,60 and the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis,60 to name a few).

The recommendation to consider a patient’s oral health before starting pharmacologic therapy is prompted by the observation of rare instances of osteonecrosis of the jaw (“ONJ”) occurring in patients taking bisphosphonates or denosumab for osteoporosis. (The discussion accompanying Recommendation #10 provides more detailed information about ONJ.) Although the evidence is not robust, it appears that the risk of ONJ can be diminished if any needed oral surgery is completed before
the patient begins taking antiresorptives. There is no need for a full dental assessment pre-therapy, however, except potentially for oncology patients who will be starting high and frequent doses of antiresorptives.

For the more typical osteoporosis patient, as noted by the Canadian Association of Oral and Maxillofacial Surgeons in its consensus guidelines, “[d]elaying the initiation of bisphosphonate therapy pending a dental evaluation rarely would seem necessary....”

For patients who have had repair of a hip fracture or are hospitalized for a vertebral fracture, the recommendation emphasizes that they can begin taking oral anti-osteoporosis pharmacotherapy in the hospital. In the past, there have been concerns that bisphosphonates might interfere with bone healing and therefore should not be given for some period of time following bone surgery. As evidence has accumulated, however, it has become clear that “[t]he efficacy of bisphosphonates in preventing secondary fractures overwhelms the possible risk of fracture healing impairment associated with the use of bisphosphonates.” Literature reviews and meta-analysis of randomized controlled trials support this conclusion and, in the HORIZON trial of intravenous zoledronic acid following hip fracture surgery, no association between zoledronic acid infusion and delayed healing was found, even when patients were provided the drug within the first two weeks following surgery. (NOTE: the discussion accompanying Recommendation #11 about first line pharmacotherapies includes information about how to take oral bisphosphonates that may be particularly relevant for some hospitalized patients – e.g., some hospitalized patients may be too ill to sit upright for 30 minutes following ingestion.)

**Intravenous and subcutaneous** anti-osteoporosis pharmacotherapies are associated with other occurrences, however, that can limit their utility in the perioperative period. Intravenous zoledronic acid and subcutaneous denosumab and romosozumab are associated with hypocalcemia, for example, which is a significant risk factor for postoperative delirium in patients undergoing hip fracture repair. These drugs are contraindicated in patients with hypocalcemia and many surgical patients are hypocalcemic in the postoperative period. The causes of postoperative hypocalcemia are not well understood but, regardless of the mechanism, it is worth noting that, in the key HORIZON Recurrent Fracture Trial, patients with osteoporosis who had recently fractured a hip did not receive their first zoledronic acid infusion until after they had taken calcium and vitamin D supplements for at least two weeks.

For patients who are severely vitamin D deficient, repletion before providing a strong intravenous or subcutaneous antiresorptive medication may be appropriate.

Patients also can experience, in addition to hypocalcemia, an “acute-phase reaction” (“APR”) following infusion of zoledronic acid, characterized primarily by fever and muscle pain. APRs usually occur within the first three days following infusion and are most common in patients who have never taken bisphosphonates before and are undergoing infusion for the first time. Around 30% of such patients may experience APR symptoms, rising to around 40% in Asian populations. Adequate serum levels of vitamin D may be protective and providing acetaminophen to patients for a few days following the infusion can reduce the incidence of symptoms by around 50% although it cannot completely eliminate the risk. Some clinicians also slow the infusion rate to provide the drug at a constant rate over 45 minutes as opposed to 15 minutes to reduce the incidence and severity of APR, although the evidence remains anecdotal at this time. APRs that occur in the hospital are particularly problematic because fever in the perioperative period can also signal infection — they therefore can trigger substantial diagnostic evaluation and potential overtreatment of a suspected infection. Finally, teriparatide and abaloparatide are associated with symptomatic orthostatic hypotension, which can complicate patient management at a time when encouraging mobility is critical and therefore should be administered at bedtime while the patient is reclining.
5. **Initiate a daily supplement of at least 800 IU vitamin D per day for people aged 65 years or older with a hip or vertebral fracture.**

Vitamin D is a critical nutrient that has an important role in calcium absorption and maintenance of serum calcium and phosphate concentrations. Patients with osteoporosis are often vitamin D-deficient. It is difficult to obtain sufficient vitamin D from diet alone because it is not present in many foods, nor in large amounts — fatty fish (e.g., salmon, tuna, and mackerel), fish liver oils, and shiitake mushrooms are the best sources — and most American dietary vitamin D is provided by fortified foods, predominantly milk. Vitamin D supplements are available in two forms — D2 (ergocalciferol) and D3 (cholecalciferol) — that have historically been considered to be equivalent although there is some evidence that, at high doses, D3 is more effective.

