UNIT NO. 1

POSTMENOPAUSAL OSTEOPOROSIS: DIAGNOSIS, FRAX® AND MANAGEMENT

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ABSTRACT

Osteoporosis-related fractures are increasing at a rapid rate, especially in Asia due to the ageing population. This would result in increased morbidity and mortality of the seniors as well as creating a strain on the healthcare system.

Efforts should be made to prevent osteoporosis, screen for osteoporosis early and timely treatment to reduce the risk of fractures. As falls are a major risk factor for fracture in osteoporotic patients, management of osteoporosis should include efforts to reduce falls.

Using a population-wide strategy for women 65 years old couple with high-risk population screening using a combination of tools such as FRAX® and OSTA as well as clinical risk factors for women below 65 years old can detect osteoporosis early for intervention.

Treatment options for osteoporosis include bisphosphonates, denosumab, teriparatide, raloxifene, menopausal hormone therapy and tibolone. Drug choices should be individualised to the patient, balancing the risk/benefit ratio.

Keywords: Osteoporosis screening; osteoporosis treatment; OSTA; FRAX®

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INTRODUCTION

Singapore's population is rapidly ageing due to the combined factors of low fertility and increased life expectancy. By 2030, the total number of citizens above 65 years old will have more than doubled from today.[1] As a consequence, the absolute number of people with osteoporosis is projected to increase significantly by 2030 with a rapid increase in the incidence of osteoporotic fractures unless there are early diagnosis and treatment of osteoporosis.

The incidence of hip fractures in Singapore has increased by 1.5 times for men and five times for women since the 1960s. This coupled with an ageing population will lead to an increase in the burden of osteoporotic fractures.[2-3] A recent study by Yong et al[4] showed that while age-adjusted fractures rates have decreased from 2000 to 2017, the total number of hip fractures have almost doubled from the year 2000 (1478 hip fractures per year) to 2017 (2729 hip fractures per year) due to the ageing population. This would translate to a greater demand for hospital and intermediate and long-term care facilities.

Mortality rates at one year for osteoporotic hip fractures in Singapore is between 20 percent to 27 percent.[5-6] For the survivors, 20 percent will be semi- or fully dependent on their activities of daily living while 39 percent will require some form of assistance.[7]

Impact of Osteoporosis

Osteoporosis is a non-communicable disease with a huge impact on the individuals as well as the burden on the healthcare system. In the Americas and Europe, disability-adjusted life years (DALYs) for osteoporotic fractures is more than that accounted for hypertension and rheumatoid arthritis.[8] In the Asia Federation of Osteoporosis Societies study, it is estimated that the direct cost of hip fractures in Asia will increase from the current 9.5 billion USD to 15 billion USD in the year 2050.[9] In order for the total number of hip fracture to remain constant over time, there needs to be an annual two to three percent decrease in incidence of the rate of hip fracture. This can be achieved through early detection and treatment of osteoporosis as well as measures of falls prevention.

DEFINITION OF OSTEOPOROSIS

World Health Organisation (WHO) defined osteoporosis as a progressive systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture.[10]

Postmenopausal Osteoporosis

Oestrogen maintains the bone quality and quantity in premenopausal women. After menopause, the lack of oestrogen leads to the increase in osteoclastic activity resulting in greater bone resorption compared to bone formation. This leads to increased bone loss in menopausal women. In the Study of Women's Health Across the Nation (SWAN), women experience bone loss from late perimenopause to early postmenopause of about 1.8–2.3 percent per year in the spine and 1.0–1.4 percent per year in the hip.[11] This would be about ten percent loss at the spine and seven percent loss at the hip over five years postmenopause. This rate of bone loss subsequently slows to about 1 to 1.5 percent per year.[12]

DIAGNOSIS OF OSTEOPOROSIS

Dual-energy x-ray absorptiometry (DXA) is the current gold

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standard for diagnosing osteoporosis. World Health Organisation defined osteoporosis using Bone Mineral Density (BMD) as measured by DXA as shown in Table 1.[13] The risk of fracture increases by two-fold for every BMD T-score (SD) decrease in Bone Mineral Density (BMD).[14]

