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UPDATE ON OSTEOPOROSIS

- **Osteoporosis is associated with increased morbidity and mortality; the prevalence is increasing**
- **Adults ≥50 years with risk factors should have their fracture risk assessed**
- **Many patients with osteoporosis are under-treated**
- **Bisphosphonates should be considered as first-line treatment**

INTRODUCTION

Osteoporosis is a disease characterised by reduced bone mass, deterioration of microarchitecture and fragility fractures.[1-3] **Fragility fractures are a major cause of morbidity in the population and are associated with increased mortality.[2,4-7]**

Up to two thirds of osteoporotic fractures occur in women;[5,8,9] it is estimated that 50% of postmenopausal women and 20% of men aged >50 years develop a fracture during their lifetime.[6] The most common types of osteoporotic fractures include hip, radius/ulna, humerus, ankle, carpus and vertebra.[9] **Hip fractures are associated with higher mortality (mortality is highest in the first year following a fracture), and a greater reduction in mobility and quality of life (QOL) than all other fractures**; many patients no longer live independently after a hip fracture.[1,5,7] **It is estimated that up to 50% of hip fractures are potentially preventable if osteoporosis is appropriately treated.[1]** The majority of vertebral fractures may not be clinically recognised, but they can cause acute pain, loss of function and often recur.[1,5] **Many patients with osteoporosis are under-treated,** even in those at very high risk of fractures.[1,4,5] The prevalence of osteoporosis is increasing due to increased life expectancy;[6] **it is estimated that the annual number of fragility fractures in Europe will rise from 3.5 million in 2010 to 4.5 million in 2025.[5]** This bulletin provides an update on the management of osteoporosis.

PATHOPHYSIOLOGY

Peak bone mass is determined largely by genetic factors, in association with other factors including nutrition, endocrine status, physical activity and health during growth.[10] Bone mass increases throughout childhood and approaches its peak by early adult life.[6] In adult life, the skeleton is continually re-modelled, whereby old bone is replaced by new bone; bone loss occurs when this balance is altered, such as with the menopause and advancing age.[10]

ASSESSMENT AND DIAGNOSIS

The aims of assessment of a patient with or at risk of osteoporosis are to 1) assess the patient's fracture risk, 2) exclude secondary causes of osteoporosis, 3) identify patients who require treatment, and 4) assess compliance with treatment if the patient is already being treated for osteoporosis. Table 1 includes fracture risk factors and secondary causes of osteoporosis that should be considered in the assessment of a patient with or suspected to have osteoporosis.

Table 1: Fracture risk factors and secondary causes of osteoporosis[1,2,5,14]

Fracture risk factors		Secondary causes of osteoporosis include:
• Age • Sex • Low body mass index (BMI) (≤19 kg/m^2) • Previous fragility fracture (fracture risk is doubled) • Parental history of hip fracture • Current smoking • Alcohol (intake of ≥3 units daily)	Medication including: • glucocorticoids • antiepileptic drugs • proton pump inhibitors • medroxyprogesterone acetate • aromatase inhibitors • androgen deprivation therapy • GnRH agonists • selective serotonin reuptake inhibitors • thiazolidinediones • calcineurin inhibitors • heparin	• Rheumatoid arthritis • Ankylosing spondylitis • Type 1 and type 2 diabetes • Hypogonadism/premature menopause (<45 years) • Prolonged immobility • Inflammatory bowel disease • Coeliac disease • Thyroid disorders • Chronic obstructive pulmonary disease • Human immunodeficiency virus • Organ transplantation

Fracture risk assessment: Guidelines recommend that **postmenopausal women and men aged ≥50 years with risk factors for fractures should have their fracture risk assessed as an absolute risk**, using a fracture risk assessment tool (without estimating bone mineral density [BMD]).[2,5,11] The Fracture Risk Assessment Tool (FRAX) is a tool used in many guidelines (available on www.shef.ac.uk/FRAX), which classifies people into low risk, intermediate risk and high risk of fractures, and includes thresholds for treatment.[1,2] **Those with: 1) a low risk should be reassured, 2) an intermediate risk should be referred for BMD assessment, followed by reassessment, and 3) a high risk should be considered for treatment.[2,5,11]** Assessment tools have limitations, for example FRAX does not take account of prior treatment or of dose responses for several risk factors.[2] Evidence suggests that a recent fracture (within the last 2 years) better predicts imminent fracture risk (i.e. risk of fracture within the next 2 years) than distant fracture.[13]