The best single indicator of a patient’s vitamin D status is serum concentration of 25-hydroxy-vitamin D ("25(OH)D") because it reflects not only dietary and supplemental vitamin D but also cutaneously-produced vitamin D and it has a sufficiently long half-life. The optimal level of 25(OH)D is a matter of controversy although serum levels in the range of 20-30 ng/mL are generally thought to be sufficient. The safe upper limit is also a matter of debate and there is substantial disagreement over whether or not to treat to a specified serum level. In the US, the recommended daily allowance of vitamin D is 600 IU for people age 51 years to 70 years, and 800 IU for people older than 70 years. The effect of vitamin D alone on the risk of fracture is not clear, although there is strong evidence that it does reduce fractures when combined with calcium supplements in individuals at high risk of deficiency. It is important to note that the published clinical trials of anti-osteoporosis medications virtually all have involved providing vitamin D and calcium supplements to the enrolled patients, and replicating those treatment regimens is an additional and powerful rationale for recommending supplementation.

6. **Initiate a daily calcium supplement for people aged 65 years or older with a hip or vertebral fracture who are unable to achieve an intake of 1200 mg/day of calcium from food sources.**

Although calcium alone is not effective in preventing fractures without pharmacotherapy, the need for adequate dietary intake of calcium is straightforward: calcium is critical for bone mineralization and strength. The US Recommended Dietary Allowance for calcium is 1200 mg for women age 50 years or older and men age 70 years or older, although many US adults consume only around half that amount. Studies suggest that obtaining calcium from foods is preferable to taking supplements, so taking a dietary history before advising supplementation is recommended. Dairy products, along with leafy green vegetables, are the primary sources of calcium in the US diet, and 1200 mg of calcium is roughly equivalent to three servings of dairy. (A short algorithm for estimating calcium intake has been published by the National Osteoporosis Foundation and a global map illustrating the results of a systematic review of dietary calcium intake is available at the International Osteoporosis Foundation’s website.)

Calcium supplements are available in many different forms (e.g., tablets, chews, gums) and often are either calcium carbonate or calcium citrate although other preparations exist. Calcium carbonate is less expensive but less readily absorbed although absorption is enhanced by gastric acid or by taking the supplement with a meal. It also may cause more gastrointestinal problems. Calcium citrate is more expensive but is more easily absorbed, particularly by older patients who may produce less gastric acid. Whichever form of calcium is used, patients should not take more than 500-600 mg at a time.
in order to maximize absorption – if they need to take a larger amount, they should divide the dose and take them spaced out over the day.\textsuperscript{33,107}

It is important to note that it is possible to take too much calcium. Total calcium intake higher than 1500 mg daily has not been shown to provide additional benefit and potentially could be harmful — hypercalcemia can contribute to kidney stones, renal insufficiency, and gastrointestinal side effects.\textsuperscript{33,107} Whether calcium intake higher than 2000mg to 2500mg/day increases the risk of myocardial infarction or other cardiovascular events remains somewhat controversial but consumption below that does not appear to raise cardiovascular risk.\textsuperscript{32,109}

\textbf{7. Because osteoporosis is a life-long chronic condition, routinely follow and re-evaluate people aged 65 years or older with a hip or vertebral fracture who are being treated for osteoporosis. Purposes include:}

- reinforcing key messages about osteoporosis and associated fractures;
- identifying any barriers to treatment plan adherence that arise;
- assessing the risk of falling;
- monitoring for adverse treatment effects;
- evaluating the effectiveness of the treatment plan; and
- determining whether any changes in treatment should be made, including whether any anti-osteoporosis pharmacotherapy should be changed or discontinued.

This recommendation addresses an issue identified as a priority by Coalition members – the importance of continuing to monitor osteoporosis patients over time. Broken bones are a leading cause of hospitalizations in US women age 55 years or older – ahead of heart attacks, stroke, and breast cancer.\textsuperscript{110} In US women age 75 years or older, the number of hospitalizations for broken bones is about the same as for heart attacks, stroke, and breast cancer \textit{combined}.\textsuperscript{110} Osteoporosis also affects patients’ health-related quality of life on the same scale as diabetes mellitus, heart disease, arthritis, and chronic obstructive pulmonary disease.\textsuperscript{111,112} Osteoporosis and broken bones constitute a chronic life-long condition that needs continuing attention and monitoring.