While Qualitative ultrasound of the heel (QUS) has been shown to predict fragility fractures, often the results are discordant and cannot be used for follow-up for patients on medical treatment for osteoporosis.[15]

Table 1: WHO definitions of Osteoporosis based on Bone Mineral Density[13]

WHO Diagnostic Category	BMD T-score (SD) (At either spine or hip)	Description
Normal	≥-1.0	Spinal or Hip BMD within 1.0 SD below the young adult female reference mean (T-score ≥-1.0)
Low bone mass (osteopenia)	<-1 to >-2.5	Spinal or hip BMD between 1.0 and 2.5 SDs below the young adult female reference mean
Osteoporosis	≤-2.5	Spinal or hip BMD more than 2.5 SDs below the young adult female reference mean
Severe/Established osteoporosis	≤2.5 plus one or more fragility fractures	BMD more than 2.5 SDs below the young adult female reference mean and the presence of one or more fragility fractures

The WHO criteria for osteoporosis is not meant to be used for premenopausal women, men younger than 50 years old and children. In these groups, the Z-score (age and sex norms) should be used (International Society for Clinical Densitometry). A Z-score ≤ -2.0 indicates a need for further evaluation to exclude secondary osteoporosis.

What is a fragility fracture?

A fragility fracture is defined as a fracture that occurs with minimal trauma such as a fall from one's standing height or lower with no other identifiable major forces.

Aims of Treatment of Osteoporosis

As with chronic diseases like diabetes mellitus, hypertension, and hypercholesterolaemia, the strategy for osteoporosis is similar. The key is to reduce the risks of fractures by managing osteoporosis and falls.

Primary Fracture Prevention

Primary prevention of any disease is key to the management of any chronic disease, and this approach is the same with osteoporosis. For osteoporosis, weight-bearing and balance exercises, adequate calcium and vitamin D intake, and falls prevention are key to preventing fractures. However, due to poor public awareness and resource limitations, there is usually a gap in this. In a multi-centre randomised trial conducted in the United Kingdom (UK)'s primary care sector, it was shown that primary prevention resulted in a reduction in hip fractures.[16] Primary care practitioners need to take on a larger role to reduce fractures in at-risk individuals.

Secondary Fracture Prevention

When an individual suffers a fragility fracture, he already has bone fragility and osteoporosis. As such, the individual needs to be treated for osteoporosis after the first fragility fracture. However, in a prospective observational study, it was noted that more than 80 percent of women with a fragility fracture did not receive osteoporosis treatment.[17] To address this, the Fracture Liaison Service (FLS), which consists of a multi-disciplinary team that includes geriatricians, orthopaedic surgeons, and a fracture liaison nurse, has been set up in many countries. Several hospitals in Singapore have also set up such FLS which has been shown to have improved the outcomes after an individual suffers a fracture.

Table 2: Risk factors for osteoporosis and fractures[18]

Family History of osteoporosis or fragility fractures
Previous fragility fracture
Ageing (high risk on OSTA)
Low body weight (High risk on OSTA)
Height loss (>2 cm within three years)
Early Menopause (45 years and younger)
Certain medications (such as prednisolone or its equivalent for >5mg/day for three months or more)
Low calcium intake (<500mg/day)
Excessive alcohol intake (>2 units/day)
Smoking
Prolonged immobility
History of Falls
Presence of disease that can lower bone density or increase fracture risks (e.g. Hyperthyroidism, diabetes mellitus or any inflammatory rheumatic disease)

Adapted from MOH ACG 2018[18]

Table 3: Falls risk

Intrinsic factors	Extrinsic factors
• Age • Female • Not married, including single and widowed • Living alone • Arthritis of knees • Stroke • Parkinson's disease • Hypertension • Diabetes • Osteoporosis • Chronic conditions • Urinary incontinence • Cognitive impairment • Depressive symptoms • Poor vision • Postural hypotension • Weak handgrip strength • Self-perceived poor health • Previous history of falls • Fear of falling	• Use of four or more prescribed drugs • Use of hypnotic, anti-depressants or tranquillisers (please refer to Table 2 for further details and other common group of drugs) • Use of walking aid • Mobility impairment • Balance deficit • Gait deficit • Inappropriate footwear & foot problems • Environmental & home hazards