Diagnosis: The WHO defines osteoporosis as a **BMD value ≥2 standard deviations (SDs) below the young adult mean value for women (T-score ≤ -2.5).[1,2]** The BMD strongly correlates with fracture risk; **studies estimate that the risk of fracture increases approximately twofold for each SD decrease in BMD.[15,16]** Dual energy x-ray

absorptiometry [DXA] of the hip and spine are the most widely used methods of assessing BMD.[2] A limitation of BMD is that **the majority of osteoporotic fractures occur in individuals who do not have osteoporosis as defined by a T-score of ≤ - 2.5.**[1,2,5,17] Osteoporosis is also diagnosed if there is a fragility fracture in the absence of other metabolic bone diseases, independent of the BMD value.[12]

Investigations: It is important to exclude secondary causes of osteoporosis and to identify co-morbidities. Table 2 summaries the assessment of a patient.

Table 2: Assessment of osteoporosis [1,2,5,6,10]

Routine assessment	Other procedures include (if indicated)
• History and clinical examination • Blood count, sedimentation rate or C-reactive protein • Serum calcium, phosphate, alkaline phosphatase, liver transaminases, creatinine • Thyroid function tests • Vitamin D levels • DXA*	• Lateral x-rays of thoracic and lumbar spine • Serum electrophoresis and urinary Bence-Jones proteins • Parathyroid hormone, 24-h urinary calcium • Serum testosterone, sex hormone binding protein, follicle-stimulating hormone, luteinising hormone • Markers of bone turnover* • 24 h urinary free cortisol, overnight dexamethasone suppression test • Endomysial and tissue transglutaminase antibodies • Isotope bone scan

* Dual energy x-ray absorptiometry; may also be used to monitor the response to treatment.[1,4,5,]

MANAGEMENT

The goals of management of osteoporosis are to reduce the risk of fractures by: 1) strengthening bone health and/or 2) reducing the risk of falls.[1,4] A multi-disciplinary approach is recommended with collaboration between healthcare professionals (HCPs) including general practitioners, geriatricians, orthopaedic surgeons, physiotherapists, specialist nurses and pharmacists.[2,18] Fracture liaison services provide comprehensive management and have been shown to be cost-effective, with improved treatment rates and adherence, reduced re-fracture rates and mortality.[1,2]

NON-PHARMACOLOGICAL THERAPY

The non-pharmacological management of a patient with or at risk of osteoporosis includes: 1) good nutrition, 2) regular physical activity, 3) the cessation or avoidance of smoking and 4) alcohol intake ≤ 2 units per day.[1,2] Fall prevention programmes have been shown to reduce fall frequency but not fracture risk.[1,2] Hip protectors have poor adherence but may reduce the risk of hip fractures in older people in nursing homes.[2]

Individuals with or at risk of osteoporosis require adequate dietary calcium intake and vitamin D.[2] The evidence supporting calcium and vitamin D supplementation in reducing fracture risk is inconsistent, especially in those not deficient.[1,2,4,19] **Increasing calcium intake either through diet or supplements results in small increases in BMD**, however there is controversy as to whether increased calcium alone reduces fracture risk.[20,21] Calcium supplements have been associated with an increased risk of kidney stones.[2,4] **A daily calcium intake of between 800 and 1200 mg is recommended, if possible through dietary intake** (a calcium dietary calculator can be used https://www.iofbonehealth.org/calcium-calculator), or by supplementation if needed.[2] **Vitamin D supplementation with 800 IU/day of colecalciferol should be considered for postmenopausal women and men ≥50 years at increased risk or with evidence of vitamin D deficiency to reduce the risk of fracture.**[2,23]