One primary purpose of following-up with patients aged 65 years or older, with hip or vertebral fractures, is to reinforce key messages about osteoporosis, including answering any questions that patients may have developed since the previous visit. Providing osteoporosis patients with adequate informational support has been shown to be critical to their health-related quality of life.\textsuperscript{113} Moreover, failure to meet patients’ educational needs about, e.g., medication, self-management, and the nature of osteoporosis, appears to be associated with poor treatment adherence, deterioration of the doctor-patient relationship, and important negative psychosocial consequences.\textsuperscript{41}

Another key rationale is to explore and address any issues with treatment plan adherence that arise.\textsuperscript{32} For example, patient adherence with oral bisphosphonates historically has been problematic.\textsuperscript{114} One reason is that patients must take the medications on an empty stomach and stay upright for 30 minutes to minimize the possibility of upper gastrointestinal symptoms.\textsuperscript{115} Such issues can be particularly challenging for patients with poorer health status and function, or who have other problems like significant comorbidities or polypharmacy.\textsuperscript{116} Adherence with oral bisphosphonates can drop to 35% at one year, even for patients treated within fracture liaison services.\textsuperscript{116} Other aspects of treatment plans,
such as exercise programs, can also be difficult to accomplish because of changes in health status, transportation issues, lack of facilities, or other problems. Nutritional status, including inadequate calcium, vitamin D, or protein intake, can adversely affect bone health. Treating clinicians need to be aware of these types of barriers and attempt on a regular basis to identify and overcome them.

As noted in Recommendation #3, it is important to routinely assess the risk of falling. That risk can change over time and asking patients whether they have fallen since the last time they were seen takes only a few seconds. Additionally, patients taking bisphosphonates should be reminded and asked about any hip or thigh pain or dental issues (see Recommendation #10).

Various sets of clinical guidelines advise on the best way to monitor patients who have suffered a fracture. While they agree on many points, they diverge on other issues such as the role of following bone mineral density (“BMD”) over time in patients taking anti-osteoporosis medications. Those in favor of BMD testing every one to two years contend that identifying patients who continue to lose bone despite treatment is critical because they may have secondary causes of osteoporosis, need changes to their medication regimens, or taking their medication incompletely or incorrectly. If BMD is stable, then the frequency of BMD measurements can be reduced. Those who believe BMD monitoring is not needed assert that change in BMD accounts for only a small fraction (<20%) of fracture risk reduction on therapy, and that most women will have a reduced risk of fracture from medication even if their BMD does not increase. They also maintain that evidence of using serial BMD testing to identify secondary causes of osteoporosis is only anecdotal. The Coalition’s clinical recommendations do not take a position on this debate; the discussion accompanying Recommendation #12 provides additional information about length of pharmacological treatment.

**Additional Recommendations**

8. Consider referring people aged 65 years or older with a hip or vertebral fracture who have possible or presumed secondary causes of osteoporosis to the appropriate subspecialist for further evaluation and management.

Many post-menopausal women as well as men with osteoporosis have factors such as underlying disease or medication use that can contribute to bone weakening. Glucocorticoids are probably the most common cause of secondary osteoporosis, but other medications, including proton pump inhibitors, selective serotonin reuptake inhibitors, barbiturates, aromatase inhibitors, loop diuretics, and anticoagulants, among others, have been associated with secondary osteoporosis. Medical conditions causing osteoporosis include endocrine disorders (diabetes mellitus, hyperthyroidism, hyperparathyroidism), kidney and liver disease, malabsorption syndromes, and autoimmune disorders, among others. More complete listings of causes of secondary osteoporosis are available through medical society clinical practice guidelines (e.g., from the American Association of Clinical Endocrinologists and American College of Endocrinology) and websites (e.g., from the International Osteoporosis Foundation), and in the medical literature.

Theoretically, identifying and addressing these factors could reduce the risk of secondary fracture and some studies have been published suggesting benefit from specific treatments for some conditions (for example, providing thiazide diuretics along with a bisphosphonate can increase BMD in post-menopausal women with hypercalciuria compared to providing a bisphosphonate alone). Various algorithms for laboratory work-ups of patients with osteoporosis have been proposed for this reason.
There is little agreement on the best approach, however, and evidence of the clinical utility of most testing is not available. Clinicians nevertheless need to consider the possibility of secondary causes of osteoporosis, conduct an appropriate history and medical examination, and consider referring patients with possible secondary causes to appropriate subspecialists.

9. **Counsel people aged 65 years or older with a hip or vertebral fracture:**
   - not to smoke or use tobacco;
   - to limit any alcohol intake to a maximum of two drinks a day for men and one drink a day for women; and
   - to exercise regularly (at least three times a week), including weight-bearing, muscle strengthening, and balance and postural exercises, depending on their needs and capabilities, preferably supervised by physical therapists or other qualified professionals.

Risk factors for fractures can be divided into two types: those that are immutable (like age, gender, family history, racial background) and those that can be modified. This recommendation addresses some of the risk factors related to patient behaviors that can be altered, other than those already emphasized (such as taking action to reduce the risk of falling or taking anti-osteoporosis medications).