Adapted from HPB-MOH CPG 2015[19]

Table 4: Common groups of drugs that may increase the risk of falls in older adults

Common group of drugs that increases the risk of falls
• **Anxiolytics/hypnotics** (benzodiazepines and others) • **Neuroleptics** (dopamine D2-receptor agonists and serotonin dopamine receptor antagonists) • **Antidepressants** (specifically tricyclic antidepressants and selective serotonin reuptake inhibitors, but may also include serotonin-norepinephrine reuptake inhibitors and monoamine oxidase inhibitors) • **Antihypertensives** (specifically diuretics, but may also include β-adrenoceptor blockers, α-adrenoceptor blockers, centrally acting antihypertensives, calcium channel blockers, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers) • **Antiarrhythmics** (type 1a) • **Digoxin** • **Analgesics** (including opioids and non-steroidal anti-inflammatory analgesics) • **Antihistamines** (especially first-generation with highly sedating and anticholinergic effects) • **Hypoglycaemics** (especially long-acting sulfonylureas with prolonged hypoglycaemic effects) • **Skeletal muscle relaxants** (anticholinergic side effects may increase the risk for falls) • **Anticonvulsants** • **Nitrates** and other **vasodilators** • **β-adrenoceptor blocking** eye drops • **Urinary antispasmodics** • **Antivertigo drugs**

Adapted from HPB-MOH CPG 2015[19]

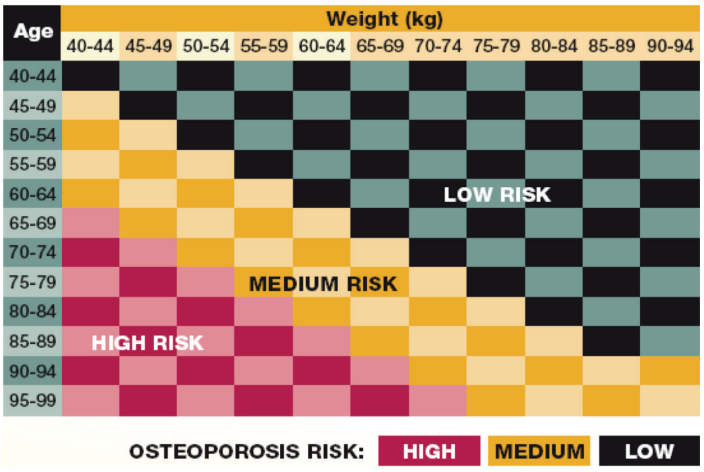
TOOLS FOR OSTEOPOROSIS SCREENING

While DXA remains the gold standard for diagnosing osteoporosis, tools have been developed for pre-screening to select patients for DXA scans to measure their BMD due to the limitation in availability of DXA scanners. There are two tools which are available for such use in Singapore. They are the Osteoporosis Self-Assessment Tool for Asians (OSTA) and FRAX®.

Osteoporosis Self-assessment Tool For Asians

OSTA is a simple tool developed by Koh et al[20] for use in Asians and allows for risk stratification based on age and weight. This tool allows for selecting high-risk Asian populations for BMD measurement. Table 5 shows the chart for classifying patients into high-, moderate-, and low-risk based on the two variables of age in years and weight in kilograms.

Table 5: Osteoporosis Self-Assessment Tool (OSTA)



From Koh LKH et al. A Simple Tool to identify Asian Women at Increased Risk of Osteoporosis. Osteo poros Int (2001) 12:699-705. Used with permission. Copyright, MSD

Fracture Risk Assessment Tools

FRAX®, a tool developed by the WHO Collaborating Centre for Metabolic Bone Diseases at the University of Sheffield, which included the three major racial groups in Singapore, namely the Chinese, Malays, and Indians, has been developed for the assessment of fracture risk and is freely available online for use (https://www.sheffield.ac.uk/FRAX/). The tool gives an estimate of the ten-year probability of major osteoporotic fracture (namely vertebral, hip, forearm and proximal humerus) and hip fracture and can be used with or without the BMD measurement. The National Osteoporosis Foundation uses a threshold of three percent at the hip and 20 percent for major fractures to start treatment. A recent study by Kwok et al. showed that for the elderly Chinese population in Hong Kong, using the NOF threshold for treatment as a pre-screening tool for measuring BMD is cost-effective.[21] There is currently no locally adopted threshold for screening or treatment for FRAX® for Singapore.