PHARMACOLOGICAL THERAPY

The use of pharmacological therapy has shown reductions in fracture risk of 30 to 70% for vertebral fractures, up to 40% for hip fractures and up to 20% for non-vertebral fractures.[2] **The choice of therapy depends on patient factors (e.g. age, magnitude of fracture risk, renal function, co-morbidities and adherence), and drug factors (e.g. effectiveness, adverse effects and cost).**[1,2,4] The current choice of therapy includes anti-resorptives (e.g. bisphosphonates, denosumab, and hormonal drugs), and anabolics (e.g. teriparatide).[3] Table 3 summarises some prescribing considerations for osteoporosis therapies currently available in Ireland. The Summary of Product Characteristics contains full prescribing information (available on www.hpra.ie or www.medicines.ie).

Table 3: Formulations, contraindications, indications and costs of pharmacological therapy[26-35]*

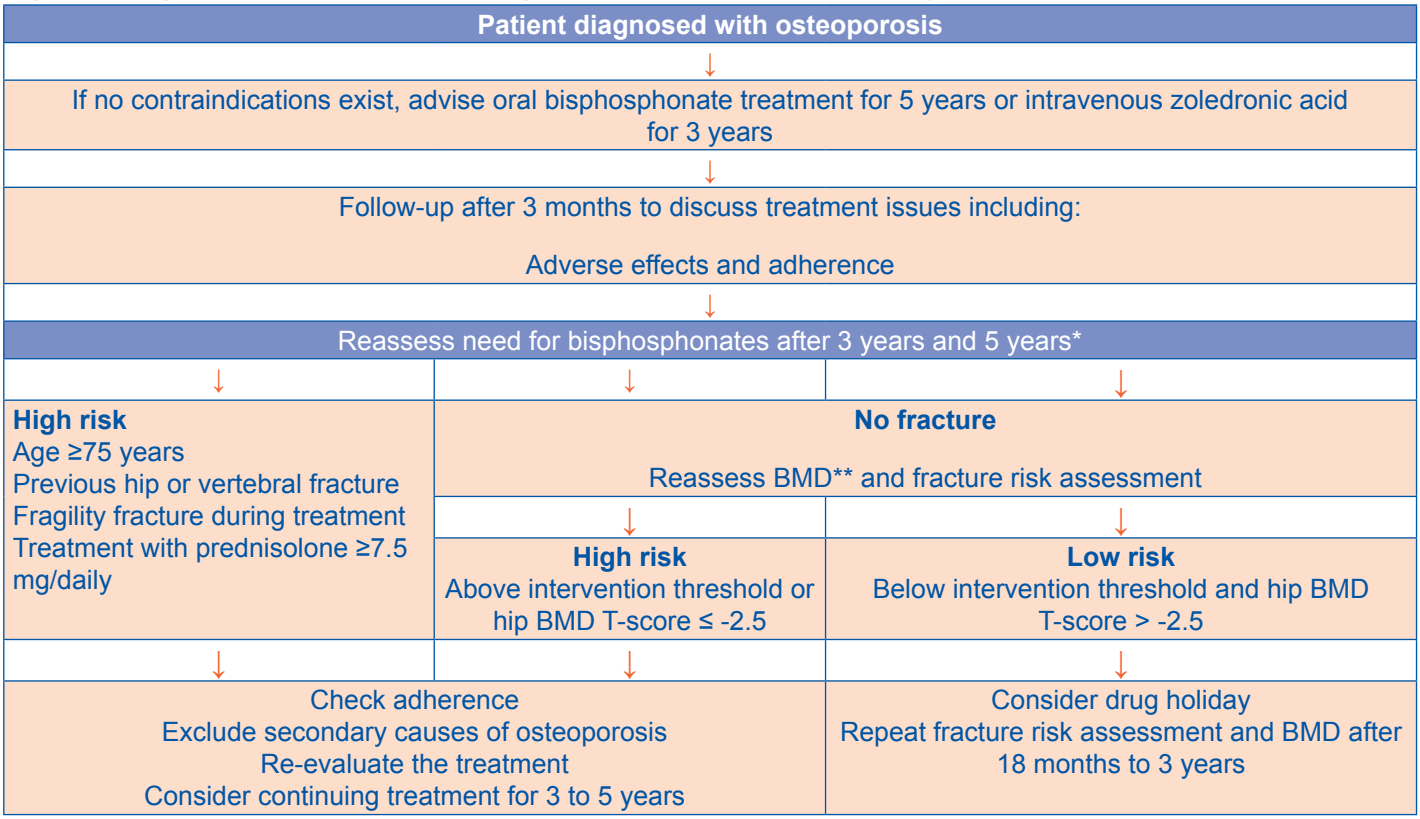
Medicine	Route	Contraindications include:	Cost per month** (Defined daily dose)
Bisphosphonate			
Alendronate #	PO (Weekly)	Hypocalcaemia, hypersensitivity, pregnancy, oesophageal abnormalities and severe renal impairment	€5.04
Risedronate#	PO (Daily; weekly; monthly)		€5.04
Ibandronate	PO (Monthly)		€11.98
Zoledronic acid	IV (Yearly)		N/A
RANK ligand inhibitor			
Denosumab 60mg	SC (6 monthly)	Hypocalcaemia, hypersensitivity	€35.20 ***
Hormone replacement therapy	PO, topical, implant	Breast cancer, unexplained genital bleeding and VTE	Various
Selective oestrogen receptor modulators			
Raloxifene	PO (Daily)	Unexplained genital bleeding and VTE	€13.72
Bazedoxifene	PO (Daily)		€22.53
Parathyroid hormone receptor agonist			
Teriparatide	SC (Daily)	Hypersensitivity, ↑ calcium, pregnancy, lactation, severe renal impairment, metabolic bone disease, unexplained ↑ alkaline phosphatase, prior radiation to skeleton and malignant skeletal disease	€224.20