Virtually all published clinical guidelines relating to fractures or osteoporosis include recommendations not to use tobacco and to limit alcohol intake because of these substances’ impact on bone health. Although tobacco use is discouraged in any amount, the recommended upper limits on alcohol intake affecting bone health vary. The consensus recommendation follows U.S. Centers for Disease Control and Prevention definitions of excessive and heavy drinking: for women, eight or more drinks per week; for men, fifteen or more drinks per week.

Clinical guidelines are also united with respect to the importance of recommending exercise for patients with osteoporosis. Regular weight-bearing and strength-training exercise can lead to improvements in bone mineral density and also decrease the risks of falls. Exercises that focus on balance and trunk muscle strength may be even more effective at preventing falls. It is critical that any exercise recommendations be tailored to the individual patient, considering their needs, limitations, and preferences, among other factors. – any increase in activity should be implemented safely. For example, activities that involve forward spine flexion and rotation, side bending, or heavy weights should be approached cautiously because they generate compressive and torsional forces on vertebrae that can result in fracture.

While available clinical guidelines are well aligned in terms of types of exercise they advise, they often do not include information about exercise dosage, progression, or contraindications. They also frequently are vague, rather than specific, and when they are specific they provide inconsistent instruction. Physicians also tend to provide advice about exercise that is too general to be useful, probably because they have little training in exercise modalities. For these reasons, physicians should strongly consider referring women and men, aged 65 years or older, with hip or vertebral fractures, to physical therapists or other qualified professionals for evaluation and exercise plan development.
10. When offering pharmacologic therapy for osteoporosis to people aged 65 years or older with a hip or vertebral fracture, discuss the benefits and risks of therapy, including, among other things:

- the risk of osteoporosis-related fractures without pharmacologic therapy; and
- for bisphosphonates and denosumab, the risk of atypical femoral fractures ("AFFs") and osteonecrosis of the jaw ("ONJ") and how to recognize potential warning signs.

For patients to make an educated and informed decision about taking anti-osteoporosis medications, they need to understand the risks and benefits of their choices – not just the risks and benefits of taking particular medications, but the risks and benefits of not taking a medication, including specifically the risk of fractures and their consequences. The prescribing physician needs to take steps to ensure that patients fully understand this material. Guidelines promulgated by the American Association of Clinical Endocrinologists and the American College of Endocrinology discuss osteoporosis risk communication strategies and provide examples of effective presentations, and educational materials are available from other organizations as well.

The discussion accompanying Recommendation #1 provided information about the loss of independence, the loss of mobility, and the increased mortality associated with broken bones. The risk of another broken bone is also substantially increased, as summarized earlier. In a recent study of more than 45,000 US Medicare patients with first fractures, 16.7% of the patients had a subsequent fracture within a year. Patients whose first fracture was of the hip or spine had even higher rates of subsequent fracture in the next year: 25.5% for hip and 20.2% for spine. In a cohort of postmenopausal women in the Netherlands, the risk of a second fracture in the first year following a first fracture was more than five times higher than the risk of a first fracture. While mortality and disability rates for patients with a hip fracture are high, the impact of vertebral fractures should not be underestimated. Vertebral fractures often progress in severity as well as to multiple levels in the thoracic and lumbar spine – these multiple and more severe fractures in turn lead to potentially disabling pain, kyphosis, loss of independence and confidence, and difficulties breathing and swallowing.

A full review of the efficacy and risks of all anti-osteoporosis pharmacologic treatments is beyond the scope of this document but a brief review of evidence concerning bisphosphonates is appropriate because inaccurate perceptions of their benefits and risks are often substantial barriers to appropriate treatment and fracture prevention. Information about a range of available treatments can be found in review articles such as that by Tu, et al.

A recent systematic review and meta-analysis examined the effects of bisphosphonates in the specific context of secondary fracture prevention. The analysis included 5670 participants with osteoporotic fractures from twelve randomized controlled trials with follow-up ranging from one month to three years. Compared to placebo, bisphosphonates significantly reduced the risk of subsequent fracture (OR=0.499) and mortality (OR=0.662) as well as pain at the fracture site and health-related quality of life. Hip, spine, and wrist fractures all were reduced. These results are consistent with other meta-analyses that have found both clinically important and statistically significant reductions in secondary fractures (hip, vertebral, and non-vertebral) in postmenopausal women taking alendronate or risedronate for at least one year.