SCREENING STRATEGIES

There are currently different screening strategies in different countries as well as professional bodies. The National Osteoporosis Foundation (NOF)[22], U.S. Preventive Services Task Force (USPSTF)[23], and ISCD (Asia Pacific consensus)[24] have recommended a population-wide approach for screening with DXA for all women aged 65 years and above. High-risk population screening using OSTA[20] has been recommended for use in Singapore.

Various countries and societies have recommended a combination of population-wide strategy for women 65 years old together with high-risk population screening using a combination of tools such as FRAX® and OSTA as well as clinical risk factors. A health economic modelling study showed that the combination of population-wide screening combined with high-risk population screening is cost-effective.[25] As such, a combination strategy shown in Figure 1 would improve the screening and early detection of osteoporosis.

SCREENING FOR SECONDARY OSTEOPOROSIS

Before starting medical treatment for osteoporosis, a careful clinical history and physical examination are essential to evaluate the patient. Laboratory tests that are listed in Table 6 should be considered to exclude causes of secondary osteoporosis.[18]

Table 6: Suggested Laboratory Tests to identify secondary osteoporosis

	Test	Clinical Rationale
More commonly indicated	Creatinine	Determine baseline renal function to inform treatment choice and exclude chronic kidney disease and renal bone disease
	Full Blood Count	Identifies a range of disorders including thalassaemia, malignancies and malabsorption
	Corrected Calcium	Increased level might indicate primary hyperparathyroidism or malignancy; decreased level might indicate malabsorption or vitamin D deficiency
	25-hydroxyvitamin D^	To evaluate baseline vitamin D (aim for >20ng/mL for optimal bone and muscle strength)
Others	Thyroid-stimulating hormone (TSH)	Decreased levels might indicate hyperthyroidism or over-replacement with thyroxine
	Erythrocyte Sedimentation Rate (ESR)	Very high ESR might indicate rheumatological disease. A raised ESR in association with raised creatinine and anaemia might indicate haematological disease such as multiple myeloma.
	Alkaline phosphatase	Increased levels might indicate liver disease, Paget's disease, recent fracture or other bone pathology
	Serum Phosphate*	Abnormal levels might indicate vitamin D deficiency or renal phosphate wasting
	Spot urine calcium/creatinine ratio	Elevated levels might indicate idiopathic hypercalciuria#

^ repeated tests are not needed
**fasting needed for more accurate results*
#Urinary calcium/creatinine level >0.6 (urine calcium and urine creatinine in mmol/l) suggests the need to do 24-hour urine calcium test.
Adapted from MOH ACG 2018[18]

MANAGEMENT

Lifestyle Approach

All women should be encouraged to eat a balanced diet with adequate calcium (1000mg/day) and Vitamin D (600 IU/day if 51-70 years old and 800IU/day if >70 years old) as well as protein, avoid excessive alcohol and caffeine intake, stop smoking, adopt active lifestyle with appropriate weight-bearing, muscle strengthening and balance exercises such as walking, Tai-Chi etc.[18]

Addressing Falls Risk

Falls in older women are usually multi-factorial. All women with osteoporosis should be screened for Falls risk, which is listed in Table 2 and Table 3. Efforts should be made to address those factors to reduce the risk of falls.[19]

PHARMACOLOGIC APPROACH

Who to treat?

Any woman with T-score ≤-2.5 either at the spine or the hip should receive pharmacological treatment. Most of the osteoporosis medications have been shown to significantly reduced fracture at this level. For those T-score <-1 to >-2.5, calculate fracture risks using FRAX®. Currently, there is no treatment threshold that has been validated for the Singapore population. Pending the setting of treatment threshold for Singapore, we could adopt the threshold recommended by NOF of three percent at the hip and 20 percent for major fractures to start treatment. Several Asian countries have also adopted the same threshold as NOF(Figure 1).