*the Summary of Product Characteristics contains full prescribing details; **- reimbursement cost per month (Defined daily dose) of the reference price or cheapest available preparation (PCRS data from December 2019); ***-note that denosumab cost for 6 months is €211.20; #-combination products with vitamin D +/- calcium are also available; PO-oral; IV-intravenous; SC-subcutaneous; N/A-cost not available; VTE – venous thromboembolism; ↑-increased

Bisphosphonates bind to hydroxyapatite binding sites in bone; they cause osteoclast apoptosis and decrease bone resorption by up to 70%, leading to an increase in BMD at the spine and hip.[3,12] **Alendronate, risedronate and zoledronic acid reduce the risk of vertebral (relative risk reduction [RRR] up to 62%), non-vertebral (RRR up to 22%) and hip fractures (RRR up to 40%) in postmenopausal women,**[3,36-40] while **ibandronate reduces vertebral fracture risk (RRR 33%).**[3,41] Bisphosphonates should be used with caution in patients with upper gastrointestinal (GI) disorders and renal impairment.[1,2] To reduce the risk of upper GI symptoms, oral bisphosphonates should be taken after an overnight fast and 30 to 60 minutes before food, drink or other medications;[26-28] tablets should be swallowed whole with a glass of water while the patient is sitting/standing upright and the patient should not lie down for up to 1 hour after taking the tablet.[2] Adverse effects include upper GI symptoms, headaches and musculoskeletal pain.[2] **Osteonecrosis of the jaw (ONJ) occurs rarely (ranges from 1/10,000 to 1/100,000) in patients receiving bisphosphonates for osteoporosis**; **risk factors include poor oral hygiene, use of glucocorticoids, invasive dental procedures and cancer.**[1,3,42,43] Preventive dentistry is recommended prior to treatment in patients with dental disease or risk factors; during treatment all patients should maintain good oral hygiene, receive routine dental check-ups and report any oral symptoms.[2,43] There is no strong evidence to support stopping bisphosphonates prior to invasive dental procedures, as the medication may persist in bone for years;[2,12,43,44] patients should be assessed on an individual basis.[2,12,44] Osteonecrosis of the external auditory canal has also been reported with long-term therapy.[2,26-29] **Atypical femoral fractures (AFF) occur rarely (up to 1/1000) with long-term use of bisphosphonates;** patients should be advised to report thigh, hip or groin pain.[26-29]