One of the issues that most concerns patients who have suffered an osteoporotic fracture is the safety of potential therapies, and particularly the risk of two specific events: atypical femoral fracture ("AFF")
and osteonecrosis of the jaw ("ONJ"). These conditions have received a great deal of media attention and some survey data suggest that the risks of anti-osteoporosis drugs are overestimated.40 Because of the importance of this issue to patients, it is important for prescribing physicians to be aware of the evidence and to be sure it is accurately communicated to their patients.

A more detailed case definition is available, but an AFF is a fracture of the femoral shaft or subtrochanteric region that occurs either without any trauma or with low-trauma and that has a transverse or short oblique configuration (not including cases of, e.g., pathological fractures due to bone tumors or periprosthetic fractures).136,137 AFFs can occur in the general population but are most common in patients who are taking bisphosphonates. There have also been reports of AFF occurring in patients on denosumab and other medications, although many (but not all) of the reported patients also had extensive prior exposure to bisphosphonates.138–142

It is difficult to be sure of the background incidence of an event as rare as AFF. Moreover, epidemiologic studies describing the incidence of AFF in the general population and in bisphosphonate users vary in the use of radiographic adjudication in their case definitions, as well as study design, treatment and comparator groups, and populations (sex, age, country), which adds to the uncertainty. One study of patients in an integrated health care system, which adjudicated cases by reviewing radiographs, reported (a) a background incidence in the range of 1—2 cases per 100,000 person-years, (b) the age-adjusted risk in patients taking bisphosphonates for four to six years in the range of 16 cases/100,000 person-years, and (c) the age-adjusted risk in patients taking bisphosphonates for eight to ten years in the range of 100 cases/100,000 person-years.143 An ASBMR task force that reviewed the literature a few years later concluded that the incidence of AFF in patients taking bisphosphonates ranges from 3.2 to 50/100,000 person years with the incidence increasing with length of treatment.137 These ranges are roughly consistent and confirm that longer duration of treatment is associated with increased risk of AFF. To place the relative risks in perspective, an ASBMR expert task force on management of patients on long-term bisphosphonates estimated that treatment prevents around 162 osteoporotic fractures for every AFF that occurs.144 The discussion accompanying Recommendation #12 provides additional information about potential long-term use of pharmacologic treatments.

Research continues into other risk factors. Metabolic factors, such as impaired response of parathyroid hormone to hypocalcemia, and bone mechanical/geometric factors (e.g., neck-shaft angle) have been suggested as contributing to the risk of AFF.145 Patients who are Asian,136,138 relatively younger (<65 to 70 years old),145,146 with higher bone mineral density,147 or have used glucocorticoids for one year or more148 may also have an increased AFF risk. Genetic risk factors may exist as well although evidence is still developing.149

It should be noted that in around 70% of the AFF cases reviewed by an expert task force, patients reported a prodrome of thigh or hip pain.137 Although it is not known whether or not AFF can be prevented, patients should be told to urgently report thigh or hip pain and should receive radiographic evaluation.80,136,145,150 DXA technology is a useful evaluation technique for detecting cortical thickening in the spectrum of AFF151,152 and some newer densitometers can provide a single energy image of almost the entire femur.

The first reports of ONJ in patients taking bisphosphonates were published in 2003.153 The only other anti-osteoporosis drug associated with an increased risk of ONJ is denosumab154 and the risk appears to be comparable to that associated with bisphosphonates.155
The exact incidence of ONJ remains unknown but is believed to be 0.001% or less annually in the general population.\textsuperscript{81,156} In patients with osteoporosis who are taking usual doses of bisphosphonates, the incidence is estimated to be only slightly higher – somewhere in the range of 0.001% (1/100,000) and 0.01% (1/10,000).\textsuperscript{81,144} More than 90% of the medication-related cases occur in patients who have advanced cancer and bone metastases and are taking substantially higher drug doses, more frequently, and often intravenously, to prevent skeletal complications.\textsuperscript{82,144,156} Denosumab-related ONJ, for example, has rarely been reported in patients who do not have cancer and who are being treated only for osteoporosis.\textsuperscript{157} Similarly, in a systematic review and meta-analysis of cancer patients on bisphosphonates, the risk of ONJ was not significantly increased for patients on oral bisphosphonates – only for those taking the drugs intravenously.\textsuperscript{158} In short, the risk of ONJ for patients with osteoporosis taking bisphosphonates or denosumab appears to be only slightly higher than for the general population and the benefit/risk ratio for bisphosphonates remains extremely favorable.\textsuperscript{81,159} The American Dental Association\textsuperscript{®} agrees that “[t]he potential morbidity and mortality associated with osteoporosis-related fracture is considerable and treatment with antiresorptive agents outweighs the low risk of [ONJ] in patients with osteoporosis receiving these drugs.”\textsuperscript{154}