Treatment options

Medications for the treatment of osteoporosis include anti-resorptive like bisphosphonates, denosumab, Raloxifene, tibolone and hormone therapy. The only anabolic agent that is available in Singapore is Teriparatide(Table 7). When choosing an osteoporosis medication for patient, one has to take into consideration the patient profile, their comorbidities as well as their needs. For example, a menopausal woman with a history of breast cancer with osteoporosis of the spine may benefit from raloxifene which can both lower the risk of breast cancer and reduce the risk of vertebral fracture. A woman with menopausal symptoms as well as osteoporosis would also benefit from menopausal hormone therapy that treats her symptoms as well as reduces all factures. Indeed, there is not a one size fits all treatment option and one should individualise osteoporosis treatment options to the patient.

Bisphosphonates

Alendronate and Risedronate been shown to reduce vertebral, non-vertebral as well as hip fractures. Ibandronate, however, is not effective to reduce hip fracture risk. Fracture risk needs to be assessed after five years of treatment and women who remain at high risk of fracture would benefit from continuation of treatment. For those at low risk, a "drug holiday" can be considered. Those on "drug holiday" needs to be reassessed at about one to two years and reinitiating osteoporosis therapy needs to be considered. Do note that difference in bone affinity between the different bisphosphonates.[27] Zoledronic acid and alendronate have a much higher bone affinity than risedronate, and hence the timing for reassessment may need to be customised to the medications involved. As for IV zoledronic acid, "drug holiday" can be considered after three years of treatment. Patients who are on bisphosphonate treatment should also undergo preventive dental treatment. Preventive dental treatment prior to starting bisphosphonate has been shown to decrease the risk of osteonecrosis of the jaw.[28]

Denosumab

Denosumab has been shown to reduce the risk of vertebral, non-vertebral and hip fractures in the initial three years of a placebo-controlled trial. Extension trial of another seven years showed continued low rates of fracture. However, BMD gains are rapidly lost with the cessation of denosumab, and there are suggestions of rebound vertebral fractures occurring after discontinuation of denosumab.[29] "Drug Holiday" do not apply to denosumab, and it is advisable to switch to bisphosphonates upon decision to discontinue denosumab for a period of between six months to one year.

Teriparatide

This is the only anabolic agent that is currently available in Singapore. It is a daily subcutaneous injection and has been approved for lifetime treatment of up to two years due to the risk of osteosarcoma in rats. It has been shown to be effective to reduce the risk of vertebral and non-vertebral fractures but not hip fracture. As the anabolic effect of teriparatide is lost very quickly, treatment is usually followed by bisphosphonates or denosumab.

Raloxifene (SERM)

Raloxifene has been shown to reduce vertebral fracture risk but not non-vertebral and hip fracture risks. Some important adverse effects to note is the risk of venous thromboembolism, hot flushes, especially for newly menopaused women and transient leg cramps. The added non-skeletal benefit of raloxifene is the reduction in risk of oestrogen receptor-positive invasive breast cancer during treatment and at least five years after treatment.

Menopausal Hormone Therapy and Tibolone

Menopausal hormone therapy with conjugated oestrogens has been shown in the Women's Health Initiative to reduce the risk of all fractures. Traditionally, the primary indication for menopausal hormone therapy has been for symptom relief. In the recommendations of the Revised Global Consensus Statement on Menopausal Hormone Therapy[30], menopausal hormone therapy, including tibolone, can be initiated in postmenopausal women at risk of fracture or osteoporosis before the age of 60 years or within ten years after menopause if there are no contraindications. As such, the decision to start menopausal hormone therapy must be balanced against the risks of breast cancer, cardiovascular risks and venous thromboembolism events which are rare before the age of 60. Do note that for tibolone, it must be used postmenopause (at least twelve months from the last menstrual period) and the increased risk of stroke in women above 60 years.[31]

CONCLUSION

Osteoporosis is a chronic disease that affects postmenopausal women which often results in fragility fractures. The subsequent impact on a woman's quality of life, caregiver burden, as well as healthcare and social costs is huge. As such, early detection through timely effective screening allows appropriate, effective treatment to be given thereby preventing the first fracture. Treatment includes lifestyle modifications, falls prevention as well as medications.