Duration of bisphosphonate therapy: There is debate over the ideal duration of bisphosphonates; the main concern with long-term treatment is due to the increased risk of ONJ and AFF, even though the absolute risks are low. [3,4,42,43] **Evidence supports the positive benefit/risk for use of bisphosphonates in osteoporosis, for a duration of 3 years for IV zoledronic acid and 5 years for alendronate, risedronate and ibandronate.**[1,4,46,47] Bisphosphonates are retained in bone after stopping treatment,[48-52] therefore some patients (e.g. those with a low risk of fracture) may benefit from a temporary cessation of treatment ("drug holiday"), where treatment is stopped and the need for continued therapy is reassessed after 18 months to 3 years.[2,4,53] Evidence suggests that for people at low risk of fracture (see figure 1), the discontinuation of alendronate after 5 years or zoledronic acid after 3 years does not appear to significantly increase non-vertebral fracture risk.[46-48,50] Evidence suggests that patients continuing on alendronate for 10 years and zoledronic acid for 6 years experience fewer vertebral fractures,[46,48,54] therefore those at high risk should be considered for continuing treatment (see figure 1). **There is no evidence from clinical trials of treatment effects of bisphosphonates beyond 10 years;**[3] patients should be assessed on an individual basis.[1,2]

Figure 1: Algorithm for patients on long-term bisphosphonate therapy[1-3]



*3 years for zoledronic acid and 5 years for other bisphosphonates; **BMD – bone mineral density

Denosumab is a monoclonal antibody that binds to and inhibits receptor activator of nuclear factor kappa B ligand (RANKL); it prevents the recruitment and activation of osteoclasts.[3] Denosumab reduces the incidence of vertebral, non-vertebral and hip fractures (RRR of 68%, 40% and 20% respectively) in postmenopausal women.[3,55] **Denosumab is rarely associated with hypocalcaemia**; monitoring of calcium levels is recommended prior to each dose of denosumab, and within 2 weeks after the initial dose in patients predisposed to hypocalcaemia or if symptoms suggestive of hypocalcaemia occur.[2,30] Adverse effects include injection site reactions, skin rash and infection; **long-term treatment has been associated with rare reports of ONJ, AFF** and osteonecrosis of the external auditory

canal.[2,3,30] **Cessation of denosumab is associated with a rapid decrease in BMD and may be associated with an increased risk of fracture.[3,4,56-59]** If considering stopping denosumab, the patient must be put on an alternative anti-resorptive therapy (e.g. alendronate or zoledronic acid);[1,2,4] **patients should be informed about the importance of not missing a dose of denosumab.[12]**

Hormone replacement therapy (HRT): Oestrogen with or without progestogen reduces vertebral, non-vertebral and hip fractures in postmenopausal women.[4,60] HRT is associated with an increased risk of breast cancer, stroke and venous thromboembolism (VTE, less risk with transdermal formulations).[4,31] HRT may be an option for symptomatic, younger postmenopausal women (e.g. <60 years of age or <10 years after the menopause) with a high risk of fracture, in whom bisphosphonates or denosumab are contra-indicated and/or not tolerated.[1,4] Tibolone (a synthetic steroid) reduces the risk of vertebral fractures and non-vertebral fractures;[61] it is another hormonal option.

Selective oestrogen receptor modulators (SERMs): Raloxifene and bazedoxifene are weak anti-resorptive agents, which reduce the risk of vertebral fractures (RRR of 30%) in postmenopausal women.[1-4,62,63] Raloxifene also reduces the risk of breast cancer.[1,2,42] SERMs are associated with increased risk of VTE and a small increase in risk of stroke.[2] Adverse effects include hot flushes and leg cramps.[42] SERMs may be an option for postmenopausal women, with a low risk of VTE, where bisphosphonates or denosumab are unsuitable.[1,2,4]