Risk factors for ONJ can be divided into four main categories: (1) drug-related (type, dose, duration); (2) local (e.g., operative treatment, anatomic factors, concomitant oral disease); (3) demographic and systemic (e.g., age, gender, co-morbid conditions); and (4) genetic.\textsuperscript{160} The risk factors themselves vary, with one set of factors identified for cancer patients taking high doses of antiresorptives and another set of factors identified for osteoporosis patients taking lower doses. The International Task Force on Osteonecrosis of the Jaw, supported by 14 international societies, including the American Association of Oral and Maxillofacial Surgeons, the Canadian Association of Oral and Maxillofacial Surgeons, and the International Association of Oral and Maxillofacial Surgeons, among others, names dental extraction and suppuration as the two most important risk factors for osteoporosis patients on bisphosphonates or denosumab.\textsuperscript{81} (More information on the risk factors for oncology patients as well as other factors that may increase risk can be found in the International Task Force's most recent review article.\textsuperscript{81}) Although roughly one-third of ONJ cases do not have any clear preceding event, the most common preceding events are local bone infection or trauma (e.g., invasive dental surgery such as tooth extraction, pressure sores from prostheses, and periodontal inflammation).\textsuperscript{81,82,155,161}

There are steps that clinicians and patients can take to try to reduce the risk of ONJ. First, as addressed by Recommendation #4, prescribing clinicians should consider a patient’s oral health before beginning bisphosphonates or denosumab. Additionally, osteoporosis patients can best minimize their risk of ONJ while taking bisphosphonates or denosumab by optimizing and maintaining their dental health. The recommendations are the same as for the general population: maintaining good oral hygiene is of paramount importance and patients should visit their dentist regularly.\textsuperscript{81,82,160,162} Minor dental procedures like fillings, inlays, crowns, and scaling can be performed routinely and even procedures like tooth extractions and implant surgery can be performed if needed on osteoporosis patients taking antiresorptives.\textsuperscript{81,82}

Whether or not interrupting antiresorptive therapy (“taking a drug holiday”) before undergoing a more extensive dental procedure affects the risk of ONJ is not known.\textsuperscript{156,162} Some dental practitioners assert that there are theoretical reasons to suspect that a two-month drug-free period before undergoing invasive dental treatment may be appropriate for patients with longer (>4 years) exposure histories.\textsuperscript{160} Nevertheless, the International Task Force, among other professional groups and academics,\textsuperscript{160,162,163} observes that there is “currently no evidence that interruption of drug therapy in patients requiring dental procedures reduces the risk of ONJ or the progression of the disease.”\textsuperscript{81}
Patients should be made aware of key signs and symptoms of ONJ, keeping in mind that in many cases there is no clear preceding dental event. While patients should contact their dentists about these signs and symptoms, the clinician who prescribes the bisphosphonate or denosumab is responsible in the first instance for providing the information to the patient. Patients should follow-up with their dentist if they experience any of the following:\textsuperscript{81,82,156}

- jaw or tooth pain
- numbness or tingling of the lower lip or chin
- loose teeth
- signs of infection (swelling, pus exudation, redness, etc.)
- bad breath
- bare bone in the mouth

Finally, more detailed patient management recommendations from the dental perspective are available from professional organizations like the International Task Force\textsuperscript{81} and the AAOMS,\textsuperscript{160} and the published literature includes descriptions of protocols for dental procedures that may reduce the risk of ONJ.\textsuperscript{164}

11. First line pharmacologic therapy options for people aged 65 years or older with a hip or vertebral fracture, include:

- the oral bisphosphonates alendronate and risedronate, which are generally well tolerated, familiar to health care professionals, and available at low cost; and
- intravenous zoledronic acid and subcutaneous denosumab, if oral bisphosphonates pose difficulties.

For patients at high risk of fracture, particularly those with vertebral fractures, anabolic agents may be useful although consultation with or referral to a specialist would also be appropriate.