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LEARNING POINTS

- **Management of osteoporotic fracture risk includes treating the osteoporosis and falls prevention.**
- **A good screening strategy for osteoporosis can allow us to detect the disease early for management.**
- **Choice of medications for osteoporosis to prevent fractures needs to be individualised to get the best outcomes.**

Figure 1: Screen Strategy and Treatment Threshold

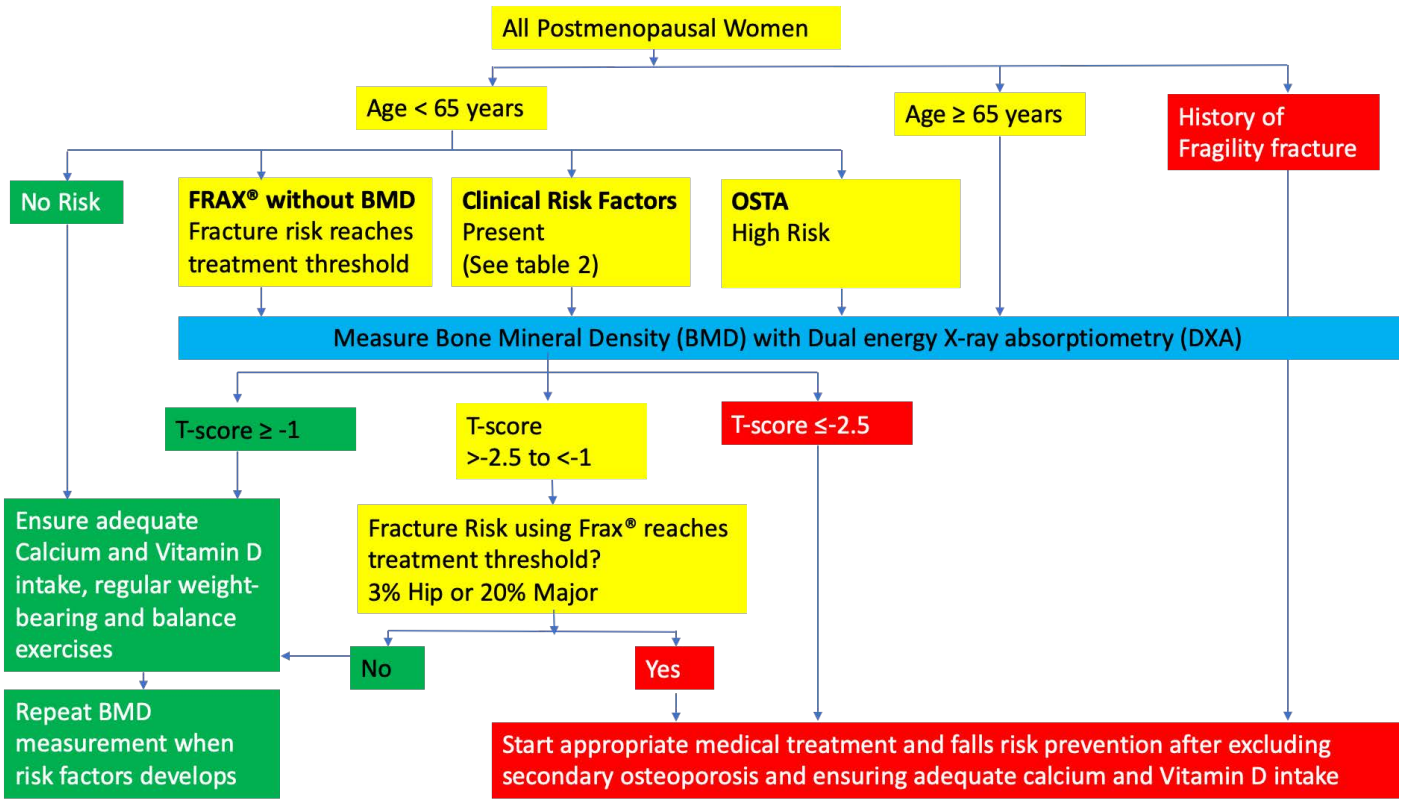

Table 7: Osteoporosis Treatment Options Available in Singapore

Medication	Evidence of Effectiveness in	Contraindications	Clinical Considerations/Precautions
Oral Bisphosphonates: Alendronate Risedronate or Ibandronate	✓ Vertebral Fracture ✓ Non-Vertebral Fracture (alendronate and risedronate) ✓ Hip Fracture (alendronate and risedronate)	• CrCl<30 mL/min • Hypocalcaemia • Oesophageal or gastric abnormalities such as gastric ulcers, achalasia, uncontrolled gastro-oesophageal reflux • Inability to remain upright for 30 min • Aspiration risk and difficulty in swallowing liquids	When taking alendronate or risedronate, advise patients to: • Swallow tablet whole with plain water at least 30 minutes before taking food, beverages, or other medications (especially antacids, calcium, iron, or mineral supplements) • Remain upright until after eating When taking ibandronate, advise patients to: • Swallow tablet whole with plain water at least 60 minutes before taking food, beverages, or other medications (especially antacids, calcium, iron, or mineral supplements) • Remain upright until after eating • Do note the small increase in risks of Osteonecrosis of the jaw and Atypical Femoral Fractures after prolonged therapy.
IV Zoledronic acid (bisphosphonate)	✓ Vertebral Fracture ✓ Non-Vertebral Fracture ✓ Hip Fracture	• CrCl<35 mL/min • Hypocalcaemia	• Give IV infusion for at least 15 minutes • Ensure patient is adequately hydrated before use • Use with caution in patients with significant vitamin D deficiency • Check serum calcium and phosphate at 9 to 14 days after infusion if the patient shows symptoms of hypocalcaemia or hypophosphatemia • Do note the small increase in risks of Osteonecrosis of the jaw and Atypical Femoral Fractures after prolonged therapy.