Teriparatide (recombinant human parathyroid hormone [PTH] 1-34) is an anabolic agent; it is administered S/C daily for up to 24 months.[35] It reduces the risk of vertebral and non-vertebral fractures (RRR of 65% and 53% respectively) in postmenopausal women.[3,64-67] Adverse effects include headache, nausea, dizziness, myalgia, arthralgia and injection site reactions.[2,35] **On discontinuing therapy, patients should be switched to anti-resorptive therapy in order to maintain the gain in bone density.[1,2,4,12]**

Romosozumab is a monoclonal antibody that binds to sclerostin (a protein that inhibits bone formation); it is administered S/C monthly. It has a dual effect both inhibiting bone resorption and stimulating bone formation.[3] It reduces the risk of vertebral, hip and non-vertebral fractures.[68] It was recently authorised in Europe but is not currently available in Ireland.[68]

PRACTICAL ASPECTS OF PHARMACOLOGICAL MANAGEMENT

Oral bisphosphonates are usually used first line; IV zoledronic acid or S/C denosumab may be considered if oral bisphosphonates are not tolerated, while HRT or SERMs are other options for postmenopausal women, unless contraindications exist.[1,2,4] Generally, it is recommended to use one drug at a time, rather than combination therapy.[1,4,5]

Failure of treatment: Patients may experience fragility fractures while on treatment. **It is important to assess adherence and exclude secondary causes of osteoporosis in these patients.[4]** Treatment failure is considered in patients with ≥ 2 fractures and significant loss of BMD; this will often lead to a change in treatment.[3] One anti-resorptive therapy is usually replaced with another anti-resorptive, however changing to an anabolic agent should be considered in those with recurrent vertebral fractures and those on long-term anti-resorptives sustaining fractures.[3,4,5]

Adherence to bisphosphonates: Compliance with oral bisphosphonates is poor and reduces over time; studies report persistence at 2 years ranging from 34.8% to 71.3% and adherence from 23 to 50%.[70] **Older patients and those prescribed weekly rather than daily bisphosphonates are more compliant.[70]** Education and involvement of patients in choice of therapy may increase compliance.[3,4]

Osteoporosis in men: There is no evidence that skeletal metabolism in men differs from that of women. **However, secondary causes of osteoporosis are more commonly found amongst men, and this requires thorough investigation.[2]** Specialist referral should be considered for younger men (<50 years) and those with severe disease.[2] Fewer studies have evaluated the efficacy of therapies on fracture risk in men with osteoporosis, however the effects on BMD and bone turnover appear to be similar in men and postmenopausal women with osteoporosis.[1,3,71-73,74] Osteoporotic therapies including risedronate, zoledronic acid, denosumab and teriparatide are currently authorised for use in men with osteoporosis; there is also evidence for alendronate in this setting.[75,76]

Glucocorticoid-induced osteoporosis: glucocorticoids are associated with bone loss and increased risk of fractures.[2] Patients should have their fracture risk assessed and those at high risk commenced on treatment.[2] **Risk factors include age (>55 years), female, low body weight, long-term use of prednisolone and doses >7.5 mg/day.[76,77]** Osteoporotic therapies including risedronate, zoledronic acid, denosumab and teriparatide are currently authorised for use in glucocorticoid-induced osteoporosis.

USEFUL RESOURCES

- FRAX, available on www.shef.ac.uk/FRAX
- Calcium dietary calculator available on https://www.iofbonehealth.org/calcium-calculator
- NOGG 2017: Clinical guideline for the prevention and treatment of osteoporosis (updated July 2018), available on www.shef.ac.uk/NOGG
- Pharmacological management of osteoporosis in postmenopausal women: an endocrine society clinical practice guideline (March 2019), available on https://academic.oup.com/jcem/article/104/5/1595/5418884
- SIGN 142: Management of osteoporosis and the prevention of fragility fractures (June 2020), available on https://www.sign.ac.uk/assets/sign142.pdf
- The Summary of Product Characteristics (SmPC) for individual medicines is available on www.hpra.ie and www.medicines.ie
- The NMIC clinical enquiry answering service is available to deal with specific enquiries: e-mail nmic@stjames.ie or telephone 01 4730589

List of references available on NMIC website. Date of preparation: June 2020