Almost all clinical guidelines that address how to reduce the risk of fractures in patients with osteoporosis recommend bisphosphonates as first line therapies (including the American College of Physicians,\textsuperscript{32} the American Academy of Family Physicians,\textsuperscript{34} the American Association of Clinical Endocrinologists and American College of Endocrinology,\textsuperscript{33} the Endocrine Society,\textsuperscript{79} the National Osteoporosis Foundation,\textsuperscript{70} the European League Against Rheumatism,\textsuperscript{14} the European Federation of National Associations of Orthopaedics and Traumatology,\textsuperscript{14} the International Osteoporosis Foundation,\textsuperscript{60} and the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis,\textsuperscript{60} among others).\textsuperscript{165} Alendronate and risedronate are oral bisphosphonates, which function as antiresorptives and have been shown to reduce the risk of hip, vertebral, and non-vertebral fractures in post-menopausal osteoporotic women.\textsuperscript{14,32,33} They also are generally well-tolerated, easier for patients to self-administer compared with an injection or infusion, and available in generic forms and therefore relatively low cost.\textsuperscript{14,165} Although the evidence of their effectiveness in men is less robust, there are no particular theoretical reasons that they should be less effective and the evidence that does exist, focused mostly on bone mineral density endpoints, supports their use in men.\textsuperscript{80,117} Oral bisphosphonates are usually taken on a weekly or monthly basis after an overnight fast and patients must then remain upright and wait at least 30 minutes before ingesting other foods or medicines.\textsuperscript{33,70} If patients cannot remain upright for that duration, have esophageal disease that could delay tablet transit, or have problems with gastrointestinal absorption, different medications would likely be more appropriate. All bisphosphonates are known to affect kidney function (regardless of the route of administration) and
should be used cautiously, or not at all, in patients with estimated glomerular filtration rates below 30-35 ml/min.\textsuperscript{33,70}

Zoledronic acid is a bisphosphonate given intravenously once a year that also has broad anti-fracture efficacy (reducing the risk of hip, vertebral, and non-vertebral fractures) – it therefore is a useful first-line option for patients who have difficulty with oral bisphosphonates as described above (including patients who have problems remembering to take their medication). Pretreating patients with acetaminophen one or two hours before infusion or for a few days following infusion can reduce the risk of a flu-like acute phase reaction (fever, headache, muscle aches) that otherwise occurs in around 30% to 40% of patients during their first infusion.\textsuperscript{33,70,99–101} Denosumab is a monoclonal antibody that binds to the cytokine RANKL (receptor activator of nuclear factor kappa-B ligand), thereby inhibiting osteoclasts and functioning primarily as an antiresorptive.\textsuperscript{166,167} It also has broad anti-fracture efficacy, particularly for preventing vertebral fractures, which it reduces by approximately 70% over three years.\textsuperscript{167} Denosumab is administered by subcutaneous injection every six months and is thought to be appropriate for patients with renal insufficiency, although any calcium deficiency, vitamin D deficiency, or secondary hyperparathyroidism should be resolved first and patients with severe insufficiency should be monitored for hypocalcemia.\textsuperscript{33,70,168,169} Unlike bisphosphonates, denosumab is not incorporated into the bone matrix and its antiresorptive effects do not continue after treatment is discontinued; rapid transition to another therapy following discontinuation of denosumab is recommended to prevent the risk of fractures from subsequently increasing.\textsuperscript{70,170}

Depending on individual medical circumstances and other factors, the anabolic agents teriparatide, abaloparatide, and romosozumab may also be useful front-line therapies. Teriparatide and abaloparatide have been shown to significantly and substantially reduce the risk of vertebral and nonvertebral fractures in patients with osteoporosis and romosozumab to significantly and substantially reduce the risk of vertebral fractures.\textsuperscript{32–34,70,80,89,171,172} In general, anabolic agents have not been recommended as first-line therapies because it is not clear whether or not they reduce the risk of hip fractures\textsuperscript{32–34,80,117} although a recent meta-analysis suggests that they might.\textsuperscript{173} They also have substantial costs (e.g., wholesale acquisition costs in the range of $20,000 to $35,000 annually\textsuperscript{171}) and are administered by subcutaneous injection – daily for teriparatide and abaloparatide and monthly for romosozumab. They are instead usually reserved for patients with severe osteoporosis (particularly those with vertebral fractures), for treating glucocorticoid-induced osteoporosis, and for patients in whom alternative therapies are contraindicated.\textsuperscript{14,79,80,117,171} Use of teriparatide and abaloparatide is generally limited to two years due to risk of osteosarcoma (based on rodent studies only, however) and a limited anabolic window, while use of romosozumab is limited to one year. Because their efficacy falls when stopped, patients should receive an antiresorptive therapy to preserve or perhaps enhance their risk reduction after anabolic drugs are discontinued.\textsuperscript{33,70,171} Side effects of these anabolic medications are generally mild and transient but the therapies should not be provided to patients with primary or secondary hyperparathyroidism, hypercalcemic disorders, or increased risk for osteosarcoma.\textsuperscript{33,80,171} Favorable fracture healing effects of teriparatide and abaloparatide have been observed in animal models, although less is known about their effects in the immediate post-fracture period.

It is critical to note this recommendation on therapy options is general in nature and does not necessarily apply to any specific patient. Choice of therapy should be determined on an individual basis by patients and their physicians in light of their particular health and personal circumstances. Additionally, more complete information on the benefits and risks of all potential anti-osteoporosis medications can be found in professional clinical guidelines, the medical literature, and the FDA-approved product labels.
12. The optimal duration of pharmacologic therapy for people aged 65 years and older with a hip or vertebral fracture is not known.