S/C Denosumab (RANKL inhibitor)	✓ Vertebral Fracture ✓ Non-Vertebral Fracture ✓ Hip Fracture	• Hypocalcaemia	• Ensure adequate calcium and vitamin D intake • Caution to be exercised in patients with pre-existing eczema, renal impairment, and recurrent infections. • Do note the small increase in

			eczema, renal impairment, and recurrent infections. • Do note the small increase in risks of Osteonecrosis of the jaw and Atypical Femoral Fractures after prolonged therapy
S/C Teriparatide (recombinant parathyroid hormone)	✓ Vertebral Fracture ✓ Non-Vertebral Fracture X Hip Fracture	• CrCl <30 ml/min • Hyperparathyroidism or hypercalcaemia • Paget's disease of bone or unexplained increased alkaline phosphatase levels • History of bone radiation	• Daily SC injection • Should not use for longer than two years and should be followed by an anti-resorptive agent
Raloxifene (Selective Oestrogen Receptor Modulator)	✓ Vertebral Fracture X Non-Vertebral Fracture X Hip Fracture	• CrCl<30 mL/min • History of or current VTE (including DVT, PE, and retinal vein thrombosis)	• To be used at least twelve months from last menstrual period.
Menopausal hormone therapy (including tibolone) can be considered for prevention of osteoporosis or fragility fractures in postmenopausal women before the age of 60 or within ten years after menopause as well as for prevention of osteoporosis in women who menopause before the age of 45. Risks/benefits for treatment needs to be weighed and discussed			
Menopausal Hormone Therapy	✓ Vertebral Fracture ✓ Non-Vertebral Fracture ✓ Hip Fracture	Undiagnosed uterine bleeding, breast cancer, oestrogen-dependent neoplasia, venous or arterial thromboembolic disease or thrombophilic disorders, substantial liver impairment	Increased risk of cardiovascular events if it started after 60 years old or after 10 years from menopause. Risk of venous thrombolism is lower for transdermal oestrogen compared to oral. A slight increase in risk of breast cancer in combined menopause hormone therapy.
Tibolone	✓ Vertebral Fracture ✓ Non-Vertebral Fracture X Hip Fracture		Increased risk of stroke in older postmenopausal women 60 years and above[31]

Adapted from MOH ACG 201818and Endocrine Society CPG 2019[26]