- General recommendations on stopping and restarting anti-osteoporosis drugs are available to individualize treatment for each patient.
- Most published guidelines recommend that the need for therapy with bisphosphonates be reassessed after 3-5 years, based on their long half-life in bone and evidence suggesting that the risk of certain rare adverse events may increase with longer duration of treatment.
- Stopping denosumab without starting another antiresorptive drug should be avoided because of the possibility of rapid bone loss and increased fracture risk. Similarly, patients stopping anabolic agents also should be placed on an antiresorptive therapy.

Several of the published medical society osteoporosis treatment guidelines acknowledge that optimal length of pharmacological treatment, particularly for bisphosphonates, is not known. Many of the pivotal trials had durations of a few years and the small number of trials with longer duration (up to ten years) provide suggestive but limited data. With respect to efficacy, one recent review concluded that data available from randomized clinical trials suggest continued reduction in the risk of vertebral fractures with bisphosphonate therapy longer than three to five years but are not consistent with respect to reduction of non-vertebral fractures. As previously noted, the risk of rare but serious atypical femoral fractures increases with duration of bisphosphonate treatment. In light of these data and their limitations, periods of bisphosphonate use longer than three to five years (three years for intravenous bisphosphonates, five years for oral) are generally recommended only for patients at high risk of osteoporotic fracture although there is not universal consensus on this approach.

Although additional relevant data on long-term use may emerge, whether or not they will clarify the situation is unknown. As various commenters have observed, it is highly unlikely that any long-term randomized studies of bisphosphonates will be conducted and observational data carry the risk of confounding. In this circumstance, patient treatment and management approaches especially need to be individualized – this particular patient population often has significant comorbidities and complicated situations, and medical decision making must be conducted within a larger context and clearly accounting for the patient’s values and preferences.

“Drug holidays,” or periods of time when pharmacologic therapy is not given, have been suggested as a clinical approach to address the uncertainty but data are only now emerging on their effects in various populations and results are inconsistent. Experiences of one large cohort of women aged 50 years or over who had used a bisphosphonate suggest that the risk of AFF is reduced by around 40% in the first year of the drug holiday and reduced by around 80% by later years. A drop in risk of AFF, however, would need to be balanced against any increase in the risk of osteoporotic fractures during the holiday and some recent studies indicate that this risk could increase by 30% to 40% within a short time of stopping the medication. Other studies, however, have not found an increased risk of osteoporotic fractures in bisphosphonate users who discontinued the drugs for a year or more. Differences in study definitions, patient populations, and methodologies, among other factors, make these results difficult to interpret but future data may help clarify the expected outcomes.

Unlike bisphosphonates, denosumab is not incorporated into the bone matrix and its antiresorptive effects do not continue after treatment is discontinued; rapid transition to another therapy following
discontinuation of denosumab is recommended to prevent the risk of fractures from subsequently increasing.\textsuperscript{70,170}

As previously mentioned, use of the anabolic drugs teriparatide and abaloparatide for more than two cumulative years during a patient’s lifetime is not recommended, primarily because of the potential risk of osteosarcoma (based on rodent studies),\textsuperscript{179,180} and use of romosozumab is limited to one year.\textsuperscript{89}

Additionally, gains in BMD are lost rapidly when anabolic drugs are stopped and patients should be continued on an antiresorptive therapy to preserve or perhaps enhance their risk reduction after anabolic drug discontinuation.\textsuperscript{33,70,89,171}

13. **Primary care providers who are treating people aged 65 years and older with a hip or vertebral fracture may want to consider referral to an endocrinologist or osteoporosis specialist for those patients who, while on pharmacotherapy, continue to experience fractures or bone loss without an obvious cause, or who have comorbidities or other factors that complicate management (e.g., hyperparathyroidism, chronic kidney disease).**

This recommendation identifies some clinical situations where physicians who are not specialists in osteoporosis may want to consider consulting with or referring their patient to an endocrinologist or other osteoporosis specialist. The decision whether to refer a patient will usually be made on a case-by-case basis, taking into account factors such as the patient’s specific clinical situation and comorbidities, the physician’s time, resources, and experience, and the availability of an appropriate specialist or FLS program among others. While less common conditions, like hypercalciuria, hyperparathyroidism, and various malabsorption disorders, may prompt consideration of referral, even some relatively common conditions, like diabetes or chronic kidney disease, can significantly complicate osteoporosis care and may also provide a basis for referral.\textsuperscript{33} This recommendation assumes that any issues of therapy adherence have already been addressed.
CITATION LIST


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